Challenges of the current medicine

Elżbieta Krajewska-Kułak, Wojciech Kułak,
Cecylia Łukaszuk, Jolanta Lewko, Mateusz Cybulski

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Edited by
Elżbieta Krajewska-Kułak
Wojciech Kułak
Cecylia Łukaszuk
Jolanta Lewko
Mateusz Cybulski

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EDITORS

Elżbieta Krajewska-Kułak
Department of Integrated Medical Care, Medical University of Białystok, Bialystok, Poland
Wojciech Kułak
Department of Pediatric Rehabilitation and Center of Early Support for Handicapped Children "Give a Chance", Medical University of Białystok, Białystok, Poland
Cecylia Łukaszuk
Department of Integrated Medical Care, Medical University of Białystok, Bialystok, Poland
Jolanta Lewko
Department of Primary Helath Care, Medical University of Białystok, Bialystok, Poland
Mateusz Cybulski
Department of Integrated Medical Care, Medical University of Białystok, Bialystok, Poland

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Nothing can stop the man with the right mental attitude from achieving his goal; nothing on earth can help the man with the wrong mental attitude
Thomas Jefferson

Dear Colleagues

The monograph periodical "*Challenges of the Current Medicine - 11 Edition"* is a collection of authors from various medical centers.

State publication of the medical sector, an essential educational section. In "The Future unmasked: life sciences and healthcare predictions 2025", the consulting company Deloitte, changed the results per setting, patients in enterprises, and where and how healthcare should be taken over in the future.

At the beginning of 2020, the health care and life science sectors, including pharmaceutical, biotechnology, and medical technology, were on a path of constant but relatively slow development. According to the United Nations, by 2025, 11% of the world's population (21% in Europe) will be people over 65. According to the International Diabetes Federation, the number of people who have diabetes, for example, is to increase to 578 million by 2030 and to 700 million by 2045.

According to Deloitte experts, in the coming years, the medical industry will have to focus on such trends as aging societies, an increase in budget spending on health care, the popularity of health and fitness applications, the use of telemedicine and virtual diagnostics, the spread of civilization diseases and antibiotic resistance.

A separate issue with long-term consequences is the continuation of many therapies for chronically ill patients in a pandemic. Finally, forced isolation, a sense of economic threat, or remote work impacted the psychophysical condition of societies.

It is expected that by 2025, medicine will fundamentally change the priorities and decision-making methods regarding the recommended treatment and reevaluate the approach to diagnostics.

According to the idea of "4P" (predictive, preventative, personalized, participatory), medicine should be predictive, preventive, personalized, and participatory.

Thanks to the latest technological achievements in the field of data set analytics, genomics, artificial intelligence, nanotechnology, or 5G communication, it will be possible to diagnose faster and better patients and conduct research and development procedures more efficiently.

Prof. Elżbieta Krajewska-Kułak MD, Ph.D.,
Prof. Wojciech Kułak MD, Ph.D.
Cecylia Łukaszuk Ass. Prof. Ph.D.,
Jolanta Lewko Ass. Prof. Ph.D,
Mateusz Cybulski Ass. Prof. Ph.D,

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SELECTED PROBLEMS IN DERMATOLOGY

Brachioradial pruritus: a rare clinical manifestation of neurologic itch

Marta Szepietowska

Student Research Group of Experimental Dermatology, Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland

List of abbreviations

BRP – brachioradial pruritis

CT – computer tomography

IFSI – International Forum for the Study of Itch

MRI – magnetic resonance imaging

NRS – numeral rating scale

INTRODUCTION

Itch (pruritus) is an unpleasant superficial sensory sensation leading to scratching [1]. In 2007 International Forum for the Study of Itch (IFSI) proposed clinical classification of itch [2]. According to this classification itch was divided into acute itch lasting for less than six weeks and a chronic itch with its duration longer than six weeks. Additionally, chronic itch should usually be related to long-term health problem, such as chronic dermatosis (e.g. atopic dermatitis or lichen planus) or other chronic systemic conditions (e.g. chronic kidney disease or hepatic cholestasis) [2]. Acute itch (e.g. itch after insect bites) is regarded as a defense mechanism, but chronic itch is consider as serious pathology. Chronic itch is a bothersome symptom frequently leading not only to sleeplessness, but also to lowering of patients' psychosocial well-being [3-6]. The IFSI itch classification also proposed six categories of itch according to its pathogenesis: cutaneous itch, systemic itch, neurologic itch, psychogenic itch, itch of mixt etiology and itch of undetermined origin [2]. The above classification has been well accepted and is currently in usage in daily clinical practice.

Brachioradial pruritus (BRP) is an rare condition representing neurologic, even neuropathic itch [7,8]. It was first described by Waisman in 1968 and was termed solar itch as

that time it was linked to intense sun exposure with frequent exacerbations occurring during summer period [9]. The prevalence of BRP is not clear, but the condition seems to be rather rare [10]. Therefore, many physicians are not aware of it [7]. The female predominance was suggested (even 70%) and it seems to be more common in women after the age of 50 years [7,10,11].

AIM OF THE STUDY

This manuscript contains the description of the patient suffering from BRP. Special attention was put to the discussion of underlying neurologic pathology and contemporary treatment modalities of BRP. We do hope this paper will contribute to the increased awareness of BRP among health care workers.

CASE REPORT

A 63-year old female was referred to our center due to long-lasting bothersome itch located on both upper extremities. Itch appeared two years ago, and that time was assessed by patient as very severe one. She was consulted and treated by general practitioner with oral antihistamines (fexofenadine 180 mg per day and then bilastine 20 mg per day) together with topical very potent steroid – clobetasol propionate without any marked improvement. After a few months the patient was referred to regional dermatologist who put her on oral methylprednisolone 4 mg daily. This treatment was continued for 4 weeks, however the itch remained without any reduction of its intensity. The patient scratched the extremities regularly obtaining only slight temporal relief.

On admission she presented with terrible itch on both upper extremities. The itch intensity according to 11-point numeral rating scale (NRS, range: 0-10 points) was assessed as 10 points, indicating very severe itch. Physical examination revealed dry skin, most probably related to the age of the patient. Additionally, some signs of lichenification with hyper and hypopigmentation were found on arms and forearms. Moreover, small single papules were noted within lichenified plaques, as well as one small, 2-3 mm in diameter, erosion located on the arm (Figures 1-3). Obtained detailed anamnesis disclosed that the patient was in general good health, she had been suffering from chronic gastritis well controlled with oral pantoprazole

20 mg daily applied only during the periods of exacerbations. The patient did not take any other drugs.

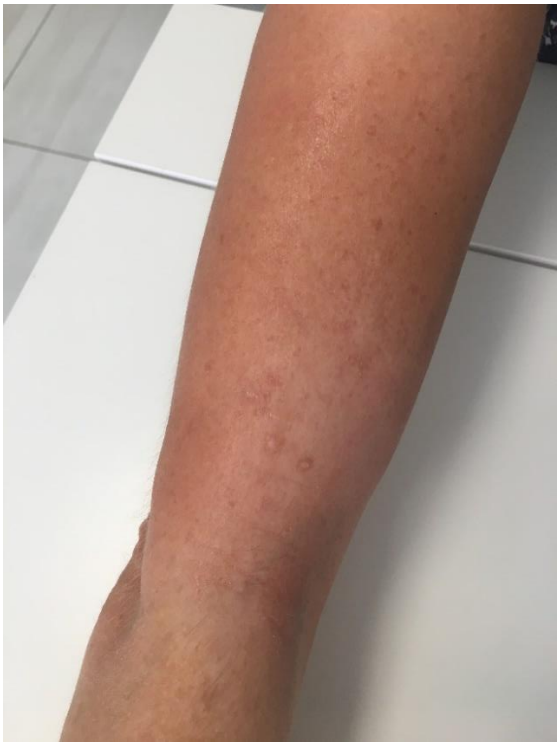

Figure 1. Secondary scratch lesions due to intensive long-term scratching on the upper extremity

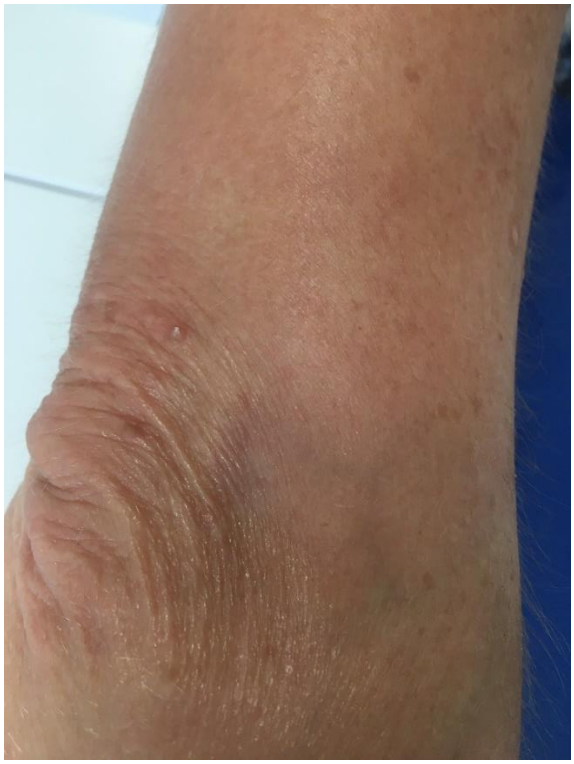

Figure 2. Dryness of the skin with some tiny secondary to scratching papules

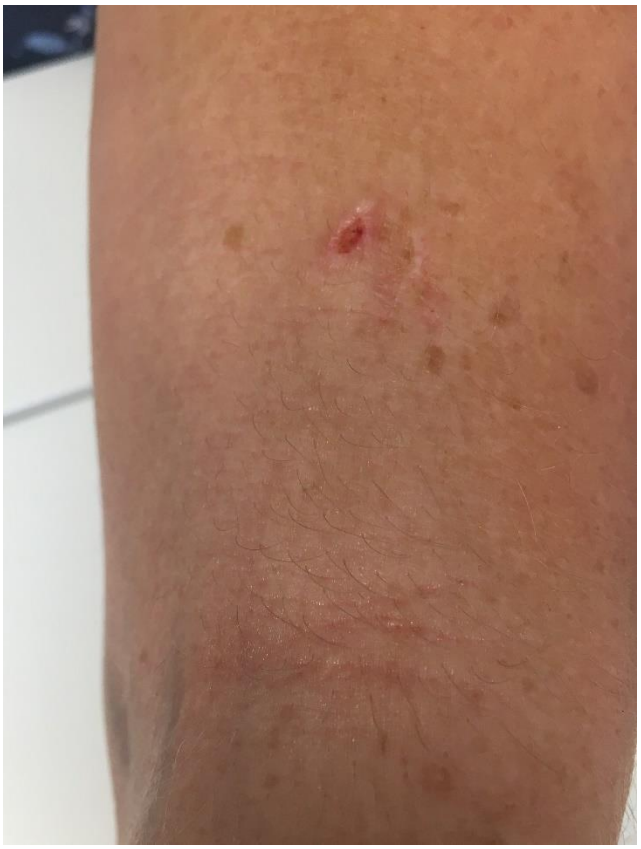

Figure 3. Small erosions covered with crusts as a result of severe itch and subsequent scratching

All taken blood samples, including IgE levels, did not show any significant abnormalities. The punch biopsy was obtained from the lichenified plaque with papule. Subsequent histology was typical for pityriasis lichenoides chronica. The epidermis showed parakeratosis with mild to moderate acanthosis. Moreover, focal vacuolar degeneration of the basal layer was noted. In the papillary dermis congestion and dilatation of superficial vessels was observed. Additionally, perivascular lichenoid lymphocytic infiltrate was documented. Based on clinical manifestation (both signs and symptoms) and histopathology the skin lesions were considered as a long-term consequence of intensive scratching. The diagnosis of brachioradial pruritus was considered. The patient was send to radiology unit for magnetic resonance imaging (MRI) of cervical spine. This examination revealed multilevel changes of cervical spine with neural foraminal narrowing. Multiple hernias of the intervertebral disc of cervical spine (levels C2-C6) were demonstrated. Moreover, lowering of intervertebral discs from level C5 to C7 was shown (Figure 4).

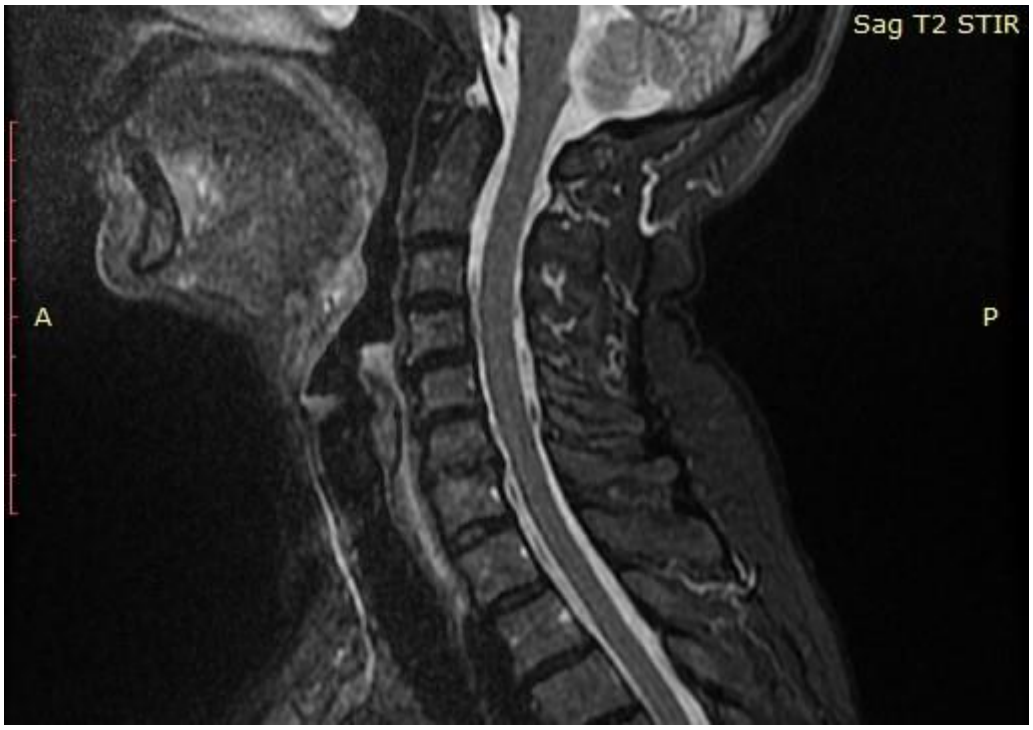

Figure 4. Magnetic resonance imaging (MRI) of the cervical spine showing multilevel abnormalities with discs' herniation and lowering of intervertebral discs from level C5 to C7

This confirmed the suspicion of clinical diagnosis of BRP. The patient was put on oral gabapentin 300 mg twice daily. Additionally, the emollient therapy was recommended for the whole skin surface with clobetasole propionate once daily topical application exclusively limited to the papules. After a month of this treatment she declared marked reduction of itch intensity (NRS=4 points), however she also reported general fatigue. The patient linked her fatigue to the taken drug. The dose of gabapentin was reduced to 300 mg daily (100 mg in the morning and 200 mg in the evening). Topic corticosteroid was discontinued. Within the next two months this treatment resulted in further reduction of itch intensity (NRS=1 point). The patient discontinued scratching and the papules flattened markedly leaving mainly mild postinflammatory pigmentation. The treatment was well tolerated, no adverse effects were observed. The patient was recommended to continue treatment with gabapentin (above mentioned dose) and emollients.

DISCUSSION

BRP is defines as localized neuropathic itch of the dorsolateral upper extremities [7,8]. The clinical manifestation of BRP may differ between patients. In the majority of patients it is

bilateral, however unilateral manifestation has also been observed [12]. Mirzoyev and Davis [8] reported that in their cohort of patients with BRP less than 25% of subjects were diagnosed with unilateral BRP. Upper arms, forearms, shoulders and even neck may be involved [8]. This is a severe itch, however the patients may also complain of other superficial sensations, like burning pain, tingling or stinging. Usually the skin does not show any abnormalities. Definitely, there is no primary cutaneous lesions present. Due to itch the patients scratch the affected skin areas and with long-lasting pathology secondary skin lesions may occur [8,13]. This was also a case of reported patient, who presented with lichenified plaques and secondary papular lesions. More than 30% of BRP patients did not note marked variations in itch intensity throughout the whole year, slightly less than half of them (46%) complained of itch exacerbation during the summer period [8].

The pathogenesis of BRP is not completely well understood. Most probably the disease is linked to the different cervical spine abnormalities. BRP is frequently a result of cervical nerve impingement due to disc herniation, degenerative join disease, osteoarthritis and foraminal stenosis [7,8,13]. In the most of BRP patients the pathology involves C5 and C6 radiculopathy [7,14,15]. Some authors suggested that ultraviolet radiation may lead to the worsening of symptoms. It is well known that sun exposure may contribute to the nerve damage and finally to the reduction of cutaneous C-fibres density. This corresponds to the flares of symptom within the summer seasons [16].

The diagnosis of BRP is challenging [13]. The delay in the diagnosis in not the rare phenomenon. Putting the correct diagnosis is usually postponed by at least several weeks as the majority of subjects do not report any pain/discomfort within the cervical vertebral column. The ice pack sign may be of help and even some authors considered it as pathognomic for BRP [16]. The patients report rapid relief of itch within the area of ice application. Usually this improvement is observed immediately after the removal of ice-pack. The imaging radiological examinations are crucial in establishing the diagnosis of BRP. One may recommend x-ray, but computer tomography (CT), and especially MRI of cervical spine could be of value [7,8,13,16]. MRI was the examination which lead us to the confirmation of BRP clinical diagnosis in our patient.

Several treatment modalities have been proposed for BRP. They include both topical and systemic treatments [8,16]. Topical anesthetics and capsaicin may be used [8,16]. Topical corticosteroids are rather recommended only if the secondary scratch lesions are present. It is important to underline that topical corticosteroids are not typical antipruritic agents, as they do

not target any element of the pathway of itch sensation starting from the dermo-epidermal zone of the skin going up to the cortex of brain. Their potential antipruritic activity is secondary to the inflammatory process ongoing within the skin [17]. Looking at the literature the effective treatment of BRP is a systemic one. It is worth mentioning that systemic antihistamines are not effective in BRP. It is understandable as histamine does not play any important role in the pathogenesis of BRP [17]. Our patient was treated with gabapentin with satisfactory clinical outcome. Gabapentinoids, including gabapentin and pregabalin, are considered as first line treatments of neuropathic itch [1]. The effectiveness of gabapentin and pregabalin was reported by numerous authors [18-21]. Other treatment options include oral doxepin, hydroxyzine, carbamazepine, lamotrigine or amitriptyline [8,16]. To the best of my knowledge due to rarity of BRP there is not well designed randomized clinical trials in BRP and there are only case reports or series of cases available in the literature. Some authors suggest also the beneficial role of physical therapy, specially designed physical exercises or even acupuncture [8].

In conclusion, BRP is not a common condition. Based on the current knowledge chronic itch in BRP is due to cervical spine abnormalities and may be exacerbated by intensive sun exposure. BRP as a form of neurologic/neuropathic itch requires holistic approach; gapentinoids should be considered as treatment of choice. All health care workers should be aware of BRP to adequately serve the patient, both in the diagnostic and therapeutic process.

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Recent advances in the laboratory diagnosis and pathophysiology of SLE (Lupus Erythematosus Systemicus)

Maksymilian Ludwig, Julia Fiołkowska, Emilia Czubaj, Jakub Cisek, Agata Kes

Medical University Piastów Śląskich of Wroclaw, Wroclaw, Poland

List of abbreviations

ACMG - American College of Medical Genetics and Genomics

ACR - American College of Rheumatology

ALCAM – Activated Leukocyte Cell Adhesion Molecules

ANA - antinuclear antibodies

ASMR - annual standardized mortality rate

CB-CAPs – Cell-Bound Complement Activation Products

CSF - Cerebrospinal Fluid

EULAR - European League Against Rheumatism

Gal-9 – Galectin-9

GWAS - genome-wide association study

IGHG3 – Salivary Immunoglobulin Gamma-3 Chain C

KIM-1 – Kidney Injury Molecule-1

LCN2 – Lipocalin-2

LN – Lupus nephritis

NGAL - Neutrophil Gelatinase-Associated Lipocalin

NLR - neutrophil-to-lymphocyte ratio

NPSLE – Neuropsychiatric Systemic Lupus Erythematosus

PD – Periodontal Disease

PLR – platelet-lymphocyte ratio

PRS - polygenic risk score

pSS - progressive systemic sclerosis

RA - rheumatoid arthritis

SLE – Systemic Lupus Erythematosus

SLICC - Systemic Lupus International Collaborating Clinics

VCAM-1 – Vascular Cell Adhesion Molecule-1

WGS - whole genome sequencing

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease. This disease exhibits a wide range of symptoms depending on the patient. They range from mild skin symptoms to severe organ changes that are fatal [1,2]. Although this disease has been known for a long time its pathogenesis, treatment and even classification is still a significant problem for physicians. Perhaps the complexity of symptoms and factors affecting pathogenesis makes this disease still an object of scientific interest and the target of many studies on its subject even today. In our paper, we present the latest reports on pathogenesis and laboratory diagnostics of SLE as two aspects that arouse the greatest controversy among SLE specialists.

EPIDEMIOLOGY

Global incidence is estimated to range from 0.3 to 23.2 per 100,000 person-years and global prevalence from 9 to 241 per 100,000 person-years. Such large discrepancies in results may be due to differences in methodology and the population on which the study was based [3].

Recent studies show a trend of increasing global prevalence and rather no change in global incidence. For example, in 2009 the age- and sex-adjusted prevalence in the US was 301.01 per 100,000 individuals, and already in 2016 it was 366.6 per 100,000 individuals. However, this may be due to changes in the classification of SLE at the turn of the year, and at the same time changes in sensitivity and specificity of criteria on the basis of which the presence of SLE in a patient is determined [2].

The incidence and prevalence of SLE has been shown to be higher among women than men and among Black, Asian, Hispanic, Native American, and Arab populations than among White populations. Women and the non-White population also have a more severe disease

course with more severe organ complications. It has also been shown that black patients are diagnosed with SLE at an average younger age than patients from the White population [2].

In 2014, the annual standardized mortality rate (ASMR) for SLE was estimated by WHO at 2.7 deaths per million inhabitants, with 0.8 deaths per million inhabitants for men and 4.5 deaths per million inhabitants for women. Similarly as for prevalence also ASMR was higher for non-white patients than in white population. Survival for SLE patients since 1990 does not seem to have fluctuated much. The leading causes of death in SLE patients are infections and cardiovascular disease [2].

A three- and twofold increase in the risk of myocardial infarction and ischemic stroke in patients with SLE has been demonstrated. Similarly, a 1.14-fold increase in the risk of all types of cancers and a 12-fold increase in the risk of hospitalization for infection have been shown in these patients [3].

Differences in genetics, epigenetics, sex hormones, and gut microbiota are included as reasons for differences between SLE traits in women and men. Differences in genetics, autoantibody reactivity, and differences in socioeconomic status and access to treatment are suggested as reasons for differences between disease characteristics among ethnic groups [3].

CLASSIFICATION CRITERIA

There are three classification systems most commonly discussed in the literature: ACR-1997, SLICC-2012, and EULAR/ACR-2019. The ACR-1997 criteria show relatively high specificity with intermediate sensitivity. The SLICC-2012 criteria introduced mucocutaneous and neuropsychiatric manifestations as well as hypocomplementemia and antiphospholipid antibody tests. These criteria have been shown to gain in sensitivity but at the cost of lower specificity relative to ACR-1997 [1].

The latest EULAR/ACR-2019 classification system shows varying efficacy relative to the other systems depending on the study conducted. In some, it shows significantly better sensitivity and specificity than the other systems, while in others it is not very different (4–7). This system is based on two new aspects such as taking the presence of ANA as an initial criterion and using a weighted scale for the rest including new criteria [4]. A comparison of these three classification systems can be found in Table 1.

In addition to aiding in diagnostic purposes, selected classification systems may also serve as prognostic criteria for disease. There was found a correlation between EULAR/ACR

set and renal damage (p=0.018) with no correlation between EULAR/ACR and cardiovascular events and deaths. No such relationship was demonstrated for ACR-1997 and SLICC-2012 [8].

Certain disease characteristics, patient characteristics and treatment modalities were associated with the number of points they initially scored. When EULAR/ACR score was more/equal to 20 points such patients were more likely to receive glucocorticoids (66.8% vs 44.6% for patients <20 points, p<=0.001) and immunosuppressive drugs (20.6% vs 14.0% for patients <20 points, p=0.010). These patients also experienced more frequent renal lesions and less frequent complete disease re-emission than patients with <20 points [9].

Table 1. Comparison of sensitivity, specificity and prediction in clinical outcome of ACR-1997, SLICC-2012 and EULAR/ACR-2019 in adults and children from 5 independent studies. Different colors (different orange and different yellow) symbolize different studies from which data was taken (1,4,6–8). Numerical values in sensitivity and specificity were rounded to hundredths, counting from 5 inclusive upwards. The "combined" values were calculated by summing the rounded numerical values of sensitivity and specificity

	Sensitivity		**Specificity**		**Combined**		**Association between criteria and clinical outcome**
Classification criteria	Children	Adult	Children	Adult	Children	Adult	Adult
ACR-1997	0,49	0,83	0,96	0,93	1,45	1,76	No association
	0,69	0,83	0,95	0,96	1,64	1,79	
SLICC-2012	0,76	0,97	0,94	0,84	1,70	1,81	No association
	0,95	0,97	0,90	0,84	1,85	1,81	
EULAR/ ACR-2019	0,81	0,96	0,92	0,93	1,73	1,89	P = 0,018
	0,92	0,89	0,89	0,89	1,81	1,78	

PATHOGENESIS

In the most available textbook [10] for medical students in Poland, which can be used as a basis for the pathogenesis of lupus erythematosus, several possible mechanisms of lupus erythematosus formation are distinguished from immunological phenomena.

1. Quantitative abnormalities in T-lymphocyte classes
2. Hyperactivation of B-lymphocytes to produce antibodies

3. Immunologic mimicry and cross-reactions with infectious antigens
4. Increased activity of proinflammatory cytokines, e.g. IL-2, TNFα and INFγ

In popular science portals often the etiopathogenesis is not described. It is described as unknown or incomplete.

GENETICS

Genetics plays a major role in each of these mechanisms. SLE heritability, which estimates at 43-66% is the evidence of the contribution of genetic factors on the development of SLE (Figure 1) [12]. Despite the advances in genetic methods, not all mechanisms involved in SLE pathogenesis have been established. To date, approximately 180 loci determining susceptibility to SLE have been identified. Each year scientists are discovering new ones [13].

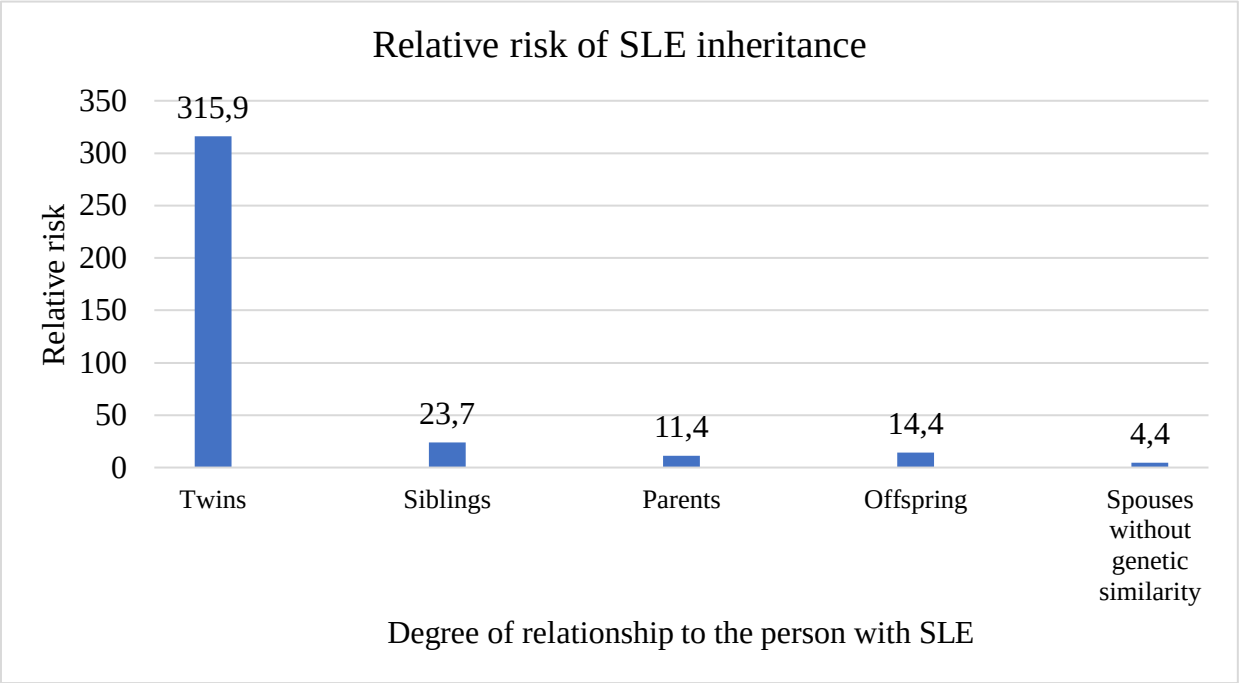

Figure 1. The relative risk of inheriting SLE in relation to the degree of relatedness to a person with SLE. Data used in this study come from the Taiwan National Health Insurance Research Database. The sample size was N = 23,658,577, of whom 18,283 had SLE. After determining the degree of relatedness between the subjects, it was shown that the relative risks for SLE were 315.9 for twins of patients with SLE, 23.7 for siblings, 11.4 for parents, 14.4 for offspring and 4.4 for spouses without genetic similarity [11]

Rare missense variant of WNT16 gene

Genetics plays a special role in the pathogenesis of many diseases. To identify the genes associated with a disease, scientists use whole genome sequencing (WGS). This method was

used to analyze the genomes of 16 individuals from 3 Chinese families, 7 of whom were affected by SLE. The obtained results were compared to data collected in the Genome Aggregation Database.

Rare missense variant of WNT16 gene causing the systemic lupus erythematosus has been identified. It has been proven that occurrence of that rare variant causes higher genetic burden than burden in common variants in SLE patients (odds ratio 1.029). Missense variant NC_000007.14:g.121329757G >C in the WNT16 gene was observed for the first time in this study. It applied five out of seven considered SLE cases and did not occur in control group. Odds ratio for pathogenic risk of that variant equaled 41.8. The WNT16 gene encodes protein which takes part in Wnt signaling [14]. Wnt signaling consists of three pathways in which proteins attend in signal transducing. This influences embryogenesis, carcinogenesis as well as physiological processes in cells. The Wnt signaling pathway is necessary for proper regeneration in adult bone marrow, skin and intestines [15]. Research have shown that due to the missense variant NC_000007.14:g.121329757G >C one of the pathways (the canonical Wnt/β-catenin pathway) cannot be activated adequately. This research has shown involvement of the Wnt signaling pathway in the pathogenesis of SLE. Therefore, further investigation should be conducted in this direction.

Monogenic SLE

SLE is divided according to the time of onset into childhood onset SLE and adult onset SLE. Childhood onset SLE occurs when the disease is diagnosed at age <18 (on average it is 11 to 12 years of age) [16]. Adult onset SLE is diagnosed in patients 18 years of age and older [17]. The two forms differ in severity – childhood onset SLE is more severe than SLE that develops at a later age [18].

SLE is predominantly a polygenic disease that is also influenced by environmental factors. However, there have been reports of lupus developing in a monogenic pathway. It pertains to childhood onset SLE cases. The monogenic pathway affected 7% of patients, which equals 7 people [18]. Novel protein changes have been found in those patients. Those gene variants have been considered as pathogenic or likely pathogenic and may affect developing SLE in mendelian inheritance pattern (Table 2) [19].

Interestingly, in this group average age of onset was lowered to 7 years, when in the whole cohort it totals 9 years [18].

Most studies claim that mendelian forms of SLE are related with disfunction of B-cells. However, this research has shown that monogenic lupus is rather connected to genes which condition innate immunity. It should also be noted that the PRKCD has not been shown to be involved in the pathogenesis of monogenic SLE as it was proven in previous studies [18].

Table 2. Novel protein changes in patients with monogenic SLE development [18,19]. ACMG = American College of Medical Genetics and Genomics

Gene	Protein change	ACMG classification	Function
C1QA	p.Ile15AsnfsTer7	Likely pathogenic	Encodes complement C1q A chain
C1QC	p.Leu41CysfsTer97	Pathogenic	Encodes complement C1q C chain
IKZF1	p.Asp120Val	Likely pathogenic	B cell development and tolerance
Lyn	Phe258Ser	Likely pathogenic	Encodes tyrosine protein kinase

Polygenic risk score

Polygenic risk score (PRS) is very promising research method. It shows association between genetic variants and defined trait, without including environmental factors. One genetic variant in the genome may have little effect, but when there are multiple variants associated with a trait, the risk of revealing the trait in phenotype increases significantly. PRS is calculated on the grounds of genome-wide association study (GWAS), which focuses on single-nucleotide polymorphisms. However, it is worth noting that the data for the GWAS mostly come from surveys conducted in European and East Asian population group. Therefore, it could not be suitable for populations of other ancestry [18]. A study was conducted to check the transferability of PRS between European ancestry group and Chinese cohort. The results have shown poor utility of PRS for SLE calculated from European population and used for Chinese group with AUC ranged from 0.62 to 0.64 [12].

Vast majority of research have shown that PRS can be used to forecast exposure of different diseases. It was proven that PRS correlate with prevalence of lupus nephritis. The renal failure is one of the most common manifestations of SLE and plays major role in mortality of patients with SLE. It is the cause of more severe clinical manifestation and it shortens life expectancy. Hence scientists have been analyzing whether there is correlation between renal involvement and genetics. Research has shown that PRS predictive power with AUC approximately 0.7. It was proven that higher PRS correlate with earlier SLE onset age [20].

Epigenetics

As we know, monozygotic twins share identical DNA sequence. Considering that, why in 40% SLE affects only one of the twins [18]? In addition to genetic factors, epigenetics and environmental factors also have an impact on the development of SLE.

DNA methylation occurs due to the attachment of methyl groups to DNA by DNA methyltransferase. There is negative correlation between quantity of methylated DNA in gene promoter region and gene transcription. A study was conducted on the methylation of so-called CpG islands (regions rich in 5'-CpG-3' dinucleotide) located in gene promoters in discordant monozygotic twins.

The differences found involved 49 genes that determine immune system function. Genes differing in the degree of methylation include IFNGR2, MMP14, LCN2, CSF3R, PECAM1, CD9 and AIM2. The ribosomal genes were also differentially expressed. Decreased methylation status was observed in 18S and 28S. Accordingly transcription of those genes was increased in SLE twin compared to the healthy twin. Research has not shown any methylation changes in PLP0, RPLP1, RPLP nor in promoter CpG island of ribosomal RNA genes [21].

Other

In scientific papers from 2018-2022 describing progress in defining accurate and complete pathogenesis and immune mechanisms, we can distinguish directions:

1. impact of PI3K/Akt/mTOR signaling pathway on the process of lymphocyte differentiation and Th17/Treg disparity
2. increased B-lymphocyte activity
3. gut microbiome

Influence of PI3K/Akt/mTOR signaling pathway on T lymphocyte differentiation and Th17/Treg disproportion

Mammalian target of rapamycin (mTOR) is a central regulator that integrates nutritional information, and activation of mTOR signaling increases protein synthesis. The mTOR can be divided into mTorC1 (complex 1) and mTorC2 (complex 2), based on its components [22,23]. The regulation of mTor can be divided into two signaling pathways: the PI3K/Akt/mTor pathway and the LKB1/AMPK/mTor pathway. In our further discussion, we will focus on the former. Phosphoinositide-3 kinase (PI3K) is a member of the lipid kinase family. Upon activation by T-cell receptor, IL-2, or growth factor receptors, PI3K can associate with tyrosine

kinase and bind to ligands, catalyzing the formation of phosphoinositide triphosphate (PIP3) from phosphoinositide diphosphate (PIP2), which consequently activates serine/threonine kinase (Akt). Akt is an important target kinase downstream of PI3K. Akt plays a linker role in the mTOR signaling pathway [24]. Continuous activation of mTORC1 leads to defosphorylation of Akt, which inhibits mTORC1 feedback. Human and animal studies have shown that PI3K activity is increased in SLE.

The PI3K/Akt/mTOR pathway regulates Foxp3 expression in thymocytes and naïve CD4+ T cells. In contrast, continuous phosphorylation of this pathway and continuous expression of Akt inhibits the differentiation of naive CD4+ T cells into Treg cells [25]. Increased expression of Akt in T and B cells is noted in SLE patients. Additionally, the active form of PI3K in studies creates lupus-like lesions in the kidneys [26,27].

Decreased numbers of Treg lymphocytes, results in increased and uncontrolled activity of Th17 lymphocytes. Th17 cells, a subset of CD4+ effector T cells, are identified by their ability to produce IL-17A, IL-17F, and IL-22, mediate inflammatory responses, and participate in the onset of autoimmune diseases. IL-17 is the major cytokine that promotes Th17 to participate in SLE. It has been confirmed that IL-17 levels are increased in the kidneys of patients with lupus nephritis, and IL-17 gene expression in urine sediment is also increased [26]. In addition, Th17 expression was also found in skin, lung and kidney tissues of SLE patients. Increased Th17 activity has been associated with disease activity in SLE. Treg are capable of modulating effector T cell function, maintaining immune homeostasis and preventing autoimmunity. Several studies have shown that the number of Treg lymphocytes in SLE patients is reduced, and their function is not preserved [28,29]. In normal conditions, Th17 and Treg lymphocytes are in a state of dynamic balance, which is disturbed in SLE [30]. At present, it is commonly believed that the increase in the number of Th17 cells is accompanied by a decrease in the number of Treg lymphocytes, and dynamic changes of both these cells are involved in the process of immune response.

B lymphocyte overactivity

Along with the production of increased amounts of IL-17, B cell stimulating factor (BAFF or BLys) is also produced. When overexpressed, it causes increased proliferation and prolongs the survival time of self-reactive B cells. The level of BAFF is positively proportional to the degree of kidney damage, it was noticed in studies on mice with lupus in the early stages of SLE.

In B-lymphocyte hyperreactivity, there is also a new aspect of regulatory B cells. They are a group of cells with negative regulation of the immune response. The main action of Breg cells is secretion of IL-10, which is responsible for suppression of Th17 cells differentiation, decrease of antigen presenting ability by dendritic cells, monocytes and other antigen presenting cells, and decrease of proinflammatory cytokines and co-stimulatory molecules production [31]. In a growing number of human SLE studies, it has been shown that the number of Breg lymphocytes in lupus patients is lower than in healthy individuals, especially in patients with lupus nephritis, and the number of these cells increases after immunosuppressive treatment. Moreover, the response of Breg cells to CD40 stimulation and IL-10 secretion were decreased in the peripheral blood of SLE patients, indicating that Breg cells are dysfunctional in SLE . IL-10 restores the balance between Th1 and Th2 cells [32].

In lupus, impaired B cell tolerance leading to autoantibody production is observed. Human regulatory T cells in physiological states suppress the production of autoantibodies from B and T cells, but in SLE their number is reduced and they are functionally damaged. Autoreactive B cells process and present self antigens to T cells, which promotes the activation of proinflammatory cytokines. Th1 lymphocyte-derived cytokines are specifically overexpressed in lupus-lesioned kidneys and promote inflammation through activation of macrophages, complement and F receptors [33]. Added to this, there are also abnormalities in B and T cell signaling that include an abnormal T cell receptor complex, alterations in proteins that differentially affect the T cell response to inflammation (e.g. mitogen-activated protein kinase), decreased levels of inhibitory molecules such as Lyn (LCK/Yes-related tyrosine kinase), impaired signaling by the B-cell inhibitory receptor FcgRIIB, and a more rapid response to a stimulus for B-cell proliferation such as the proliferation-inducing ligand (APRIL) or B-lymphocyte stimulator (BLyS) [34].

The formation of antibodies with pathogenic potential occurs. The presence of overactive and overreacting B and T lymphocytes and prolonged exposure to nuclear antigens leads to the formation of autoantibodies directed against nuclear structures, which are the immunological hallmark of SLE.

The intestinal microbiome

The contents of the intestinal lumen can influence B cell differentiation in many mammalian species. This is influenced by the presence In 2018, researchers revealed that in

mice, the earliest B-cell repertoire is formed in the intraluminal lamina propria of the small intestine, concurrent with intestinal bacterial colonization [35].

The researchers hypothesized that intestinal exposure to bacteria-derived primitive orthologs of the protein synthesis machinery may be responsible for the selection of autoreactive T and B cell clones in humans. Focusing on the RNA-binding protein Ro60, a well-known SLE autoantigen, they found that the major Ro60 epitopes targeted by T and B cells were highly homologous to Ro60 orthologs from commensal bacteria including Bacteroides the taiotaomicron and others associated with the skin and oral mucosa. In addition, memory T cell clones isolated from healthy individuals and SLE patients were able to cross-react and be stimulated by both human Ro60 and orthologous Ro60 derived from bacteria.

In another study using a cross-sectional analysis of SLE patients with a wide range of clinical disease activity, my group linked intestinal expansions of the intestinal symbiont Ruminococcus gnavus to SLE [36].

Serum IgG responses to this potential pathogen directly correlated with disease activity and anti-native DNA levels.

The composition of the gut microbiome is influenced by various factors such as genetics, sex hormones, diet, drinking water, and the use of antibiotics and probiotics. Using next-generation sequencing techniques to assess potential dysbiosis (altered microbiome composition) [37], demonstrated lower levels of Firmicutes to Bacteroidetes ratio in feces in SLE patients than in healthy individuals. Importantly, intestinal dysbiosis has been linked to an imbalance between regulatory and pathogenic (Th17) T cells in SLE [38].

More recent data support the hypothesis of a "leaky" intestinal epithelium in SLE, leading to translocation of the intestinal pathobiota (Enterococcus gallinarum) to the liver and lymph nodes, thereby increasing the expansion of autoreactive T cells [39].

In a landmark study [40], they reported that translocation of the bacterium, Enterococcus gallinarum, from the small intestine to the liver induces a lupus-like state in autoimmune-prone mice through activation of the aryl hydrocarbon receptor (AhR) system (a pathway that can induce T helper 17 cell production), resulting in a systemic type I interferon signature and production of anti-dsDNA antibodies. Intriguingly, this commensal bacterium has been detected in liver biopsy samples of patients with autoimmune hepatitis and in several patients with SLE, suggesting that this mechanism is involved in human autoimmune pathogenesis.

LABORATORY DIAGNOSIS

For years scientists have been trying to find the ideal marker for SLE. It should be an indicator that is relatively easy to determine qualitatively and quantitatively with already known methods and reflect changes in the body. Ideally, its concentration should make it possible to distinguish the chronic state of the disease from the acute state [41]. For a given marker to be included in use, it must have appropriate sensitivity, specificity and predictive value, moreover, it should be sufficiently stable and insensitive to external factors. SLE diagnostics is often problematic due to lack of visible signs of the disease in its early stages, so a marker secreted relatively soon after the onset of pathogenesis would be needed [41,42].

Limitations of classical SLE markers

Basic biomarkers of SLE can include proteinuria, haemolytic anaemia, white blood cells, lymphocytes, platelets, ANA, anti-Sm antibodies, CRP, C3, C4 and LE cells [41,42].

ANA antibodies have been used to diagnose SLE for 60 years, however their prognostic value is increasingly questioned. Their secretion fluctuates constantly due to changes in the B cell population. Research on the influence of factors such as race, ancestry or genetics on ANA secretion is continually being conducted. The main disadvantage of this "gold standard" in SLE diagnostics is its low specificity - according to studies up to 30% of patients suffering from this disease do not secrete these antibodies [43]. Moreover, they are detected even in 5-20% of healthy population, usually in elderly people. In turn, anti-dsDNA antibodies show a relatively low sensitivity (52-70%) [41,42], and anti-Sm antibodies are detected in only 20-30% of patients (42). As for CRP concentration, it is usually higher in patients with SLE, but the change in the level is not always noticeable during periods of disease exacerbation [44].

Changes in blood morphology

It is a well known fact that the pathogenesis of SLE involves the presence of inflammation which causes deregulation in blood morphology. Leukopenia occurs in patients with a frequency of 22% to even 51.6%, lymphopenia in 15-96.6% and neutropenia in 20-60% of patients [45]. However, these are not specific markers, the determination of NLR and PLR indices is much more useful. Their values are higher in patients with active SLE, compared to inactive, and in patients with LN, than in patients without this condition [46,47].

Also, NLR, unlike PLR, shows an increase during the disease flare. NLR is particularly useful in patients in whom C3 and/or anti-dsDNA assay did not provide a clear diagnosis. Importantly, NLR could become an important part of SLE diagnosis in less developed countries where serological testing is not widely available [46]. The NLR is an easily measurable biomarker and provides more information than single determination of individual leukocyte fractions because they are sensitive to changes in body hydration and the method of sampling [47]. NLR and PLR provide the most information when assayed simultaneously [48].

The NLR index shows 85% specificity but only 59% sensitivity. On this basis, we can conclude that this marker can be used in the diagnosis of SLE, but mainly as a complement [46].

Populations of lymphocytes

Recent research has also turned to the analysis of B cells and T cells populations as potential SLE markers. As is well known, these cells play an important role in the pathogenesis of the disease. As far as diagnostics is concerned, the DNeg of T cells (CD3+CD4-CD8-) population should attract attention. In healthy people they constitute only 5% of CD3+ T cells, but in SLE patients their number is significantly increased. The novelty of the diagnosis is that it increases along with the development of the disease. At the same time, a proportional decrease in the number of B cells is observed. It has also been shown that there is a link between changes in DNeg cell population and kidney function. Similar studies have also been carried out among paediatric patients and the same conclusions were reached [49].

On the other hand, the team of Colucci Manuel et al. studied IgM anti-Tcells antibodies present on the surface of these cells. They found out that they usually appear in patients with active SLE and that this is an indicator independent of kidney damage. This potential biomarker showed a very high sensitivity and specificity in the diagnosis of SLE (AUC=0.97, $p<0.001$), while classical markers such as ANA or anti-dsDNA antibodies have a lower AUC value (0.96, $p<0.001$ and 0.90, $p<0.001$, respectively). Furthermore, while 100% of the patients in the study had ANA, anti-dsDNA antibodies were only detectable in 80% [50].

Of course, not all lymphocyte subpopulation tests provide relevant information to the diagnosis of SLE. Some of them are subject to excessive fluctuations caused by external factors, as exemplified by the plasmoblast population ($CD19^{lo}CD20^{-}CD27^{hi}CD38^{hi}$) [51]. However, the cited studies confirm the utility of determining DNeg populations and T cells with IgM antibodies in the diagnosis of SLE [49,50].

Biomarkers in body fluids

Body fluids are an enormous source of biomarkers, resulting in the continuous discovery of new parameters of greater or lesser importance, which may apply their application in diagnostics. For the purpose of this paper we discuss only some, out of many studied, that have shown potential in detection and monitoring of SLE in patients.

Serum

One of the basic biological materials for testing is serum. It contains many markers that are able to detect SLE, monitor its progress or inform about the involvement of other organs in the disease process. Cell-bound complement activation molecules (CB-CAPs) have been extensively studied. Due to their higher stability and longer half-life span, they show greater diagnostic utility than their soluble forms. Depending on the cell with which CAPs are bound, they show different sensitivity and specificity towards SLE, which makes it possible to create different diagnostic panels, also combining them with standard parameters. Additionally, some of them express association with other key markers, such as platelet-bounded CAPs (PC4d), which positively correlate with antiphospholipid antibody. This allows PC4d to be used in a diagnostic panel for patients at increased risk of thrombosis. CB-CAPs have also been tested as biomarkers for monitoring disease activity. Good results were obtained for reticulocyte-bounded C4d, but due to the short lifespan of these cells, the RC4d value expresses only the current status of the patient. Moreover, both C3d and C4d associated with erythrocytes showed their usefulness, their levels being higher in SLE patients as opposed to controls and, additionally, even higher in patients with active disease [44].

Galectin-9 (Gal-9) - a β-galactoside-binding lectin - also deserves special attention. The study made by Matsuoka et al. aimed to prove its use in monitoring disease activity. They demonstrated significantly higher serum Gal-9 levels in SLE patients in opposition to healthy controls, and noted that these levels were highest in patients with active disease, suggesting their correlation. What is also important, it was proved that Gal-9 values were higher in patients who had damage to other organs as a result of the disease process [52].

They also evaluated the association of this parameter with the chemokine CXCL-10, which was as well detected in higher levels in these patients. CXCL-10 has shown not only the best ability to assess the active form of SLE among interferon-regulated chemokines, but capacity to predict disease exacerbation of the disease too [51].

The study of biomarkers allows a wide spectrum of possibilities, although only CB-CAPs and Gal-9 have been mentioned more extensively, they are not the only ones that have recently given promising results. Undoubtedly, this is an area of research worthy of further development.

Cerebrospinal fluid

Despite the still incompletely understood mechanism of neuropsychiatric SLE (NPSLE), more and more new discoveries continue to be made in the diagnostic field. In addition to routinely used markers such as anti-β2-glycoprotein I, advances in science allow new features to be considered.

Recently, lipocalin 2 (LCN2, also known as neutrophil gelatinase-associated lipocalin - NGAL) was found to be present in higher concentrations in cerebrospinal fluid (CSF) in patients with NPSLE. This was confirmed by a study that demonstrated the ability of LCN2 to distinguish individuals with NPSLE from controls as well as other neurological disorders, in two ethnic groups, with an AUC of 0.85. Nonetheless, not in all NPSLE individuals high levels of this marker appeared so it seems necessary to confirm or deny whether LCN2 is associated with a specific subset of the disease in a larger study group. So far, aquired results proves the potential of usage of LCN2 as a biomarker mostly due to the positive predictive value of the test rather than it being able to rule out the presence of NPSLE [53,54].

Also, other recently studied biomarkers, such as the single-pass transmembrane protein α-Klotho, IL-6 or G-CSF, have promising potential in the diagnosis of NPSLE. α-Klotho was able to distinguish NPSLE patients from healthy subjects, yielding sensitivity and specificity of 82.4% and 94.0%, respectively, and an AUC of 0.94. IL-6, present in CSF, yielded sensitivity and specificity of 87.5 and 92.3% for the diagnosis of lupus psychosis (LP), while the AUC reached 0.956 [55]. G-CSF, on the other hand, despite its low specificity (50%), shows high sensitivity (100%) in evaluating the body's response to therapy [56]. Taking into consideration the obtained values, the mentioned parameters may serve in the future as new biomarkers in the diagnosis of NPSLE.

Urine

Because of the frequent occurrence of kidney diseases in SLE, urinalysis plays a major role. It is mainly aimed at monitoring the involution of this organ, which may indicate the development of lupus nephritis (LN).

Vascular cell adhesion molecule 1 (VCAM-1) and activated lymphocyte cell adhesion molecules (ALCAM) are examples of biomarkers that have found potential use in the diagnosis of lupus and renal involvement in the disease process. Studies presented by Parodis et al. have shown that sVCAM-1 is present in higher concentrations in SLE patients, in contrast to the control group, while no statistical difference has been noted for sALCAM levels in both groups. After the adjustment using creatinine present in urine, higher values of both parameters were noticed in SLE patients than in controls. In addition, authors of the paper demonstrated that only the sALCAM/creatinine value was higher among patients with a history of LN prior to the study, but both parameters, along with the application of the adjustment, effectively detect active LN. Importantly, their work also revealed the fact that the sVCAM-1/creatinine value can be used to predict long-term renal function damage [57]. Taking all of the above into account, both ALCAM and VCAM-1 may bring many advantages to the diagnosis of SLE.

Diagnostic utility has also been proven for the kidney injury molecule 1 (KIM-1). Although the first mentions appeared much earlier, it was only relatively recently that scientists decided to more thoroughly test the application of this parameter. In the study conducted by Ding et al. it was proved that higher concentration of the molecule present in urine, together with NGAL, can contribute to monitoring of active form of LN and can predict future kidney damage. In addition, they observed the link between KIM-1 levels and proteinuria in patients with lupus nephritis and a decrease in the amount of the molecule during remission. An advantage of the potential use of KIM-1 and NGAL in diagnosis is that they are found directly at the site of lesions, which better illustrates renal status [58].

Saliva

Recently, saliva has been attracting more and more scientific attention as a potential source of biomarkers. Research has focused on parameters that are also found in serum of SLE patients, which could enable non-invasive diagnostics of this disease.

Cytokines have proven to be of great diagnostic importance, especially IL-6, which is involved in the pathogenesis of SLE. Its elevated concentration in saliva showed a correlation with the concentration found in the serum of patients. MCP-1, IL-1β and IL-33 were also studied and all were present in higher levels in SLE patients compared to controls. Additionally, IL-1β was shown to be associated with the duration of disease in patients, while IL-33 could be connected with high disease activity [59]. The results obtained demonstrate the usefulness of

saliva as an alternative to monitor the inflammatory process in patients, which may prove useful for both diagnosis and assessment of disease activity and progression.

Another potential biomarker is immunoglobulin gamma-3 chain c (IGHG3), the levels of which are higher in SLE patients, especially in those with LN. In a study by Jung et al. the sensitivity was 78%, the specificity 64.6%, and the area under the ROC curve 0.75. Moreover, a correlation between IGHG3 levels in saliva and ESR, anti-dsDNA levels, and renal inflammation was demonstrated, making this parameter a promising marker of ongoing disease activity [60].

However, despite its diagnostic potential, one should be aware of the limitations of its use. The condition of patient's oral cavity may cause difficulties in saliva diagnostics by interference of measured parameters. Periodontal disease (PD) may be present in SLE patients, which may lead to changes in salivary cytokine concentrations due to ongoing inflammatory process. This is the case of the previously mentioned IL-6 and IL-1β, which are present at lower levels in PD compared to controls [59,61]. Another limitation is that some proteins and proteases naturally present in saliva, which can further reduce cytokines [59]. To overcome these limitations, more sensitive and specific methods need to be developed and thoroughly validated.

The use of the various branches of omics

Omics is a branch of science that has been developing particularly rapidly in recent times. It is an approach that focuses on the broad analysis of processes in the body. It consists of genomics, epigenomics, transcriptomics, metabolomics and proteomics.

Genome research has made it possible to determine the so-called PRS (Polygenic Risk Score), which, as it turns out, could serve as an element of SLE diagnostics, as its high value directly correlates with a high risk of developing SLE and its multiple organ complications [41]. Epigenomics provides information on gene regulation. Recent studies on the use of epigenomics in diagnosis have drawn attention to the methylation level of the IFI44L promoter.

It turns out that it is significantly higher in patients with SLE than in healthy individuals or those suffering from other autoimmune diseases. Due to its high sensitivity and specificity, according to Ming Zhao et al., it would be a good marker of SLE [41,44].

Important epigenomic tests in SLE are also analyses of microRNAs - non-coding RNA frequencies responsible for regulating mRNA function. MicroRNA is much easier to analyse than mRNA due to the fact that it exhibits RNase resistance. A number of miRNA-related

disorders have been discovered in SLE patients. For example, in a study in which researchers Elias Stagakis et al. demonstrated a link between the expression of m21-RNA, which regulates T cell function, and the development of the disease. In turn, the amount of miR146 is inversely proportional to disease progression [44,62]. In distinguishing between active and inactive SLE, the study of serum levels of miR-371b-5p and miR-5100 proved useful. Moreover, the former showed a correlation with 24-h proteinuria [62].

Also, the occurrence of particular types of circRNA is organ-specific, so that this assay would serve as a better marker of organ damage than linear DNA. Several types of circRNAs that are associated with SLE have been investigated. An example is hsa_circ_0044235, which correlates with the presence of both anti-dsDNA and anti-RIB-P antibodies and is significantly decreased in SLE patients [63].

An interesting and promising set of tests may be the determination of the levels of five types of lncRNA - long non-coding RNA molecules. A study showed its strong association with SLE and determined an AUC of 0.966. It could also be used in distinguishing SLE from RA and pSS (AUC of 0.683 and 0.910 respectively).

From the above considerations, it appears that different types of RNA molecules can serve as potential markers of SLE. A clear advantage is the ease and accessibility of the techniques, as mainly the PCR reaction is used [55].

Transcriptomics focuses on the analysis of transcription factors. Their analysis in T cells, B cells and peripheral blood cells showed an increase in as many as 18 factors in all these cell types in patients with SLE. Of particular note are STAT1 and STAT2, involved in the IFN type 1 signalling pathway [41,44].

Metabolomic studies using mainly gas chromatography-mass spectrometry show the association of metabolites such as l-valine, pyrimidine or L-leucine with disease development and indicate their usefulness in diagnosis [41].

The appliance of proteomics focuses on the use of SELDI (Surface-Enhanced Laser Desorption/Ionization) and MALDI-TOF-MS (Matrix-Assisted Laser Desorption/Ionization-Time Of Flight) techniques. The latter allowed, among others, the detection of abnormalities in cytokeratin expression in patients' skin lesions [64]. Proteomics could help distinguish SLE patients with and without LN due to the level of coronin-1A [41]. Approximately 200 proteins that show an association with disease progression have been found, so they could potentially serve as biomarkers. Further studies in this direction are therefore needed [44].

CONCLUSIONS

We have presented the latest update on classification, pathogenesis and laboratory diagnosis of Lupus Erythematosus Systemicus. SLE could be a very dangerous disease, that's why it is vital to investigate this topic in order to be able to detect this illness earlier and treat it more effectively. The studies about the pathogenesis could enable us to invent a new way of treatment in the future, based on the pathogenesis of this condition. Better classification system and more accurate diagnosis are good steps to make the detection of SLE more efficacious. It is a very important and dynamic topic. Although many studies have been performed, there is still a big need of improvement in this area.

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TORCH syndrome - complications that can be prevented

Ewelina Kopczyńska , Zuzanna Szczepaniak, Agata Szlązak

Wroclaw Medical University, Wroclaw, Poland

INTRODUCTION

TORCH syndrome refers to a compilation of symptoms resulting from the congenital infections caused by a group of pathogens with known teratogenic effects. These microorganisms include bacteria, viruses and parasites. TORCH infection classically encompasses:

- *Toxoplasma gondii*
- Other infections (*Varicella*, *Treponema pallidum* and Parvovirus B19)
- Rubella
- *Cytomegalovirus* (CMV)
- Herpes simplex virus (HSV).

Additionally, other pathogens associated with congenital infections comprise Hepatitis B virus, human immunodeficiency virus (HIV) and Zika virus (ZIKV). Furthermore SARS-CoV-2 infection during pregnancy has a potential risk of transmission to the fetus therefore it is sometimes listed among the TORCH complex [1,2,3].

EPIDEMIOLOGY

The incidence of infections from the TORCH group varies depending on the region of the world. What is more of all congenital anomalies, approximately 2% to 3% are attributed to perinatal infection [2].

Congenital CMV infection is one of the most common intrauterine viral infections (10% to 40% of all cases). It is estimated that 30 to 80% of people in the world have antibodies proving a past infection with this virus. Among women of reproductive age in Poland, anti-CMV antibodies were detected in almost 80% of all the respondents during the pre-conception period and their percentage was greater with the increasing age of women (74,3% to 94,2%).

The highest risk of transplacental transmission (30 to 35%) is associated with primary infection. Due to the high seroprevalence rates, congenital infection usually results from non-primary maternal infection and these have a much lower risk of transmission (1,1 to 1,7%). Congenital CMV infection is associated with as much as 30% mortality. Worldwide, this infection occurs at a frequency of 5 to 7 per 1000 live births. However, about 10% is symptomatic and the remaining 90% is asymptomatic. In the group of infants with asymptomatic CMV, as many as 13,5% suffer from late, dangerous consequences, mainly sensorineural hearing loss [2,4,5].

Toxoplasmosis infection has more than 60% of some populations. In healthy and immunocompetent adults, more than half of the cases of infection are asymptomatic but may cause self-limiting symptoms such as malaise, fever, maculopapular rash, headache and tender lymphadenopathy. Seroprevalence rates are based on geographical areas and increase in regions that have hot, lower altitudes and humid climates because oocyst grow faster and survive better there. What is interesting, only congenital CMV is observed more frequently among infections transplacentally acquired than congenital toxoplasmosis. Congenital toxoplasmosis develops in the fetus when the mother's parasite infection occurs shortly before conception or during pregnancy and when the old infection was reactivated during immunosuppression. In Poland, 14 cases of congenital toxoplasmosis were reported in 2019 and in 2020 there were 9 of them. The risk of transmission to the fetus in Europe is 1,6 to 3,5 per 1000 births but no more than 22% of these infected fetuses will develop congenital toxoplasmosis. The risk of transmission is the greatest at the end of the pregnancy (in the first trimester it is 15%, in the second trimester it is 30%, in the third trimester it is 60%). However, in over 80% of infection cases in the first trimester of pregnancy the virus may cause miscarriage, intrauterine death or very severe damage to the fetus [1,6,7,8].

Approximately 50 to 70% of people in developed countries are seropositive for oral herpes simplex virus (HSV-1). Genital herpes simplex virus (HSV-2) is present in 10 to 40% of the population and about 22% of pregnant women. The risk of HSV infection of the newborn which occurs in the third trimester of pregnancy is 30 to 50%, on the other hand in early pregnancy it is around 1%. There is not enough time for mother's body to develop antibodies that inhibit replication in case of the primary infection at the end of the pregnancy. About 85% of transmission in the perinatal period occurs during childbirth. HSV-2 infection is related with a worse prognosis than HSV-1 infection [1,9,10].

Before the introduction of the vaccine, up to 4 babies in 1000 live births were born with congenital rubella syndrome. The commonly used rubella vaccine (RCV) is safe and effective,

with one dose being around 97% effective in preventing the disease. In Poland, the selective vaccination of adolescent girls since 1989 explains 81% of cases among males aged 15 to 29 during its outbreak in 2013. During the epidemic in 2013, the risk of congenital rubella has increased in the early stages of pregnancy. There were 2 cases of congenital rubella, but this number was underestimated. Since then, no cases of congenital rubella have been reported in Poland [11,12].

Another crucial illness is syphilis. Worldwide, 5,6 million people are infected with syphilis each year. Every year, both in Poland and in the world, there is an increase in the number of cases of this illness. Experts point to changes in sexual behavior as likely causes of this phenomenon. According to the data of the National Institute of Public Health - National Institute of Hygiene in Poland, in 2020 there were 710 cases of syphilis (including 3 cases of congenital syphilis) and in 2019 were 1607 cases (including 14 cases of congenital syphilis). However, the 2020 data may be underestimated due to the Covid-19 epidemic. Data refers only to episodes reported at sanitary and epidemiological stations. Syphilis is curable, so most cases of congenital syphilis are seen in untreated women [1,8,13].

Contact with chickenpox is common among pregnant women, especially those who have young children. Since the vast majority of pregnant women have immunity, primary infections are rare. It is estimated that this applies to 0,7-3 per 1000 pregnant women. Other congenital TORCH infections are much less common [1,2,14].

TRANSMISSION

Vertical transmission is where infectious agents (bacteria, viruses, and other organisms) can pass between mother and baby in the utero. This type of transmission is also known as mother-to-child transmission. The pathogen reaches the placenta through the mother's blood (hematogenous transmission) or the reproductive tract of the pregnant woman and must have the ability to overcome the placental barriers - syncytiotrophoblast interface, decidual–trophoblast interface, and physical obstacles composed of fetal cells and the maternal tissues [15,16,17].

The specific symptoms of transmitted infections depend on the individual pathogen and the stage of pregnancy at the time of infection. For example rubella virus infection in the first months of pregnancy results in a miscarriage and after 22 weeks of pregnancy is not dangerous for the fetus [33].

Toxoplasmosis: oocysts - the stage of *Toxoplasma gondii*, cause toxoplasmosis through inhalation of fecal particles or by the ingestion of infected tissue. When the mother gets infected there is a transplacental transmission of the parasite to the fetus causing congenital toxoplasmosis.

Syphilis: vertical transmission most commonly occurs transplacentally but can also occur due to peripartum exposure to vaginal fluid.

Varicella-zoster virus (VZV) and Rubella virus are transmitted from infected individuals through aerosols. They also pass from the infected mother to the fetus transplacentally.

Cytomegalovirus: is mainly transmitted through mucous membranes, blood transfusions or organ transplants. It can pass from mother to fetus transplacentally but also by contact with cervical or vaginal secretions during the birthing process.

Herpes infection: HSV-1 and HSV-2 are passed from direct contact with mucous membranes, saliva or sores. This virus is primarily passed to the infant during delivery when the mother has an active infection of the reproductive tract [18].

CLINICAL SIGNIFICANCE

Infections during pregnancy can be associated with serious consequences to the pregnant mother and developing fetus. Maternal history is important, especially a febrile illness with or without rashes and poor maternal weight gain. Mothers should be informed about the possibility of getting pre-pregnancy vaccinations. The first symptoms of infection can be seen at different times, such as the intrauterine period, at birth, in infancy, or not even until years later. In general, physical findings of infant may reveal abnormal growth parameters or developmental abnormalities. Relatively often different syndromes overlap with the final clinical condition of the newborn. The most common symptoms include: low birth weight, rashes which can be maculopapular, purpuric or petechial, jaundice, chorioretinitis, microcephaly, hepatosplenomegaly and cardiac anomalies [1,2].

Congenital Toxoplasmosis has wide-ranging clinical manifestations from being completely asymptomatic (about 75%) at birth to severe neurological and ocular disease. The classic triad of chorioretinitis, hydrocephalus, and cerebral calcifications presents itself in a limited number of infected newborns. It will show by causing intrauterine growth restriction and low birth weight, neurological manifestations (micro or macrocephaly, seizures,

nystagmus, hydrocephalus, cerebral calcifications, meningoencephalitis), chorioretinitis, jaundice, hepatosplenomegaly and thrombocytopenia [1,6]. On the other hand, maternal infection is subclinical and symptoms occur in only 5% [19].

The letter "O" in the acronym 'TORCH' stands for others pathogens, such as *Treponema pallidum*, varicella-zoster virus, parvovirus B19, Zika virus and human immunodeficiency virus sometimes also SARS-CoV-2. *Treponema pallidum* is a well-characterized teratogen. Women with syphilis treated with penicillin during pregnancy have 98% of preventing congenital syphilis. Moreover, in utero, there may be fetal loss or *hydrops fetalis*. In untreated infants symptoms usually appear around three months of age and present themselves with cutaneous lesions on the palms and soles, hepatomegaly, jaundice, rhinitis, rash and generalized lymphadenopathy [13,19]. Infants perinatally infected with the varicella-zoster virus develop skin lesions, limb hypoplasia, neurological abnormalities and developmental delay [1,14]. Parvovirus B19 can lead to spontaneous abortion, severe neurodevelopmental deficits and hydrops fetalis. Although, 67 to 76% of infants are unaffected even if the mother was infected [1]. ZIKV infection can lead to neurological complications such as Guillain-Barré syndrome and peripheral nerve involvement. Increase in the incidence of microcephaly in newborns is associated with maternal Zika virus, however, symptoms of Zika virus are usually mild and self-limited [20,21]. When it comes to congenital HIV, clinical manifestations are diverse and often nonspecific, patients may have lymphadenopathy, hepatosplenomegaly, microcephaly, oral candidiasis and invasive bacterial infections [2]. Most recently case reports from COVID-19-positive pregnant women describe the risk to the fetus. Symptoms of infants born to SARS-CoV-2 infected mothers include shortness of breath, fever, thrombocytopenia, abnormal liver function tests, tachycardia, vomiting, and pneumothorax [3].

Congenital rubella syndrome occurs in up to 85% of babies born to mothers infected with rubella during the first 12 weeks of pregnancy [1]. The primary manifestations include sensorineural deafness, cataracts, congenital heart problems, central nervous system deficits, impaired mental development, bone defects and hepatosplenomegaly [22].

Cytomegalovirus is the most common congenital infection. Pregnant women with CMV infection are rather asymptomatic. Maternal symptoms are similar from EBV infection and contain fever, malaise, headache, pharyngitis, lymphadenopathy, hepatosplenomegaly, arthralgias, and rash. Approximately 10% congenital CMV develop clinical manifestations: jaundice, petechiae, hepatosplenomegaly, microcephaly, intracranial calcifications, intrauterine

growth restriction, pericardial effusion and ascites. CMV is the main cause of nongenetic congenital hearing loss. Placental inflammation and fetal death are also observed [1,2,4,19].

Congenital Herpes Simplex Virus (HSV-1 and HSV-2) infection is a rare entity and may pose a life-threatening disease for the newborns. HSV classically causes a baby to be born with manifestations: skin-eye-mucous membranes (SEM), central nervous system and disseminated disease. Additionally, symptoms contain viral sepsis, organ failure (lung, liver), intravascular coagulation, encephalitis and bulging fontanelle [2,9].

TREATMENT

- **Toxoplasmosis:** There are a lot of opinions of the drug regimens. Fetal prophylaxis preventing intrauterine infection consists mainly of spiramycin. Treatment of evolving fetal infection is a combination of pyrimethamine, a sulphonamide (sulphadiazine or sulphadoxine) and folic acid [6].
- **'O' others pathogens:**
    - **Congenital Varicella Syndrome:** Chickenpox requires compulsory treatment of pregnant women, in all forms of severity, as there are reports suggesting that it may minimize penetration virus across the placenta. In the absence of vaccination or pieces of an information about the history of disease, after a contact with a person with chickenpox, immunological tests are advisable. Thereafter, a decision to use Varicella Zoster Immune Globulin (VZIG), when treating the mother should be made preferably within 96 hours of exposure. Acyclovir is recommended for women who developed the disease. Additionally, prophylaxis is also available in the form of specific immunoglobulin VZIG, which is used in post-exposure prophylaxis in newborns whose mothers had chickenpox between day 5 days before through 2 days after delivery. If the newborn is developing clinical signs of active infection, acyclovir should be administered intravenously [14].
    - **Congenital Syphilis:** Infection of *Treponema pallidum* must be diagnosed and treated immediately. Pregnant women should be treated compulsorily when testing positive for infection. Therapy for neonates born to mothers adequately treated during pregnancy and more than four weeks before childbirth or have a non-reactive Rapid Plasma Reagin test is recommended benzathine penicillin G 50,000 units/kg per dose intramuscularly in a single dose. Infants with confirmed congenital

syphilis receive aqueous crystalline penicillin G 50,000 units/kg per dose intravenously every 12 hours in the first seven days of life and then as directed [2,13].

- **Parvovirus B19 infection:** There is no treatment for the causative agent of infection and no methods of active (vaccine) or passive (immunoglobulin) immunization. In case of a confirmed maternal infection before the 20th week of pregnancy, an appropriate fetal surveillance is implemented [19].
- **HIV infection:** Prevention mother-to-child transmission and further management of the newborns depends on viral suppression during the pregnancy. A newborn from a mother with a low viral load should receive zidovudine (4 mg/kg, twice daily) for the first 4 to 6 weeks of life. Multiple drug regimens are used when pregnant women are not receiving antiretroviral therapy [21].

- **Congenital rubella:** Prevention is the most important since just a single dose of rubella vaccine before pregnancy to mother can produce life-long immunity. There is no cure for the developed syndrome of congenital rubella [22].
- **CMV infection**: No vaccines and no safe therapies are accessible. In some cases, trying to use oral valganciclovir or intravenous ganciclovir is applied. CMV hyperimmune globulin (CMV HIG) routine use is not recommended [4].
- **Congenital Herpes Simplex Virus infection:** The primary symptomatic infection with HSV-1 and HSV-2 is indication for pharmacotherapy. Clinical trials have shown that high-dose intravenous acyclovir should be applied for acute therapy. The duration of treatment depends on the severity of the clinical condition. An ophthalmologic examination and neuroimaging should be performed on all infants with neonatal HSV disease. Acyclovir can be used in the treatment of recurrent infections from starting from the 36th week of delivery. This approach reduces the frequency of cesarean sections caused by symptomatic infection [9,23].

PROGNOSIS

The prognosis for TORCH infections may vary depending on the severity of the initial symptoms.

Children born with congenital toxoplasmosis may die early as a result of severe infection, whereas others survive but have neurological disorders. The most frequent

consequence of congenital toxoplasmosis is retinochoroiditis, but intellectual disability, deafness, seizure can also occur, even years later in children who was born asymptomatic [24,25].

The prognosis of infants with congenital varicella syndrome is worrying. Among infants the death rate is 30% and is often caused by intractable gastrointestinal reflux, severe recurrent aspiration pneumonia, and respiratory failure. The mortality rate for untreated disease is 31% [26]. The clinical spectrum in congenital syphilis includes:

- stillbirth,
- neonatal death,
- nonimmune hydrops,
- early congenital syphilis,
- classic stigmata of late congenital syphilis.

Manifestations of early congenital syphilis are often seen in the perinatal period, but most infected babies are asymptomatic at birth [27,28].

The characteristic manifestations of early congenital syphilis (onset at < 2 years of age) include a maculopapular rash (spares the palms and soles, desquamates), snuffles, jaundice, periostitis, osteochondritis, chorioretinitis, congenital nephrosis [27,29].

Late congenital syphilis is defined as congenital syphilis diagnosed more than 2 years after birth. Neurologic manifestations like eighth cranial nerve deafness usually occur around 8-10 years of age and interstitial keratitis (commonly bilateral) develops in patients aged 5–20 years. What is more chronic meningoencephalitis also leads to intellectual decline (juvenile paresis) [27,30,31].

The constellation of eighth cranial nerve deafness, interstitial keratitis, and Hutchinson teeth (notched, thin, upper incisors with abnormal spacing) is called the Hutchinson triad. Furthermore bone lesions may result in depression of the bridge of the nose (saddle nose), destruction of the palate, anterior bowing of the tibia (saber shins), maldevelopment of the maxilla, and knee joint can be affected with hydrarthrosis (Clutton's joints) [27,31].

Parvovirus B19 infection during pregnancy may range from an uncomplicated pregnancy to severe non-immune hydrops, fetal anemia and intrauterine fetal death. There is a higher fetal loss rate before 19 to 20 weeks of gestation compared to that happening after 20 weeks [32].

Prognosis of rubella congenital depends on the maternal stage of infection:

1) infection in the first weeks of pregnancy - fetal death and miscarriage,

2) infection in the first or second trimester - many types of birth defects,
3) infection after the 22nd week of pregnancy is not dangerous for the fetus [33].

90% of newborns with congenital cytomegaly are born asymptomatic and 90% of them remain asymptomatic, while the rest of children develop progressive hearing loss, cognitive impairment, microcephaly and paresis. The remaining 10% of newborns have symptoms from birth and they are at high risk for sensorineural hearing loss, developmental delays, microcephaly, epilepsy and paresis [34].

HSV infection in the first trimester of pregnancy can cause spontaneous abortions and intrauterine fetal growth restriction. Virus rarely crosses the placental barrier, but when the virus reaches the fetus, it can result in severe birth defects such as microcephaly, hepatosplenomegaly, intrauterine fetal death and intrauterine growth restriction [35].

The prognosis of HIV-positive infants born to HIV-positive mothers is worrying. The delay of treatment may result in a rapid progression of the disease and overall mortality rate of more than 90%. The average time from infection to death is 8-10 years. Neonates may not display any symptoms and remain asymptomatic until they reach 3-5 years of age [36,37].
The most commonly exhibited manifestations of HIV infection include:

- increased opportunistic infection,
- recurrent bacteremia,
- generalized lymphadenopathy, splenomegaly, hepatomegaly,
- oral candidiasis,
- cancers,
- growth delay,
- delayed cognition.

Antiretroviral therapy during pregnancy minimizes risk of HIV transmission to the baby during pregnancy, labor and postpartum. The rate of transmission of HIV to neonates has been reduced to less than 1% with the implementation of appropriate strategies [37,38].

Congenital Zika syndrome includes microcephaly, problems with limbs or joints, hypertonia, damage to the back of the eye, hearing problems and brain atrophy. Some babies with smooth brain do not have serious health problems, but unfortunately others stop developing after 3 to 5 months and many die before they reach 2 years old [39].

Prognosis for Neonatal HBV infection increases the risk of chronic hepatitis, cirrhosis, and hepatocellular carcinoma [17].

PREVENTION OF TORCH INFECTIONS

Health education has an enormous influence on health behaviors. Pregnant women should be one of the most important groups in this process for the reason of the special needs connected with this period of life and influence of body and mental health on the fetus. Pregnancy is a state characterized by big changes that take place in maternal organisms. This phenomenon results in increased risk of infection and requires a healthy lifestyle, proper nutrition and immunization [41,42].

VACCINATIONS BEFORE AND DURING PREGNANCY

In Poland, for women planning pregnancy, recommended vaccinations are: rubella, measles, mumps, chicken pox, whooping cough, hepatitis B and influenza. They are advisable for future mothers who are not inoculated against those diseases and, in case of chicken pox, who did not come through infection. After immunization with a live-attenuated vaccines (rubella, measles, mumps, chicken pox) women should wait at least one month before starting trying to get pregnant. Vaccination by live-attenuated vaccines is not recommended during pregnancy, however in gestation period inactivated vaccines can be safely used. In this time vaccinations against influenza and whooping cough are advisable. Ongoing pandemic was a reason for which one more vaccination – against COVID-19 should be practiced. At the beginning vaccination was not recommended during pregnancy but according to the latest data of European Medicines Agency, they can be administered before and during pregnancy. Recommended vaccines in Poland protect women and fetuses from infections of Varicella, Rubella, hepatitis B and SARS-CoV-2 from TORCH complex pathogens [43,44].

Indications from the website of Centers for Disease Control and Prevention (CDC) coincide with polish data [45,46,47,48,49,50]. CDC recommends MMR vaccination to protect women planning pregnancy from rubella and chickenpox vaccine for children, adolescents, and adults who have never had chickenpox and were never vaccinated. For this reason, women of childbearing age are usually vaccinated and, if not, have a chance of getting vaccinated before pregnancy [45,49,50]. Vaccinations which are advisable during pregnancy are: the inactivated flu vaccine, the Tdap and COVID-19 vaccine [46,47,48]. In some cases, vaccinations against Hepatitis A, Hepatitis B, Meningococcal, Polio, Anthrax, Rabies, Typhoid, Smallpox and

Yellow Fever are also performed in gestation period. Decision is based on the risk and benefits of that [47].

MATERNAL NUTRITION

Moderate physical activity and proper nutrition play a very important role during pregnancy. Healthy diet is necessary for fetus development, but it also affects the immune system. Maternal nourishment should include: vegetables, fruits, legumes, carbohydrates with low glycemic index rich in fiber, fish, olive oil, nuts, proper dose of proteins and high-quality fats. Furthermore, the supplementation of minerals and vitamins is necessary. Vitamins A, B, C, D, E, folate, and minerals such as zinc, iron, and selenium assist the physiological immune system in pregnancy. Malnutrition on the other hand leads to decreased immune resistance for infection, especially for viral infection such as Zika virus and CMV. Food insecurity is also connected with higher risk of HIV mother-to-child-transmission and worse response to HIV treatment. It is commonly known that malnutrition adversely affects the immune system but obesity also has a bad influence on the responses of the immune system. This connection is observed in SARS-CoV-2 infection and in this case obesity also during pregnancy is a risk factor of severe COVID-19 infection. Nutrition disorders and deficits of some elements lead to decreased immunity and higher possibility of infections [41].

OTHER

Apart from vaccinations and nutrition habits, pregnant women should know about some customs, which can prevent them and their babies from infections. There are general rules such as washing hands and avoiding contact with people suffering from contagious diseases, but also rules specific for each pathogen [51].

Toxoplasma gondii

- Washing hands before preparing meals and before eating.
- Washing hands after contact with raw meat, carefully washing utensils such as knives and cutting boards after contact with uncooked meat.
- Cleaning the cat litter box every day (removal of oocysts prior to conversion to an invasive form).

- Using gloves during handling litter boxes and garden work and also washing hands after these activities (reducing the risk of cat excrement contamination).
- Washing fruits and vegetables before eating.
- Filtration of the water before drinking.
- Avoiding contact with stray cats.
- Not eating raw or undercooked meat [52,53].

Varicella-zoster virus

- Avoiding contacts with people infected by varicella-zoster virus [54].

Treponema pallidum

- Avoiding risky sexual behavior, reduction the number of sexual partners, using condoms.
- Avoiding direct contact with primary changes appears on the body of the infected person [55].

Parvovirus B19

- Frequent hand-washing.
- Avoiding close contact with young children [56].

Virus Zika

- Avoiding travels to areas with Zika.
- Protecting body against mosquito bites in areas with risk of Zika: using protective clothes, mosquito nets, EPA-registered insect repellents.
- Avoiding sexual contact with people who may be infected with the Zika virus and using condoms [51,57,58].

Rubella virus

- Avoiding contacts with people who have infection symptoms [59].

CMV

- Avoiding contact with saliva and urine of little children, especially under 2 years (for example: not sharing food, liquids and cutlery with children, not taking pacifiers into the mother's mouth).
- Frequent hand-washing, particularly after diaper changing and feeding [60].

HSV

- Avoiding primary infection by not engaging in risky sexual behavior, using condoms and not engaging in sexual activity during 3rd trimester with men who has history of herpes [61].

CONCLUSIONS

TORCH syndrome is a serious widespread problem which causes congenital diseases, premature births and intrauterine deaths. It is a specific condition since it involves babies and affects their whole life. The majority of complications of these infections can be prevented by appropriate prophylactic and early treatment. Raising awareness about the danger of infections among women from preconception to the early postnatal period and special education for this group is crucial. TORCH syndrome represents one of the challenges of the current medicine and working to improve the situation in this regard gives hope for a better future for many lives.

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An update on epidemiology, risk factors and the use of AI (artificial intelligence) in the detection of malignant melanoma

Julia Fiołkowska, Maksymilian Ludwig

Wroclaw Medical University, Wroclaw, Poland

INTRODUCTION

Melanoma is a malignant skin tumour that develops from melanocytes, the melanin-producing cells in the skin. Despite increasing opportunities for an early detection of this disease and advanced surgical treatments, it continues to be a problem for clinicians [1] and there is no indication that the incidence of melanoma is expected to decrease in the coming years [2]. In our paper, we focus on an update on epidemiology and the up-to-date possibilities of using AI for a rapid detection of melanoma.

EPIDEMIOLOGY

Melanoma is the 20th most common cancer worldwide. In 2018, there were 287,723 new cases, of which 60,712 were fatal, 5 - year prevalence was 965,623 cases. When it comes to Europe, the statistics are even more poignant. Melanoma is there the 6th most common cancer in the overall population, accounting for 3.4% of all cancer cases. The area with the highest incidence is Oceania (as high as 28.3 per 100,000 people), while the least affected are Asia and Africa (about 0.5 per 100,000 people) [3]. In Poland, it is about 6.5 per 100,000 [4].

RISK FACTORS

Several risk factors are known to significantly increase the risk of developing melanoma. The most important of these are the presence of moles, skin phenotype, exposure to UV light especially at a young age and previous sunburns. Genes are also an important factor - there are somatic genetic aberrations that significantly affect the histology of skin lesions, but

also their location [3]. In recent years, a significant increase in the willingness to test for the above mutations has been observed in certain parts of the world [5].

There has been a steady increase in incidence in recent years, especially in Caucasian populations. The incidence globally increased by as much as 39% between 2006 and 2016 [2]. The team of Lashway et al. studied this trend among US residents, where melanoma now accounts for 1.1% of fatal cases. They noted that while 10.5 per 100,000 cases occurred in 1980, in 2016 it was already 25.38 per 100,000, more than doubling [6]. However, it affects thin rather than trick melanomas to a greater extent. In Europe, an example is Italy, where between 1990 and 2016 the incidence increased from 1.6 to 21 per 100000 in males, and from 2 to 17 per 100000 in females). In contrast, in Poland, the National Cancer Registry recorded an increase of 70% in 10 years (between 2007 and 2017) [4]. According to Miola et al. the global increase can be attributed to an ageing population, the use of immunosuppressants, better accessibility to health services, more sophisticated screening tests, allowing the risk of malignancy of a lesion to be determined with greater accuracy, and people's growing awareness of cancer [7]. However, the most important change is people's increased exposure to light, which is estimated to account for 86% of melanoma cases in the UK [3]. Nevertheless, globally this is due to environmental factors such as global warming and the ozone hole, which can not only damage DNA, but also weaken its repair systems [2]. Clothing trends have also changed over the years, with people starting to wear more and more revealing clothing, which is most evident among women. In men, it was the decreasing use of headgear. We are also seeing a trend towards tanned skin, this makes us more and more willing to spend our leisure time sunbathing. Unfortunately, it leads to a higher number of sunburns among people, despite the increased use of sunscreen. What's more, people tend to opt for artificial UVR (tanning beds). One research in US shows that up to 50% of adolescents show a positive attitude towards sunbed use [6].

According to Memon et al. about half of all cases are diagnosed in patients over 65 years of age. They calculated that the risk of contracting melanoma by 75 is 1.34% in men and 1.34% in women. Unfortunately, among the middle-aged (35-64) and older (65 plus) the incidence continues to rise. However, this research was one of the first in Europe to record a stabilisation in those younger than 35 [3]. At a young age, a large association with incidence is the amount of freckles, which has been studied in the Australian and English populations. Australian men, who are higher in the statistics of melanoma incidence than English men, have a higher prevalence of freckles [8].

In general, male gender is a risk factor. After the age of 45, men start to dominate the statistics, and after the age of 75, they are three times more likely to develop melanoma than women [9]. This leads to the conclusion that the pathogenesis of this disease is gender-related.

There are many theories on this subject. One of them is that hormones, and in particular oestrogen, is a prospective factor. However, this theory is increasingly being challenged, as no change in incidence has been observed among women taking hormonal contraception and women going through pregnancy [9]. Furthermore, the greatest increase in disparity between men and women is seen in older age, when hormones no longer play such a large role in the body [7]. This has pushed researchers to propose a new theory that relates to the effect of the presence of reactive oxygen species on the development of the disease. The study found that men have statistically lower levels of antioxidants, which means they are more susceptible to DNA damage, stimulation of cell proliferation and inhibition of APC [9]. The Memon et al. team proposed that the gender discrepancy in incidence is due to the fact that men are more likely to be exposed to prolonged sun exposure and show less awareness of their cancer risk [3]. It is suspected that women tend to worry about their health more, as their histopathological samples statistically show a better prognosis [7]. Another likely reason, may be the different distribution of melanocytes in the skin [2]. As a contrast, it has been found that among those younger than 45 years, it is women who turn out to lead the statistics. It is suspected that this is due to the fact that women place more importance on a tan and therefore enjoy sunbathing and use tanning beds more frequently. This trend is indeed noticeable despite the fact that women are more likely to use the sunscreen [6]. There are also differences in the location of malignant skin lesions between men and women. While in men it is mostly the trunk, in women it is the lower limbs. In general, it has been established that the risk is greater in those with shorter but more intense exposure (lesions mainly in the trunk and lower limbs), an increase of which has been observed in recent decades, rather than in those continuously exposed to certain doses of sunlight (head and neck) [3,6] The lesions caused by natural radiation are more often seen in the posterior trunk location than on the chest [3] and single people, due to easier access, are more likely to have lesions in the head and neck, resulting in quicker diag [6].

Another differentiating characteristic is race. Although it is the Caucasian race that is inherently more prone to the disease, black people have a higher mortality rate [10]. It is best to study the impact of race on morbidity are the US, where the population is multicultural. There, among non-Hispanic white men the incidence is 26.6 per 100,000 while among Hispanics it is 4.7 per 100,000. For Asians it is 1.4 and for non-Hispanic black men 1 per 100,000 [11].

Table 1. The comparison of the most common sites of primary lesions in regard to gender, type of exposure, type of radiation, marital status and the biggest increase of incidence in men and women separately [3,6)]

Characteristic	Common site of primary lesions
Gender	
Male	Trunk
Female	Lower limbs
Type of exposure	
Intermittent	Trunk, lower limbs
Chronic	Head, neck
Type of radiation	
Natural	Posterior trunk
Artificial	Anterior trunk
Marital status	
Singles	Head, neck
Biggest increase of incidence	
Male	Trunk, upper limbs
Female	Trunk, upper limbs

The higher mortality rate among ethnic minorities may be explained by less access to healthcare or less willingness to use these services. NHB generally show less awareness of risk, not prompting them to often visit the doctor [10]. Among those surveyed, 18% of Hispanic and 26% of NHB were diagnosed at late-stage, while NHW at 12%. Moreover, considering those diagnosed by a dermatologist - 90.9 % were NHW, while Hispanic and NHB are more likely to receive a dermatological consultation in the emergency department (10.5% and 18.3% respectively). The skin lesions of patients diagnosed by a dermatologist are statistically thinner than those without professional consultation, resulting in lower mortality among this group (10.2%) compared to those who did not visit a dermatologist (15.4%). For these reasons, among others, mortality among minorities is approximately 1.96 - 3.01 times higher than that of white citizens [11].

Globally, cancer mortality in poor and developing countries is ca. 20% higher than in developed countries. This trend is also maintained for melanoma. A drastic example is Poland, where the mortality rate is 20% higher than in Western countries, due to the lower effectiveness of the therapies used (69.8%) compared with Germany (93.1%) [4]. A study by Brady et al.

found that living in a poor neighbourhood is associated with a 5% increase in difficulty receiving primary healthcare [10]. In 2018, the poverty rate in the US was 11.8%, of which among NHB it was 22%, Hispanic 9%, American Indian 24% and NHW 9%. This results in people from ethnic minorities being less frequently insured than NHW or being insured in a fee-for-service manner, resulting in detection of disease at a more advanced stage. Furthermore, it has been studied that better educated people tend to develop thinner lesions than the less educated [11].

Large differences in incidence according to place of residence are also apparent. According to Cortez et al. the figure for rural areas is 22.4 per 100,000, while it is 21.8 per 100,000 in urban areas. People living in rural areas may experience more difficult access to secondary healthcare, making them more likely to seek care from a general practitioner (26.3%) than urban residents (17.7%). This is due, among other things, to the lower number of dermatologists in rural areas (where there are 52 dermatologists per 100,000 people) compared to cities (309 per 100,000). Hence, rural residents are more likely to present with advanced-stage lesions, which influences the mortality rate among them to be 20% higher than in urban patients [11].

The place of residence also has an impact in terms of exposure to sunlight. Indeed, it has been shown that at higher altitudes, each 1 000m increase in altitude results in a 10-12% increase in UV radiation. Thus, an increase in mortality is apparent in populations living at altitudes above 700m. This is evident, for example, in a study by the team of Núñez-González who studied the death rate in Ecuadorians and compared results between regions of the country. They found that the rate was higher for regions in the highlands and close to the equator, which would indicate a damaging impact of intensive exposure [12]. Another study was done in Italy and compared the change in incidence between 1990 and 2017 between the Veneto region and its alpine province of Belluto. Data on AAPC (average annual percent change) was used, which was found to be higher for the province of Belluto compared to the rest of the region. The difference is evident for both sexes - for women it is 4.4 versus 2.8, for men it is 5.7 versus 3.5. Furthermore, a significant difference was found in the anatomical location of the skin lesions. In the Alpine population, lesions were much more frequently diagnosed in the face (20.21%), compared to only 10.94% in the rest of the region, where lesions on the trunk were more common. This is therefore consistent with the previously stated theory of the location of lesions depending on the type of exposure (intermittent or chronic) [2].

The next risk factor is the occupation, as some workers are particularly exposed to harmful UVR. These include, for example, sailors who spend long hours on board and are at

risk. Unfortunately, the majority of those surveyed by the team of Asadian et al. showed an inability or unwillingness to take specific protective measures. In addition, half of the respondents showed misconceptions regarding measures such as sunscreen or wearing long sleeves [13]. Studies have also been carried out in the population of firefighters, who may not be frequently exposed to the sun but work in fire conditions. They showed a significant relationship between this occupation and the risk of developing melanoma (SIR 1.21; 95% CI: 1.02-1.45). One reason may be firefighters' exposure to PCBs (polychlorinated bi-phenyls), which are considered carcinogenic. These are compounds that had been widely used in the construction industry in the 1950s,60s and 70s, before they were banned. However, PCBs can also be created de novo, from materials used today (14). Finally, melanoma was globally declared an occupational disease in 2015 [13].

METHODS OF EARLY DETECTION USING AI

Early detection of melanoma already allows an almost complete cure and is therefore crucial in dealing with this disease. The delay can cause the tumour to grow, in which case it spreads into the thicker layers of the skin until it reaches the blood and lymphatic vessels [15]. The 5-year survival rate when detected early is as high as 98%, but when regional or distant metastases are already present, it is only 64% and 23% respectively [11]. Melanoma manifests as skin lesions, which are usually asymmetrical, irregularly framed and fuzzy and relatively larger in size. It is accepted that a benign lesion is up to 6 mm in size [16]. To facilitate the detection of such lesions, the ABCDE principle has been established as an acronym for features - asymmetry, borders, colour, diameter and evolution [16-18]. Often a lesion is detected during self-examination, but it is very subjective as we tend to under- or overreact [19]. When consulting a dermatologist, the accuracy of diagnosis is about 60%, which has been greatly improved by the introduction of dermoscopes to between 75% and 84% [15]. Another screening option is TBSE (total body screening examination), which is a method used mainly for people with numerous moles. A study was conducted among US workers, which showed that only 8% had received a skin examination from a doctor in the past 12 months. Furthermore, only 24% of those considered at risk had confirmed receiving a TBSE in their lifetime. A major breakthrough in the diagnosis of melanoma has come with the development of teledermatology, which is a relatively good alternative to in-person visits to a specialist [20]. However, there are many places such as developing countries or agricultural areas where the number of dermatologists is insufficient [21]. This and the fact of an increasingly fast pace of life has

contributed to the search for the possibility of detecting disease without the involvement of a doctor. This is possible using AI (artificial intelligence), which is increasingly being used in medicine. As the number of smartphone users is already very high (UK - 80% of adults [22], Brazil - 78% of adults [21], applications for disease detection have started to be developed. Between 2014 and 2017, 235 dermatology apps were created, but most of them used teledermatology technology [22].

AI technologies are divided into Machine learning (ML) and Deep learning (DL) [23]. One example of ML is Transfer learning, which involves using the solution to a problem to solve other problems. Another is CNN (convolutional neural network), which is a technology that allows automatic, advanced analysis of image data [16], which results are already comparable to histopathological evaluation [24]. Deep learning methods are still less understood and mastered, in 2017 DL algorithms reached an accuracy equal to that of a dermatologist's assessment, while already 2 years later they were used in the creation of smartphone apps [24]. Such apps can be dedicated either to patients or physicians. In the first case, they focus on analysing the photo, giving instructions for taking it beforehand and assessing the risk of malignancy of the skin lesion. Physician-directed applications analyse the uploaded photo, allow the creation of a customised database and, with the result, show the doctor ancillary photos of other lesions to facilitate diagnosis [20]. Both types of applications focus on distinguishing a benign lesion from a malignant one; in the case of melanoma, this is not easy, as it is a melanotic type, just like a benign nevi [15]. In order to analyse the image as efficiently as possible, it is necessary to process the image so that the algorithm obtains the best image quality. First, so-called lesion segmentation is performed, which involves cutting off the lesion from the rest of the skin in the image. Next comes noise removal, which aims to remove visible hair or freckles. Finally, the algorithm gets the data of each lesion, allowing a diagnosis to be made [25].

To date, many models using AI have been developed. Some of the first were trained on the HAM10000 dataset, in which 10000 dermoscopy images of different types of skin lesions can be found. Unfortunately, a huge limitation in its use was the fact that a dermoscope had to be used to access this dataset. However, later, Pacheco and Krohling developed a model based on clinical images, which would make it much easier to use in an application in the real world. Castro et al. then made improvements to this model and developed a patient-directed application based on it. In their study, it showed 85% accuracy and 96% recall when it came to distinguishing lesions into cancer and non-cancer. It was also found that clinical information is very important for accurate diagnosis - access to such information by the app improved

accuracy and recall by 1.4 % and 2.4 % respectively [21]. An example of a similar app is Melatect, developed using the ML technique. The team of Meel et al. found its accuracy in lesion assessment (benign/malignant) to be as high as 96.6%, suggesting its usefulness for patients [16]. An independent group, Kousis et al., conducted a study of multiple AI-based models and applications used for skin cancer detection. Their results indicate that the DenseNet169 model has the highest accuracy (92.25 %). Based on it, an app was developed that not only displays information on whether a lesion is benign or malignant, but also indicates how much time a person can stay in the sun without worrying about sunburn. This is based on data on the patient's phenotype, place of residence and the power of the sunscreen used [15]. In contrast, Soenken's team has developed a novel system relying on the 'ugly duckling' rule, which analyses different photos of lesions from one patient and can detect a lesion that stands out [20]. However, the most widely used application is SkinVision. Once a lesion photo is uploaded to the app, the algorithm calculates the risk of malignancy and, in the case of high - risk, suggests a visit to a specialist. After several redesigns, a sensitivity of 95% and a specificity of 78% was achieved [25].

THE FLAWS OF SMARTPHONE APPLICATIONS

A number of flaws have been noted regarding research into these applications and the risks of their use. CE (Conformit Europenne) has only allowed the circulation of 2 apps of this type, while the United States Food and Drug Administration (FDA) has not yet given its approval. On the other hand, two other apps, MelApp and MoleDetective, have been subject to penalties due to incorrect accuracy of the result, which would mean a delay in diagnosis for patients [27]. Many authors point out the inappropriate selection of patients for app studies. Some studies were conducted with a prior selection of patients by dermatologists, which does not illustrate the general population [28]. For example, some of the SkinVision application studies were only performed on cohort groups, or clinical and cohort groups combined, which may result in overestimation of results [29].

Meel et al. highlighted the problem of melanoma detection in the dark-skinned population and acknowledged that their result on the accuracy of the Melatect application may be biased, due to the small number of lesion images in this population when training the model [16].

And Donk et al. analysed deep learning models and showed that, typically, testing them with more images resulted in reduced accuracy, which in turn reduces the reliability [23].

Another important issue is the number of false positives received. In the case of the SkinVision app, whose test results seem very promising, its use in a real-world population with low prevalence would mean detecting 20,000 false positives in a group of 100,000 users [22].

This, in turn, could cause damaging effects on the patient's psyche and burden the health service [25]. Moreover, it is worth remembering, the application of such a large database as required by CNN is not always possible to download for patients for technical reasons [21].

Another complication is that the presence of another person is required to take pictures of a lesion located in a hard-to-reach area, which is not always comfortable for the patient. A study of nevi monitoring apps was also carried out and users' feedback was analysed. It turned out that only 25% of the subjects conscientiously used the app throughout the 3-month study [30].

In the future, the accuracy results of the app should be confronted with the number of false positives to balance the benefits against the risks of misdiagnosis [26].

Furthermore, consideration should be given to retraining the models used by database of a specific medical population, which would positively influence the outcome [17].

The flaws of smartphone applications
<u>The problem of false negative results</u> • **Delay in the diagnosis**
<u>The selection of data for studies</u> • **To many cohort studies** • **Too few images of dark-skinned patients** • **The decrease of accuracy while testing on larger number of images**
<u>The problem of false positive results</u> • **Damaging effect on patient's psyche** • **Burden on the healthcare system**
<u>Technical problems</u> • **The weight's size of database – not applicable to an average patient's devise**
<u>Patient's engagement</u> • **Gap between the willingness and actual participation in the process**

Figure 1. The flaws of studies on smartphone applications (16,21–23,25,28–30)

CONCLUSIONS

Melanoma continues to take its toll, especially in white-skinned populations. A more thorough understanding of the epidemiology and risk factors allows for effective prevention of the disease. Our work also reports on the latest technologies that will probably be widely used in the future to determine the malignancy of skin lesions. However, one should be particularly careful when allowing smartphone applications on the market because of the high risk of misdiagnosis. More objective studies on the accuracy of these technologies need to be performed.

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Factitious disorder in dermatology: a multidisciplinary problem

Barbara Białynicka-Birula, Marta Szepietowska

Student Research Group of Experimental Dermatology, Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland

INTRODUCTION

Dermatitis artefacta is a condition in which patients cause damage to themselves, resulting in the skin lesions [1].

Classification, terminology and differential diagnosis of this group of diseases have been a challenge for clinicians. Therefore, in 2013 European Society for Dermatology and Psychiatry (ESDaP) suggested a new classification based on the effort that was put in analyzing existing data by dermatologists, psychiatrists and psychologists [1].

Dermatitis artefacta was classified by ESDaP as a self-inflicted skin lesion (SISL). SISL cannot be confused with other lesions, which are only a result of mental disease, accompanied by many other symptoms, like obsessive compulsive disorder (OCD) or delusional infestation. Therefore, SISL can be characterized as any skin lesion produced by the patient which is not a result of any other coexistent mental or physical disorders. Furthermore, ESDaP suggested three more questions to diagnose and classify the SISL more precisely. First, it should be inquired whether the behaviour causing the lesions is hidden or no. Second, provided the first answer was positive, it should be asked whether there are any external incentives which might be the reason for these actions. Third, if the answer to the first question was negative, compulsive and impulsive spectrum must be differentiated. In this system dermatitis artefacta falls into the category of factitious disorders. They are defined as fake or artificial, self-induced diseases, occurring without clear, immediate external reasons. Some classification systems maintain that the patient suffering from dermatitis artefacta always withholds the truth about the origin of the lesions [1], while other say it is a pattern, but it is not necessarily a criterium for the diagnosis [2].

AIM OF THE STUDY

This article presents a case of a patient suffering from factitious disorder in dermatology, who has been admitted to our department twice over a year. We hope that introducing this case will raise awareness among the healthcare workers regarding the SISL. Factitious disorder in dermatology (dermatitis artefacta) is a difficult disease to diagnose, as it can mimic many conditions and the patients are often not cooperating with the physician [2].

CASE REPORT

A 32-year-old man was admitted to our department because of disseminated pruritic skin lesions. At the time of admission he was married having two small children. His wife was on maternal leave. The patient had secondary school education and was professionally active working as copper miner. First lesion appeared about one and half year ago and was located around the right ear. Within a few weeks the lesions spread affecting the face, chest and upper extremities. According to anamnesis they presented as erythematous highly pruritic papules. Due to the intense itch, assessed retrospectively on the numeral rating scale (NRS) as 10 points, the patient scratched the lesions. This lead to multiple excoriations and scarring process. The patient denied any factors, including stress, exacerbating the skin lesions.

Upon admission he presented with ulceration (4 cm x 2 cm) of the left cheek in close deposition to the ear. Moreover, several excoriated lesions and scars were found on the chest and both upper extremities. Some lesions, including the ulceration showed signs of secondary bacterial infection. Again he reported intense itching (NRS = 10 points). All laboratory tests were within normal range. Based on clinical experience the suspicion of factitious disorder in dermatology (dermatitis artefacta) was put forward. The psychiatric examination revealed neutral mood with raised anxiety level accompanied with the increased tendency to manipulation. Finally, the patient was diagnosed with generalized anxiety disorder. According to the psychiatric consultation the patient was put on pregabalin 75 mg twice daily with subsequent dosage increase to 300 mg per day. Additionally, due to secondary bacterial infection the antibiotic treatment with topical fusacid acid and 10-day course of doxycycline 100 mg twice daily. After a few days of further hospitalization the patient with slight local clinical improvement was discharged home with a recommendation of follow-up in regional out-patient setting.

A year later, the patient was again admitted to our department. It appeared that after the first hospitalization he continued treatment with pregabalin only till finishing the whole medicine pack. The treatment was well tolerated without any adverse effects. However, the patient did not show up for follow-up visit and the therapy was discontinued. That was a patient's own decision. He reported that during this whole period he had been still suffering from this disease accompanied with intense itch. As he experienced that the cure was not possible without professional therapy he decided to seek again the medical advice. During the examination he disclosed that his family problems appeared. He considered them due to the lack of full understanding within the family members. Physical examination showed the presence of the previously described ulceration on the left cheek, however the ulcer enlarged to 6 cm x 3 cm (Figure 1).

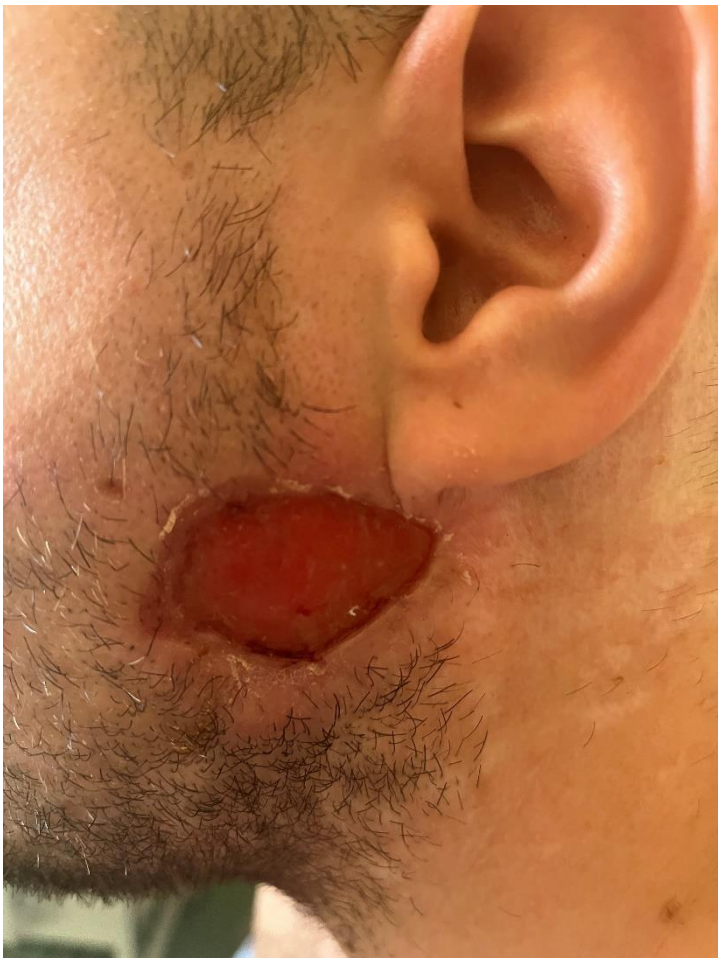

Figure 1. Large ulcer due to self-harm on the cheek

Moreover, numerous scars were found all around the body with additional involvement of the neck and scalp (Figure 2). Repeated psychiatric examination confirmed the previously

diagnosed generalized anxiety disorder. Based on clinical manifestation and disease course, the patient was again diagnosed with factitious disorder. He was put again on pregabalin 75 mg twice daily. The psychiatric long-term management was recommended and the patient at this stage agreed with this proposal.

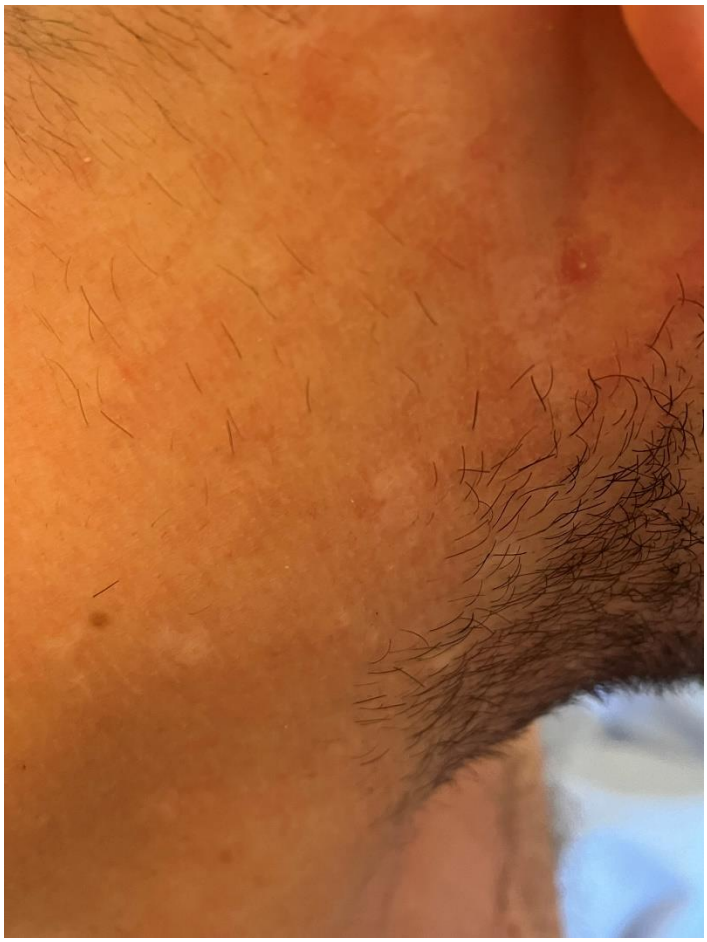

Figure 2. Multiple small whitish scars on the face as a result of healed self-inflicted skin lesions

DISCUSSION

Factitious disorder in dermatology, previously called dermatitis artefacta, seems to be an underdiagnosed disorder that can be a challenge for dermatologists [3]. The UK study of psychiatric patients frequenting the dermatological clinic showed that even one third of them were diagnosed with dermatitis artefacta [4]. Despite the fact that the condition is the most prevalent in early adulthood, it might also appear in any age. Factitious disorder in dermatology

is much more common in females [5]. According to one study, female to male ratio was 3:1 [6].

Clinical manifestation of this condition can vary among the patients, presenting with bizarre lesions [7]. In most of the cases the lesions are however scattered around easily accessible parts of the body, like extremities or neck and face, as in the presented case. The lesions are self-inflicted, and the action of self-injury is satisfying to the patient, who is often suffering from some underlying psychic problems. However, dermatitis artefacta is considered to be a primary psychiatric disease and should not be confused with other mental disorders manifesting with self-harm [8]. The lesions can be produced either by the fingernails of the patient, or they can also be aggravated with some sharp objects like knives or pens. If so, deeper, more linear skin damages are observed. When the lesions are produced by burning the skin with the tip of the cigarette, numerous circles of the same diameters are seen. Sometimes patients might use caustic material, or even self-inject some substances, like feces or urine, subcutaneously. These actions result in cellulitis and even fever. It is vital to stay very open-minded when it comes to identifying the origin of the lesions [8].

The etiopathogenesis of factitious disorder in dermatology is multifactorial. The condition is quite often developed along other psychic disorders, like borderline personality disorder or post-traumatic stress disorder (PTSD). The disease is diagnosed in patients who have some basic mental problems, originating from very early stages of their life. These issues emerge from a difficult relationship with a parent, traumatic childhood experience, or other challenging situation at the formative stage of life. This results in the distorted image of the body and causes high index of insecurity, along with lack of maturity. Young adults, who are most often diagnosed with dermatitis artefacta, exhibit their inner struggles through the self-harm, and it might be very hard to heal for them, as their mental health is very unstable. They are not capable of coping with problems in a mature way [7]. The patient who appeared in our department was struggling with some family problems, probably over the longer period of time, but would disclose details reluctantly, only after a longer inquiry. In the study of 43 patients presenting with self-harm conditions observed throughout 12 years, 30% percent of them, mostly women, continued to produce lesions for this time because of the lack of change in their environment. Not therapy, but their personal situation seemed to have played the biggest role in the healing process [9].

As the awareness of this disease is not high, it might be difficult for a dermatologist to come up with a right diagnosis [10]. It is important to notice that the patient does not express much concern regarding their condition, even when the lesions are looking severely. That kind

of behaviour is a crucial diagnostic clue for clinicians [3]. Moreover, factitious disorder in dermatology can often mimic other diseases, like vasculitis or any other skin disease manifesting with chronic ulcerative lesions [7,11]. Therefore, the diagnosis should be based on ruling out other conditions rather than looking for specific symptoms. The laboratory work-up coming out negative should be a hint for the physician to look closer at the psychic aspect of the patient. Another relevant signal suggesting dermatitis artefacta is the fact that the lesions heal very well when occluded during hospitalization [10].

The treatment of factitious disorder in dermatology demands very close cooperation between dermatology and psychiatry specialists. At the early stage it is important to form a good relationship between the dermatologist and patient, so that the further steps could follow [12]. It might be good to focus on the emotional aspect of the disease instead of interrogating the patient how the lesions were produced. The not long-lasting problems and those in younger patients are linked with better prognosis [12]. The ESDaP experts recommended a psychological and psychodynamic approach. The most important is to have psychotherapist convinced of the possibility of success [12]. The dermatological treatment should always be applied. Occlusive dressing may allow the skin lesions to heal and this could also be a confirmation of the correct diagnosis put. Antiseptic agents and antibiotics are used in case of superinfection [7,12]. The underlying mental problems must be addressed and treated. However, no psychiatric agents were found to have excellent effect in factitious disorder in dermatology [7]. One can use antidepressants, especially selective serotonin reuptake inhibitors (SSRI), which may be beneficial in lowering depressive reactions, impulsivity and aggressive behavior. Koparde et al. [13] reported good effects with sertraline 200 mg per day in patient with severe dermatitis artefacta. Moreover, antipsychotics could be tried, especially in those patients not responsive to SSRIs. Our patient was put on pregabalin as the general anxiety disorder was diagnosed by psychiatrist. It is well known that gabapentinoids could be effective in anxiety disorders [14,15].

Factitious disorder in dermatology is usually a long-term process and needs holistic approach to patients. The maintenance therapy, is required, especially in patients with borderline personality disorders. Although the psychological consulting is recommended for months the prognosis is not perfect in the majority of patients.

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Morgellons disease: distinct entity or delusional infestation?

Alicja Dąbrowska, Marta Szepietowska

Student Research Group of Experimental Dermatology, Department of Dermatology, Venereology and Allergology, Wroclaw Medical University, Wroclaw, Poland

INTRODUCTION

Nowadays, one of the most controversial disorders within dermatology is a disease named Morgellons disease. Morgellons disease is a poorly understood and debilitating disorder. Afflicted individuals identify themselves as having non-healing skin lesions with excretion or emergence of fibers from the skin while having other disturbing cutaneous sensations, such as formication [1]. The illness usually manifests with multiple non-healing, often ulcerated lesions. It is common among patients suffering from Morgellons disease to present additional somatic, neurologic, and psychiatric complaints, including fatigue, myalgias, itching, burning, stinging, and foreign body sensations [2]. Patients might also self-report extrusion of fibers, hairs or other materials from the skin and later present them to the doctors [3,4].

EPIDEMIOLOGY AND PATHOPHYSIOLOGICAL ASPECTS

Delusional infestation (DI) is the conviction that patient is infested with pathogens, despite medical or microbiologic evidence to the contrary. One can divide those pathogens into the animate and inanimate ones. The main object of this study is infestation with inanimate pathogens, specifically fibers or filaments, which has been controversially termed Morgellons disease. The patients themselves, believe that this is not a psychiatric disease but rather a new organic condition or a skin manifestation of an infection [5]. The term Morgellons was formally introduced in 2002 by biologist Mary Leitao, who continued to find visible fiber protrusion from the skin of her son accompanied by recurrent bouts of itching. After the increased recognition of Morgellons in 2002, the number of cases has steadily increased. Epidemiologic studies show that the prevalence in a private office setting was 83.23 per million people, which is likely an underestimation [6].

Spreading the awareness by e.g. creating Morgellons Research Foundation lead not only to the website registering over 15,000 affected people from over 15 countries, including all 50 states of USA, but also to a host of media attention with stories written in The Atlantic [7] and Newsweek [8]

among others. It is not surprising that Morgellons has been called an internet meme and one of the first diseases socially transmitted over the internet [9,10]. As a consequence, the Centers for Disease Control (CDC) performed a large population study from 2006-2008 and whereas both infectious and psychiatric etiology have been proposed [1]. A large-scale study by CDC on patients presenting with Morgellons clinical manifestations did not find evidence of fibers in the skin nor an association with any infection, including Lyme disease [11].

The prototypical patient with DI is often described as a middle-aged to elderly woman with no past history of psychiatric disease who develops an isolated false belief that she is infested with pathogens. Those patients believe they are infested most commonly with insects or worms. Other common manifestations might include elderly patients with vascular encephalopathy and cortical atrophy (with our without dementia), elderly patients with dementia-associated psychosis, and younger men (<50 years of age) with acute onset of clinical manifestations, most likely secondary to illicit drug use. It is important that the nature of one's delusions may vary from patient to patient, thus the management needs to be chosen carefully [12,13]. Historically, DI was described as having no underlying organic or psychiatric cause. However, the complied evidence presenting distinct biological underpinnings. Numerous studies have revealed three main brain dysfunctions that might lead to primary and secondary DI, which include dysfunction of the fronto-striato-parietal network, active structures correlated with itching and ischemic changes of the brain [14-16]. The dysfunction of the fronto-striato-thalamo-parietal network is demonstrated both functionally and structurally, which correlates with the "two-factor model of delusions". This cognitive-behavioral model might explain the neurobiological basis of the delusions, as the delusions include, both, content of the delusional belief, such as hallucinatory sensations of infestations and impaired judgement caused by abnormalities in the frontal parts of the brain [17]. The next significant dysfunction is associated with brain structures processing the itching. Recently, there has been discovered the network between the right posterior insula, SMA, pre-SMA, anterior midcingulate cortex and basal ganglia. The studies have shown that patients with DI present stronger activation of right posterior insula and secondary somatosensory cortex as compared to controls. It is believed that DI patients experience strong pruritus related to abnormal activation of higher cortical itch processing [15]. The last well-described dysfunction is caused by brain lesions leading to secondary delusional infestations. The most common brain lesions include ischemic lacunar lesions and gliosis [18].

On the other hand, the MD patients not only experience filamentous dermopathy, but also, they frequently present Lyme-like symptoms such as musculoskeletal, neurological and cardiovascular manifestations suggestive of spirochetal etiology [19-21]. There are numerous cohort studies that have proven most patients with MD test positively for Borrelia burgdorferi infection and/or have a clinical Lyme disease (LD) diagnosis [22,23]. Thus, it is believed that MD might be

a response to spirochetal infection in genetically predisposed patients. Borrelia infection is caused by members of the Borrelia genus encompassing the LD group, also known as Borrelia burgdorferi (Bb) sensu lato (Bbsl), and the Relapsing Fever Borrelia (RFB) complex, the causative agents of LD and relapsing fever (RF), respectively. Both, Bbsl and RFB have been repeatedly and consistently detected in tissue and fluid specimens taken from MD patients [20,24]. What is more, two separate cohort studies have showed that MD affects approximately 6% of LD patients [25,26]. Middelveen et al. [27] conducted a separate cohort study of 30 MD patients. It turned out that 90% of these patients tested positively for exposure to and/or infection with Borrelia spirochetes using serological and molecular techniques [27]. To the best of our knowledge, five independent laboratories have confirmed the presence of Borrelia DNA in MD skin specimens using PCR technology and confirmatory DNA sequencing, and seven independent laboratories have detected Borrelia DNA by direct testing or in cultures of blood, genital secretions and skin specimens taken from MD patients. Middelveen et al. [28]. studies indicate that excluding the presence of cutaneous filaments seen in MD lesions, it is common for MD patients to present lesions resulting from spirochetal infection. Furthermore, regardless of location and variation in characteristic appearance, MD lesions would represent the same infectious process [28].

Histology taken from skin lesions of severe MD patients showed an inflammatory infiltrate (mainly macrophages), hemorrhage and Borrelia aggregate colonies. Most importantly, severity of lesions corresponded with the level of intracellular anti-Bb immunohistochemistry staining of macrophages, primarily in the dermis, a finding that suggests chronicity. Bb may survive phagocytosis by macrophages and persist intracellularly leading to a pathogenic mechanism [29,30]. As a result, it may contribute to spirochete persistence and recalcitrance, like survival within keratinocytes and fibroblasts. Thus, significant Borrelia accumulation might result in cell rupture and formation of aggregate colonies [31]. It is hypothesized that MD filaments originated in subcutaneous locations or the basal cell layer, which reacted greatly with anti-Bb immunohistochemistry staining. Some authors suggested that this specific staining pattern might indicate a direct association between MD filament formation and Borrelia infection. The presence of Bbsl, and possibly co-involvement of other pathogens might induce the production of aberrant filaments, as a consequence of altered gene regulation and expression of keratin, collagen and melanin [20,24]. However, as written above CDC did not confirm evidence of skin fibers nor an association with spirochetes infection [11].

CLINICS

Rocati and Piscioli [32] have recently reported a MD patient. They have observed a 49-year-old Caucasian woman affected by typical MD symptoms. In particular, the patient presented an

increase in the viscosity of her tear film and saliva, followed by the elimination from epidermal spots of small spherical granules and/or narrow long wires, grayish in color, placed on her hands and arm [32]. Nunziato et al. [33] have also described cases of MD patients. The first one of them, a 59-year-old man presented "green slime" oozing from his right hand. The patient was well known to have undergone an exhaustive and ultimately entirely negative workup for infectious, metabolic, and neurological diseases. Only a radiograph showed scapholunate advanced collapse, for which he was referred to a hand specialist, where there was no evidence of any green substance or other cutaneous condition. The patient repeatedly requested a surgical "fix" for the slime; however, he was unlikely to benefit from any surgical procedure. The next patient, a 56-year-old right-hand-dominant woman presented to a hand specialist with a 2-year history of "fiberglass coming out of her left hand". She also said she had an overgrown nylon suture from a prior procedure on the right hand. On examination, there was no evidence of foreign body. Another patient, a middle-aged man presented to a hand specialist with bilateral elbow pterygia, saying he was infested with an unusual parasite. In addition to the pterygia, he had ulcerations and webbing about his neck and left index finger from self-excoriation, which he said happened mostly when he was sleeping. He brought a plastic bag of thin metal wires (with skin fragments) that he reportedly dug out of his arm [33].

The above reported cases illustrate the diversity of clinical manifestation of MD. However, most commonly the patients report extrusion of fibers or other materials from their skin, which is frequently associated with itching or burning sensation. The well-known "specimen sign" from delusional parasitosis – bringing the collected material to the physician's office for examination and confirmation [34,35] is not a rare phenomenon also in MD [3,4]. Moreover, the patients with MD may produce self-inflicted skin lesions putting their efforts to eliminate the fibers from the skin [5].

MANAGEMENT

Management of MD is a real challenge for clinicians. As it is generally accepted that MD is a type of DI the patients require psychiatric treatment. However, the patients mainly present themselves to dermatologists and they do not consider their problems as of psychiatric origin. Therefore, putting these patients on psychiatric agents is not an easy task [5]. As the disease remains controversial the therapy of MD is unstandardized and recommendations are mainly based on single case reports and serious of cases. There is lack of classical clinical trials in MD. Antipsychotics are drugs of choice in the treatment of MD [2,5]. Several antipsychotic agents have been reported to be beneficial in reducing the symptoms of MD. Usually the low doses of these agents are efficacious for Morgellons. Aung-Din et al. [2] reviewed treatment modalities used for MD and concluded that risperidone and trifluroperazine seem to be the most effective agents in alleviating symptoms and

placing patients into remission. Risperidone should be applied in the dose up to 2-3 mg per day and trifluoperazine in the dose 2-3 mg per day [2]. One may also use other antipsychotics, like aripiprazole, olanzapine or pimozide (not available in Poland). The effectiveness of antidepressant agent - escitalopram has also been demonstrated. Usually psychiatric treatment is combined with simple dermatological therapy, mainly with topical antiseptics and topical antibiotics [2].

CONCLUSIONS

Today's Morgellons most likely represents a psychosomatic delusional disorder on par with delusions of parasitosis. The journey through the history of MD is a particular lesson on the power of the Internet in the dissemination of information and creation false believes. This could influence even more the field of psychodermatology in the future. Unfortunately, regardless of etiology, MD is recurrent, difficult to manage and burdensome condition to both clinicians and patients. Once the diagnosis of DI is made, the cornerstone of treatment are antipsychotics, although this is often quite challenging, as patients are reluctant to take these medications.

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The role of modern therapies in the care of patients with acne scars

Karolina Wanda Borkowska, Anna Grajewska, Edyta Rysiak

Department of Medicinal Chemistry, Medical University of Bialystok, Białystok, Poland

Acne vulgaris is one of the most common inflammatory dermatoses, affecting more than 85% of teenagers and young adults aged between of 18 and 35 years. The pathophysiology of acne vulgaris includes increased sebum production and proliferation of *Propionibacterium acnes bacteria*, which thrive in an anaerobic environment inside the hair follicle. Enzymes that are produced by the aforementioned bacteria decompose triglycerides contained in sebum. This process results in the release of irritating fatty acids and potent inflammatory and chemotactic substances. External factors such as diet, stress and skin care cosmetics are also important factors in the course of acne vulgaris. In the clinical picture of acne vulgaris, the changes involve the hair and sebaceous unit. Skin lesions usually are located on the face and back. They are also less common on the buttocks, chest and extremities. Depending on the type of skin lesions, there are several types of acne. These include comedonal acne, papulopustular acne, purulent acne, keloid acne, fulminant acne and acne from scratching [1,2].

It should be emphasized that pathogenesis of acne vulgaris is strictly correlated with the condition of the skin micriobiome. It is composed of microorganisms that determine the proper functioning of the macroorganism and the immunity of the skin. It is a protection from infection by bacterial pathogens and viruses. The aforementioned microorganisms are colonized by the appendages of the skin, such as hair follicles, sebaceous glands, and the stratum corneum of the skin. Environments where the microbiome is present, also include oral cavity, gastrointestinal tract, respiratory tract, and genitourinary tract. The skin microbiome is colonized by archaea and eukaryote bacteria, commensal and symbiotic microorganisms. It is also not free of those causing infectious diseases. As a physical barrier and a habitat for microflora, the skin is an integral part of the immune system. It constitutes the first line of defense against pathogens. In addition, the skin microbiome is responsible for maintaining the body's homeostasis, modulating the innate immune response and influencing the development of the acquired response [3,4]. Inhibition of the growth of pathogenic microorganisms is determined by the secretion of AMPs or antimicrobial peptides and the stimulation of epidermal keratinocytes to

produce them. Dysbiosis of the skin microbiome leads to a decrease in its barrier function and is one of the etiological factors in course of acne vulgaris.

The composition of the microbiome in adults is influenced by anatomical and physiological conditions. Women's skin microbiome is different in addition to men's skin microbiome. Differences are most apparent during pregnancy and menopause. During the teenage years, an increase in androgen activity is noticeable, which results in higher activity of the sebaceous glands, which is a habitat of *Propionibacterium acnes bacteria*. These bacteria, by hydrolyzing triglycerides present in the sebum to free fatty acids, participate in the formation of the skin's hydrolipidic mantle. Excessive growth of *P. acnes* contributes to the development of a dermatosis such as acne vulgaris [4].

In the clinical picture of acne vulgaris, one of the first, noticeable symptoms are excessive keratinization of the hair follicle mouths and overproduction of sebum. Seborrheic skin is characterized by the presence of dilated sebaceous glands filled with sebaceous masses. The first stage of acne vulgaris involves excessive proliferation of corneocytes and their accumulation in the distal part of the sebaceous gland tubule. These cells do not undergo the normal process of exfoliation. The sebum flux results in the dissolution of the lipid mantle in the follicle and a decrease in cholesterol, ceramides and linoleic acid, thus disrupting the keratinization process. The abnormal course of this process leads to an increase in the permeability of the hair follicle wall, facilitating the development of inflammation, promoting faster septation of *Propionibacterium acnes*. The above-mentioned mechanisms lead to the formation of the primary lesion in acne vulgaris, which is a blackhead. A consequence of the course of acne vulgaris is also the appearance of secondary lesions in the form of pustules, papules and cysts, abscesses and fistulae [5,6]. Patients caused by acne vulgaris struggled not only with primary and secondary lesions. The long-term consequences of the course of this dermatological disease are acne scars. Damage to the skin caused by the healing of inflammatory lesions starts the activation of repair processes. The defect created by the disruption of the autonomic continuity of the skin is replaced by granulation tissue. Over time, this defects fill in with connective tissue. Scars, as a result of above mentioned process are an areas on the skin that are distinguished by its texture, color, lack of hairiness, and elasticity. In acne vulgaris, these are usually atrophic (atrophic) or hypertrophic scars [7].

The multiformity of acne vulgaris in cosmetology is a complex problem, and its therapy is a challenge for many specialists in this field. Most often, it requires combination therapies, in which the beauty therapist selects appropriate cosmetological treatments depending on the

severity of acne lesions. A significant problem in the course of this dermatosis is not only inflammation, located in different areas of the patient's body, but also the scars as a long – term defect of the disease. These defects develop during the transition of the disease from non-inflammatory to inflammatory conditions, resulting in rupture of the inflammatory blister wall. Consequently, this phenomenon leads to the release into the dermis, *Propionibacterium acnes bacteria*, keratin, fat. These components enhance the development of inflammation. When periorbital abscesses tend to heal, scars generally do not form. On the other hand, as a result of their incomplete absorption, multichannel fistulas and scar formation can occur.

In the ECCA (*European Acne Group*) classification, atrophic acne scars were divided into V - shaped (Ice - pick), U - shaped (Boxcar) and W - shaped (Rolling). In 2015, this division was expanded to include papular scars, which are hypertrophic in nature. The classification was expanded by Dr. Stephanie Gan and her co - researchers. Proper characterization of the type of scar is helpful in the correct choice of therapy. V-shaped scars can extend deep into the dermis, which contributes to the ineffectiveness of conventional cosmetic treatments. Rolling atrophic scars are wider and have a fibrous attachment, covering the area from the dermis down to the subcutaneous tissue and therefore should be treated at this level of the skin. Boxcar scars can come in two types: shallow and deep. Those of a superficial nature are more amenable to treatments involving skin revitalization, while in the case of deep ones, treatments based on superficial action do not provide satisfactory therapeutic results. Conventional cosmetological acne scars treatments are based on the use of chemical peels, ablative laser or dermabrasion. The use of microneedling is also quite popular [8].

Currently, one of the quite popular treatments for acne scars is the use of bipolar micro-needle radiofrequency. Therapies using it involve inducing a thermal effect in the tissue. The application of high temperature results in the stimulation of fibroblasts to produce new collagen and elastin. In addition, the application of heat causes blood vessels to dilate, which affects the nutrition and oxygenation of the skin. An additional technique used for micro-needle radiofrequency is micro-puncturing. Needles are inserted at a depth of 0.5 to 3.5 mm. Treatment using this method was performed by Dr. Hantash [8]. The reticular layer of the skin in his patients was thickened 10 weeks after one treatment session. An increase in hyaluronic acid and elastin levels was also noted. The treatment was carried out using a five-needle head, emitting a temperature of 72°C. The needle insertion time was 4 seconds. The results of Omi T. [8] were consistent with Dr. Hantash's results, while additional effects mentioned in his work were an increase in fibroblast activity, normalization of collagen fiber structures relative to their

histological image. Active protein and collagen production was noted by the phenomenon of "swelling" of atrophic areas in acne scars. Omi T. explains the additional effect of bipolar radiofrequency, micro-needling by using the higher energy of the radiofrequency used to treat the patients in his study. The post-treatment effects obtained by this method are widely discussed in available literature. In order to standardize the parameters used in bipolar radiofrequency, micro-needling treatments in 2014, a team of 11 experts developed specific guidelines. The appropriate values used for the treatment of acne scars were considered to be the insertion of needles to a depth of 0.5 mm to 2 mm, while the energy level should oscillate between 4 and 7. The results of the studies described above prove the effectiveness of the use of bipolar radiofrequency micro-needling for the treatment of acne scars. With the proper application of parameters and the correct course of the treatment procedure, the therapy is effective and the aesthetic effect is satisfactory.

Another modern method for treating acne scars is fractional or pulsed dye laser treatments. They are recommended in cases where the scar is linear, irregular or overgrown. Laser treatments are used when previous forms of therapy have proved ineffective. The basis of fractional laser action is the phenomenon of fractional photothermolysis, which was developed in 2004 by Manstein et al [9]. It involves the production of pinpoint microdamage on the surface of the skin, leading to zones of heat damage. These areas are surrounded by a margin of living, intact tissue, making the recovery and regeneration process smooth. This is one of the biggest advantages of fractional laser therapy, cited as an argument when discussing its high efficacy and low risk of side effects. The mechanism of action of the ablative fractional laser in the treatment of scars has been illustrated by means of in vivo studies. Under the influence of the emitted laser beam, rapid thermal damage to the skin occurs. The zone becomes colonized by epidermal cells after 48 hours. Remnants of dead tissue remain within the stratum corneum and after 7 days are completely exfoliated. The entire process is accompanied by an increase in the mitotic activity of fibroblasts. By a month after the laser beam, the cells of dead tissue are replaced by a normal layer of corneocytes. It should be noted that the use of fractional laser effectively affects any type of acne scars. Previous recommendations for the use of combination therapy, based on isotretinoin and fractional laser treatment, assumed an interval between the start of laser therapy and the end of the drug treatment. Currently, there are no recommendations indicating the appropriateness of delaying fractional lasers in patients who have been using isotretinoin or have just finished taking it. Kim et al [9] performed ablative fractional lasers (AFLs) in patients treated with the above-mentioned drug. The healing process

went well in all subjects. They also showed a high level of patient satisfaction rates with the therapy. The study authors noted that the use of ablative fractional lasers in patients using isotretinoin was safe. Ortiz et al [9] ocused on the long-term effectiveness of laser therapy. Follow-ups of patients undergoing this type of treatment were carried out one and two years after the therapy. They showed improvements in local skin condition and overall life satisfaction in 74% of cases. The difficulty of selecting a laser therapy method lies in the lower susceptibility of certain types of acne scars to fractional laser treatment. Boxcar and rolling scars, described above, are more resistant to laser therapy than ice pick scars. The coexistence of different types of acne scars on the skin of a single patient raises the need for combination therapies. These usually use radiofrequency or platelet-rich plasma injections. The use of laser therapy in the treatment of acne scars as a single method or as part of a combined therapy leads to an improvement in the structure, tone and color of scars. Thus, the leveling of defects caused by acne leads to an improvement in the quality of life and well-being of patients.

Another fairly modern method in the treatment of acne scars is the use of chemical peels. One that is mentioned quite often is trichloroacetic acid. TCA (trichloroacetic acid) in the case of leveling acne scars is used at a concentration of 15%, at which it shows a superficial effect, and 40%, at which it shows a medium-deep effect. It is a chemical peeling that, due to its small particle size, shows easy penetration into the epidermis and dermis. The higher its concentration used, the stronger and deeper the penetration is. TCA with a concentration of 50% is used for the treatment of U-shaped (boxcar) scars. In the treatment of other types of atrophic scars, such as ice peaks, higher concentrations of this acid are used, reaching even this 50% - 60%. This is only a spot treatment due to the possibility of the appearance of hyperpigmentation, new scars or skin damage. An interesting aspect of the use of trichloroacetic acid in scar therapy is the CROSS TCA method, developed by Lee et al. in 2002 [10]. This method consists of applying the acid in higher concentrations only to acne scars covered by the treatment. The study by Lee et al. involved 65 patients with atrophic scars resulting from acne vulgaris. Therapy of their skin was carried out from July 1996 to July 2001. The study participants were divided into two groups. In one, consisting of thirty-three patients, TCA was applied at a concentration of 65%, while the other group applied the same acid at a concentration of 100%. The common method in both groups was CROSS TCA. Twenty-seven patients in the first group saw a noticeable improvement in their skin's clinical appearance after treatment. All patients were satisfied with the results. In the second group, the desired therapeutic effect was also noted. A common feature

of both groups was the absence of side effects. The results allowed the researchers to conclude that the CROSS TCA method was effective, with minimal risk of complications.

Acne scar's treatment requires proper identification of the type of scar and selection of the appropriate treatment method. The therapies mentioned in this manuscript are considered as one of the most effective these days. The treatment of scars and scarring in both cosmetology and dermatology is a therapeutic challenge.

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Psoriasis - a physical, psychological and socio-cultural issue

Anna Grajewska, Karolina Wanda Borkowska, Edyta Rysiak

Department of Medicinal Chemistry, Medical University of Bialystok, Białystok, Poland

INTRODUCTION

It is estimated that psoriasis affects around 3% of the population worldwide. Currently, psoriasis is one of the most commonly diagnosed diseases in dermatology practice. Moreover, psoriasis is incurable and the patient has to struggle with it for life. Psoriasis is considered a systemic disease but, importantly, its course does not involve the skin alone. The disease affects the patient's physical and mental health. In addition, the patient has to contend with comments from other people about their appearance. The totality of these factors significantly reduce quality of life, can exclude the patient from social life and affect the patient's health [1].

PSORIASIS – A COMPLEX HEALTH PROBLEM

Psoriasis is a chronic disease of unknown aetiology, but it is classified as an autoimmune disease and two types of factors are indicated. The first group are factors contributing to the development of the disease - genetic, hormonal. The second group are factors that promote recurrence and exacerbation of lesions - medications, infections, stress. The disease process consists of accelerated division of all phases of the cell division cycle, increased intensity of cell division and incomplete differentiation of cells. Based on the location and size of the skin lesions, types of psoriasis are distinguished: plaque psoriasis, nail psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis. The symptoms of the disease affect the skin, but there are also forms involving the joints. The clinical picture of the disease is red and brown papules covered with silver scales. The scales tend to clump together and spread on the surface of the skin. There are two characteristic features of psoriasis: Auspitz's sign and Köbner's phenomenon. Auspitz’s sign is pinpoint bleeding at the site of scraping of the psoriasis scales, while Kobner's sign is the seeding of psoriatic lesions at the site of epidermal damage within 7 to 12 days. In addition, patients indicate persistent itching of the

skin. The location of psoriatic lesions is the hands and feet, the surface of the extremities, the knees and elbows, the lumbosacral region, the hairy scalp and the nails. In nail psoriasis, onycholysis, thickening and brittleness of the nail plate and keratosis under the nail plate are observed [1, 2]. The treatment of psoriasis is difficult because to date no effective drug has been found that results in a complete cure. In nail psoriasis, onycholysis, thickening and brittleness of the nail plate and keratosis under the nail plate are observed. The treatment of psoriasis is difficult because to date no effective drug has been found that results in a complete cure. Treatment therefore depends on which form of psoriasis is present and it is important to bear in mind that some medications may additionally exacerbate skin lesions. Therefore, the most common treatments for psoriasis are immunomodulatory drugs, cytostatics and biologics. In addition, topical treatment and supportive treatment are used. Importantly, well-matched patient care helps to treat skin lesions and prolongs asymptomatic periods [2].

The contribution of stress to the genesis of psoriasis is significant. Stress is defined as an overload on the body that exceeds a person's previous adaptation. Moreover, such a situation requires the activation of new human adaptation mechanisms in order to regain equilibrium. There are three categories of stress: environmental stress, physiological stress and psychological stress. In the case of psoriasis, each category can account for the occurrence and exacerbations of the disease. Environmental factors include smoking, unhealthy diet, air pollution and noise. Physiological factors are those that provoke the seeding of new psoriatic lesions - disease, infection, trauma, epidermal damage. Psychological factors include depression, impaired social relationships, work problems and family troubles [2, 3].

The skin is the largest human organ and, consequently, is also the most visible. It has the function of protecting the body from external factors and protecting the internal organs. But importantly, by what skin looks like, it also has psychological functions, the image and evaluation of the whole body, as well as a sense of worth and psycho-emotional state. There are many reports in the literature of an association between psoriasis and depressive disorders. According to Borzęcki et al. [4], research into the role of psychological factors in the onset and course of psoriasis was analysed in detail in Europe and the USA in the 1970s. The authors report that the skin is an organ of communication and perception, and that somatic factors play a significant role in exacerbating or triggering the disease process. The skin is the most important organ for human communication. The occurrence of psoriasis can significantly affect the patient's condition, self-image perception, sense of self-worth and self-esteem. In addition, they point out that the disease has a huge impact on daily, professional and personal life. Most

patients avoid social contact and have difficulty making new friendships. Patients also have difficulties in family relationships, partnerships and an intimate life.

According to Gupta et. al [6], psoriasis patients respond differently to stress. Patients who indicated that stress exacerbated their symptoms coped less well with daily life. In addition, patients who responded strongly to stress showed greater clinical severity of disease, more frequent psoriatic lesion exudation, the occurrence of lesions on visible parts of the body: face, head, neck, hands, and had greater pruritus. It should be emphasised that, in studying the relationship between stress and psoriasis, individual differences between patients and their ways of responding to stress, personal characteristics, are very important. Many researchers also point out that the onset of psoriasis and the awareness of living with the disease is a source of great stress for the patient. So stress influences the development of psoriasis, but living with psoriasis is also a severe source of specific stress. The stress of psoriasis is also associated with a disruption in the ability of the skin to perform its psychological functions properly [4,5,6].

Psoriasis must therefore be regarded as a disease that disrupts the skin not only on a physiological and morphological level, but at the same time interferes with its psychological functions, making it difficult or impossible for the sufferer to fulfil many important needs. The stress of psoriasis is therefore associated with a disruption in the ability of the skin to function properly psychologically. In terms of stimulus perception, psoriasis becomes a source of many unpleasant sensations, such as itching, pain, burning or hypersensitivity of the skin. It also impairs the communicative function of the skin by making other people avoid physical contact with the sick person, or the sick person himself avoids such contact for fear of negative reactions from other people, which can have a significant impact on the sick person's psychological state. Disruption of the aesthetic function performed by the skin contributes in psoriasis patients to an increased fear of negative judgement from others, feelings of rejection and stigmatisation, and an unfavourable self-image, especially if psoriatic lesions occur on areas of the body important for self-esteem, such as the face or genital area. Psoriasis can also interfere with sexual function, in which the skin is involved [5,6].

In a study by Gupta et al [7], almost half of patients with psoriasis declared that the disease had reduced their sexual activity. Several authors emphasise that disease-induced impairments in the realisation of the psychological functions of the skin can and should be recognised in terms of disability or incapacity. The chronic course of psoriasis means that the stress of the disease is present on a daily basis in the lives of patients in the form of physical complaints, negative emotions, unpleasant experiences in social situations, difficulties in work,

problems in interpersonal and intimate relationships and numerous limitations in daily functioning. As the difficulties and problems associated with psoriasis become most apparent in a social context, many authors refer to psoriasis-related stress as psychosocial stress [5,6,7].

In a study by Owczarek and Jaworski [8], patients' needs for improvement of quality of life in specific areas in patients were characterised according to the severity of psoriatic lesions. The results of the study indicated that patients with psoriasis had a reduced quality of life in several areas of functioning, such as overall quality of life and general health. Among the reasons for this were intrapsychic problems caused by the perception of one's own skin and an overall negative self-image. This is due to disturbing signals from the social environment that stigmatise the psoriasis patient. Patients with severe psoriatic lesions were significantly less satisfied with their lives than patients with moderate lesions. Decreased quality of life was evident in the physical, psychological, social and environmental spheres.

In contrast, a study by Lakuta et. al. [9] examined the relationship between psoriasis and depression. Research has indicated that psoriasis is highly stigmatising, and that misconceptions that psoriasis is contagious and infectious are common. In addition, the stigma associated with visible skin lesions and the unpredictability of the course of the disease places a strong psychological burden. The authors point out that patients often have to adjust their lifestyle, educational and occupational plans because of their disease. Many are grieving their plight before adjusting to life with the illness. Prolonged stress and exclusion develop psychiatric disorders, most commonly depression.

The aim of the study by Zięciak et. al [10] was to demonstrate the relationship between feelings of stigma and depressive symptoms in patients with psoriasis. The study took into account the severity of feelings of stigma and depressive symptoms, as well as factors such as gender and the visibility of skin lesions. This study also confirms that it is an ever-present task to change social attitudes towards people with psoriasis. Equally important is psychotherapeutic work with sufferers aimed at self-acceptance to overcome feelings of stigma and protect against depression. In addition, the authors emphasise that dermatologists should pay attention to depressive symptoms and the tendency to self-stigmatise in people with psoriasis, provide information about the course of the disease, treatment prognosis and prevention, which positively influences the perception of the disease and prevents negative psychological and social effects. So it can be seen how serious the problem of psoriasis is on many levels and in many aspects. Psoriasis affects both the physical, psychological and social spheres of the

patient, significantly reducing their quality of life and negatively affecting their functioning [11,12,13].

SUMMARY

Psoriasis is a dermatological chronic disease. Because it is a skin disease, it is associated with stigma. Psoriasis should be considered not only as a skin problem, but also as a psychological and social problem. Society still has a prejudice against psoriasis patients. This is because there is still insufficient knowledge of the subject. This attitude leads to the stigmatisation of sick people. Patients feel alienated, struggle with depressive disorders and exclusion. In addition, the accompanying stress exacerbates the skin lesions in psoriasis. The issue of psoriasis is complex. The issue of this disease needs to be normalised in society. Effective dermatological treatment must be implemented to help patients. Psychological care and support from loved ones are also important.

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Psychodermatology in acne vulgaris: new challenges and treatment options for dermatological patients

Przemysław Kubicki[1], Maria Greniuk[1], Joanna Grudniewicz[2], Jakub Cisek[1], Mateusz Mierniczek[1]

1. Medical University Piastów Śląskich of Wroclaw, Wroclaw, Poland
2. Pomeranian Medical University in Szczecin, Szczecin, Poland

Acne vulgaris is the most common disease of the sebaceous glands, associated primarily with overproduction of sebum. It affects 80-100% of people in the 11-25 age group. Characteristically, the onset of changes is observed during adolescence, but more and more often the disease affects adults as well, even >30 years of age. Lesions are localized in seborrheic areas - most often on the forehead, nose, chin, chest and back.

The purpose of this article is to draw attention to the serious need of psychological care of patients suffering from acne vulgaris. This is an issue that is often downplayed and overlooked. In the holistic care of the patient, all of the patient's needs must be met. The exact form of psychological help that should be provided for the patient needs to be discussed.

MATERIAL

The survey was completed by 126 people. There were 24 males who make up 19% of the survey group and 102 females who make up 81% of the survey group.

The group of respondents who completed the survey was divided into 4 age groups:

1. From 10 to 15 years old, which included 2 people, accounting for 1.6% of the total.
2. From 16 to 19 years old, in which there were 35 people, accounting for 27.8% of the total.
3. Between 20 and 25 years of age, there were 60 people, accounting for 47.6% of the total.
4. Over 25 years of age, in which there were 29 people, accounting for 23% of the total.

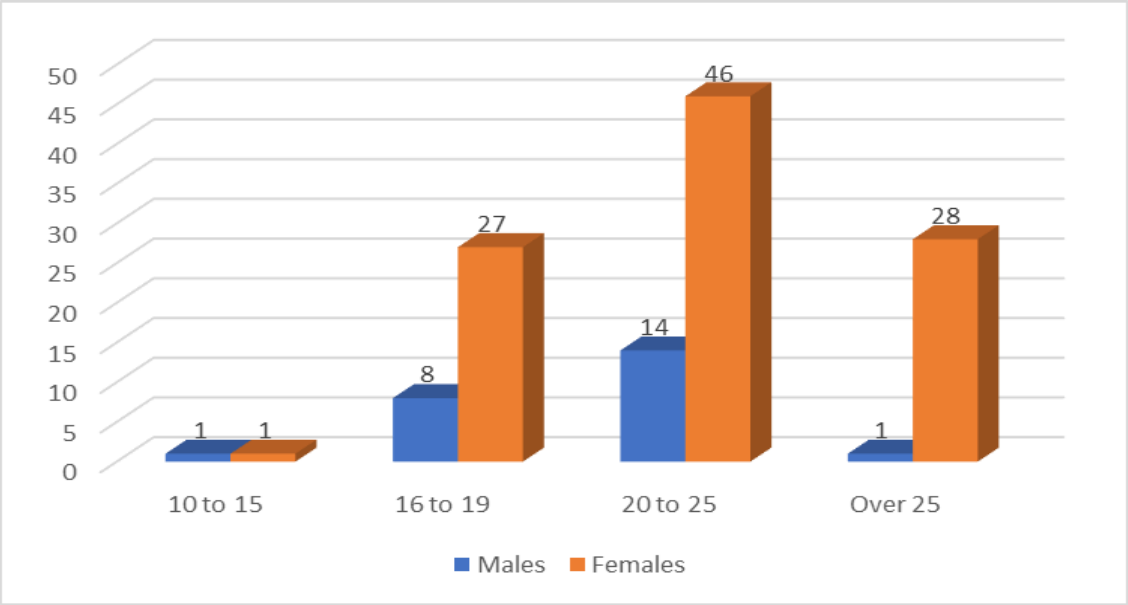

Figure 1. Age and sex of the respondents

METHODS

We included certain issues in the survey that did not allow the interviewees to qualify to a study group. The issue of mental health is related to many environmental as well as endogenous influences. Therefore, in order to obtain reliable information about mental health related solely to a dermatologic disease, the survey allows only a subset of respondents to qualify to the final group. Among the issues discussed were:

- Having a diagnosable mental disorder that is not related to a dermatologic disease. In this group, the answer "Yes" was marked by 8 people, representing 6.3% of the total. They were not qualified due to the possible overlap of two factors.
- Responders who reported mental deterioration during treatment with oral acne medications (including isotretinoin, spironolactone, and cyproterone acetate). These medications have a possible side effect of depression and/or mental deterioration [1], so there is a risk of overlap between the two triggers. Mental deterioration while taking any of the above medications was specified by 4 subjects, representing 3.17% of the total.
- Suffering from a dermatological disease other than acne vulgaris. There were 2 subjects, representing 1.6% of the total.

- 47 people, accounting for 37.3% of the total specified that dermatological disease has no effect on their mental condition.
- 1 person was not qualified because of other reason.

A total of 62 people, representing 49.2% of the total, were not qualified to the final group.

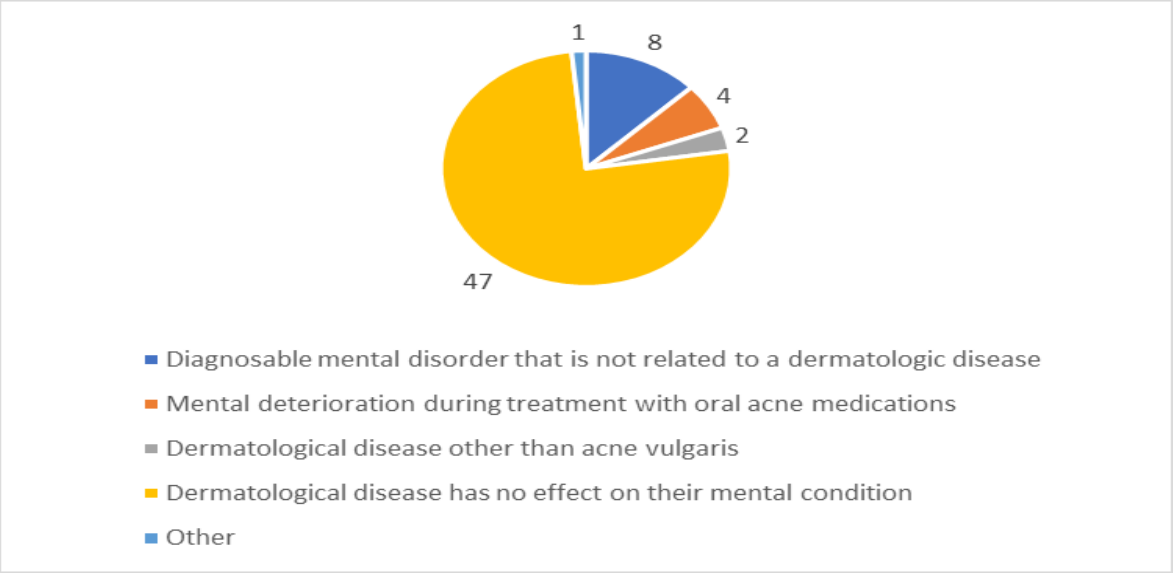

Figure 2. Respondents who were not qualified to the final group

The group of 64 individuals (representing 50.8% of the total) who were qualified for the final group are shown in figure 3.

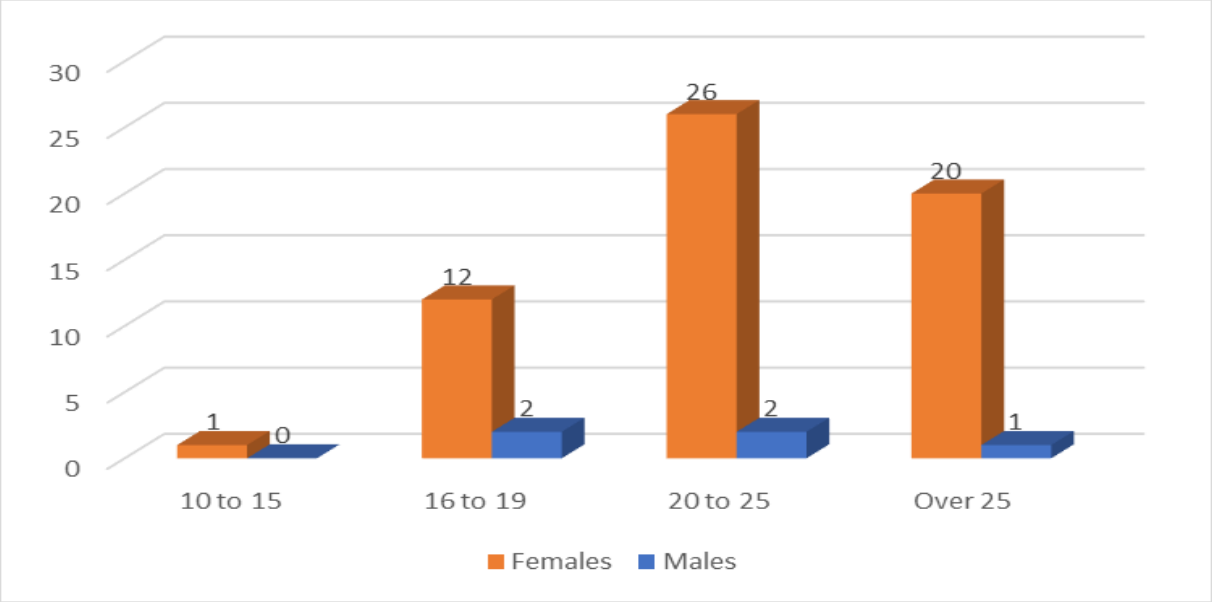

Figure 3. Final qualification of the respondents

In this study, our objective was to determine how patients suffering from a psychological disorder as a result of a dermatological disease, in our case acne vulgaris, cope with their mood deterioration. We addressed questions such as:

- Was help sought from a specialist (psychologist, psychiatrist)?
- Was support from loved ones substantial in dealing with mood deterioration?
- Was knowledge about acne and ways to deal with it sought from scientific sources?
- Was help sought on forums and websites bringing together a community that suffers from the same condition?
- Were visible skin lesions being covered even though it could worsen the state of the skin (e.g with excessive makeup or clothing that was not suitable for the weather)
- We also asked the participants if they had any other methods that help them.

At the very end we asked which way was the most helpful in the long run.

INTRODUCTION

Many factors contribute to the formation of acne. The essence of the disease is the excessive activity of the sebaceous glands, excessive sebum secretion and following inflammation of the hair follicle. Increased sebum secretion is influenced by hormonal balance (impact of androgens), genetic factors, as well as susceptibility to increased keratinization of hair follicle duct. This creates good conditions for the growth of anaerobic bacteria, including Cutibacterium acnes, which increase the inflammation around acne lesions. The second element of pathogenesis is a disorder of keratinization of the hair follicle duct and increased adherence of keratinized scales. This leads to a narrowing, and later complete blockage of the hair follicle duct [2]. The following clinical forms are distinguished:

- **Comedonal** - On the face, especially on the forehead and cheeks (the so-called T-zone), there are numerous open and/or closed comedones. It is characterized by the presence of seborrhea and early onset (even around 9 years of age).
- **Papulopustular** - In addition to single or multiple comedones, inflammatory lesions in the form of papules and pustules are present. The lesions may be localized besides the face, on the back and on the frontal surface of the chest. The severity of the lesions varies, sometimes the face is minimally involved or remains unchanged and more severe lesions occur on the back.

- **Nodulo-cystic** -Initially, there are inflammatory nodules and tumors that weep and break through to the outside, forming channels and fistulas. They exude purulent, bloody or purulent-bloody discharge, sometimes in large amounts. These lesions later progress into scarring, usually atrophic and pitted.
- **Scar** - Scarring formed as a result of acne lesions.

The face is usually the first part of the body that draws attention to itself. Acne can negatively affect the perceptions of third parties. The effects on the psychological zone can severely impact quality of life to a similar degree as is seen in people with asthma, epilepsy or arthritis. Young adults and adolescents with acne have higher levels of anxiety, depression, and significantly lower self-esteem than healthy individuals. That is the reason why we focused on the group of people between 10 and 25 years old [3].

RESULTS

- Results of assessing the severity of lesions and determining the type of acne in the subjects. We asked acne patients to subjectively rate the severity level of their skin lesions on a scale of 1 to 10. The most numerous group were acne patients whose severity level was described as 5. The next most numerous group described the severity level of their lesions as 3. The severity level described as 7 was the third most frequent. This is shown in Figure 4.

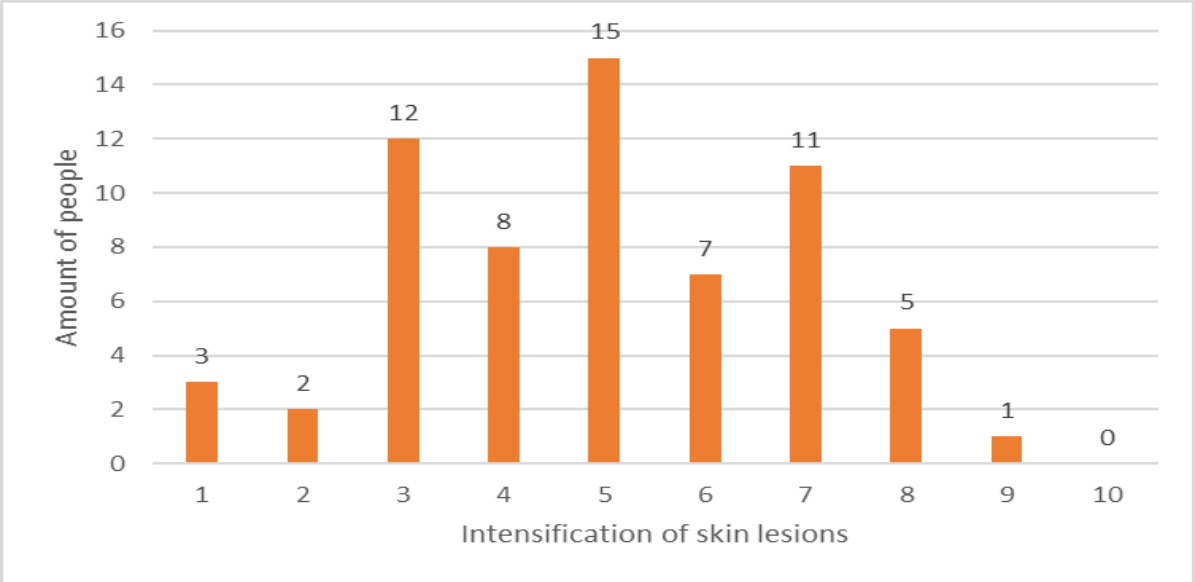

Figure 4. Assessment of lesion severity in the study group of acne vulgaris patients

In the group of patients suffering from acne vulgaris we distinguished patients with different types of acne. The most numerous group are patients with papulopustular acne. The whole group is presented in Figure 5.

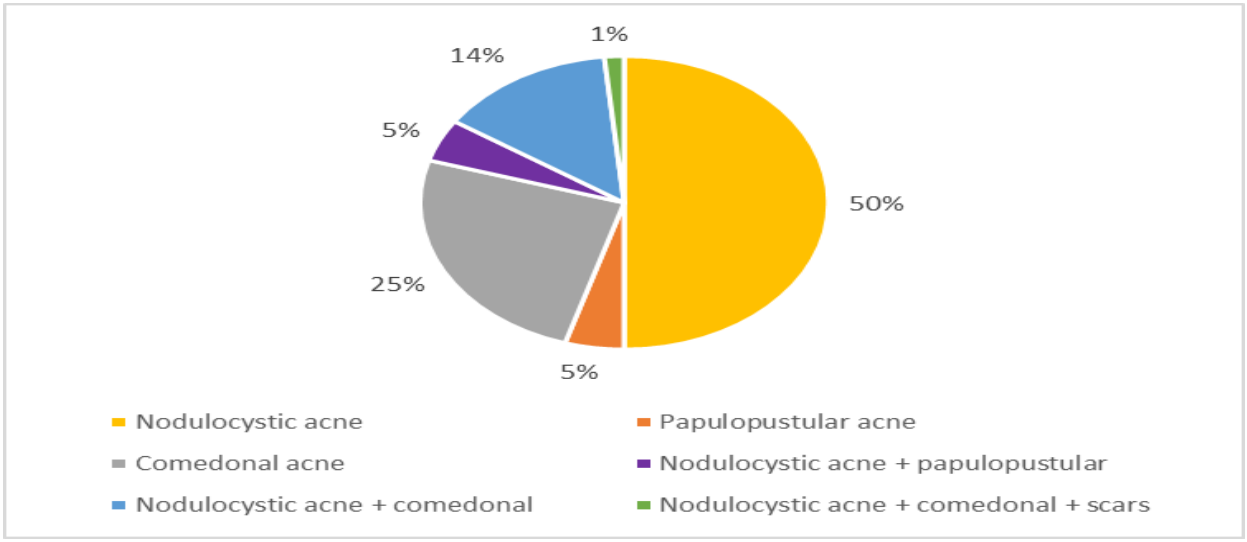

Figure 5. Varieties of acne vulgaris in the study group

- Results identifying the stage of illness at which the most noticeable mental deterioration occurred. The entire data is presented in Figure 6.

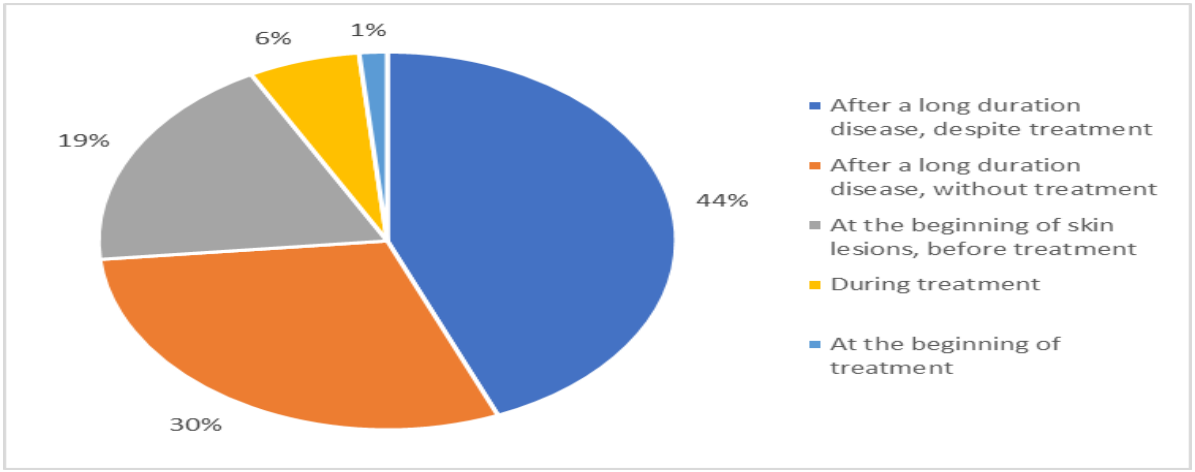

Figure 6. Stage of illness with most noticeable mental deterioration

In the group of patients studied, the most noticeable mental deterioration occurred most frequently in the long-term patients who used medication, followed by the long-term patients who did not use treatment. In the third place, it occurred at the beginning of the illness

period. The least populous group is those reporting significant mood deterioration at the beginning of treatment. The entire data is presented in Figure 6.

- Results indicating whether individuals who report mental deterioration have reached out for specialized help. Among the patients surveyed, the vast majority did not seek the help of a mental health professional. The second most patients chose to see a psychologist and the least patients chose to see a psychiatrist. Detailed data are presented in Figure 7.

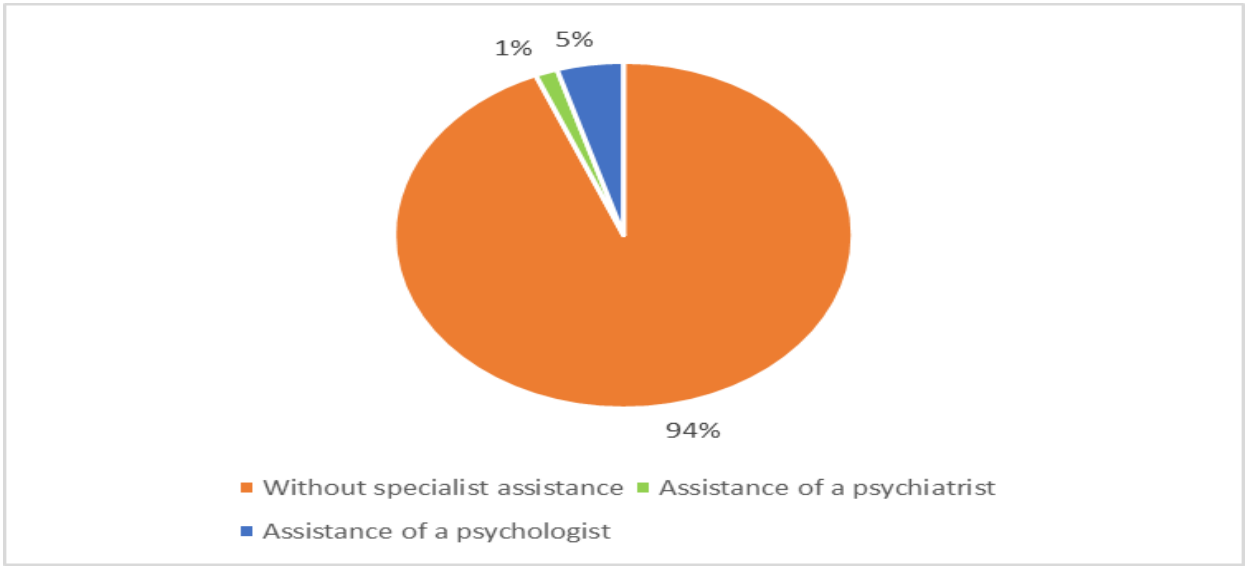

Figure 7. Use of a mental health professional among respondents

- Results indicating the use of loved one support. Most patients specified that they benefited from the support of loved one's (family, friends, colleagues).

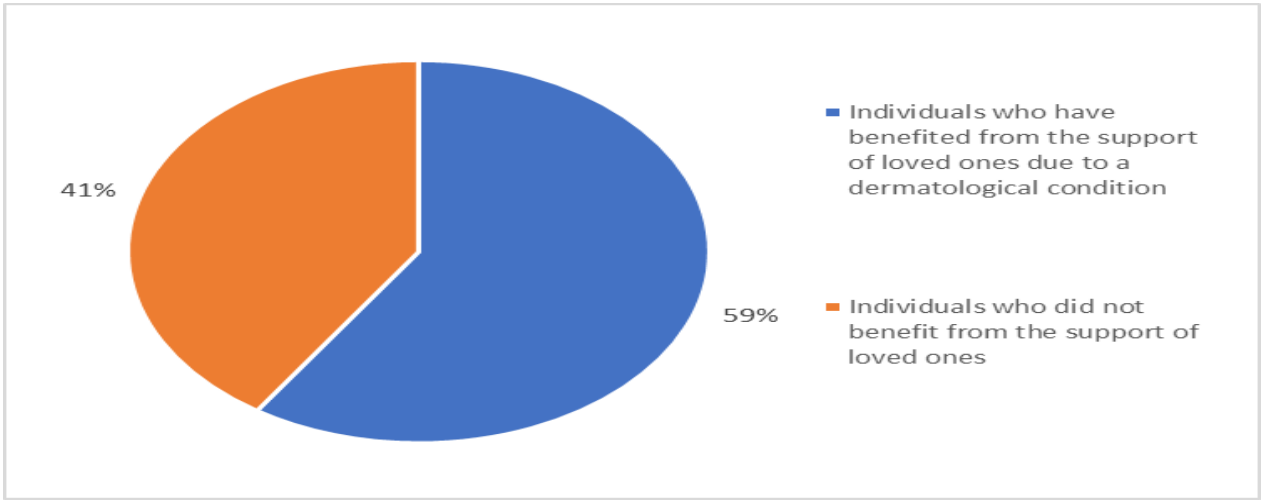

Figure 8. Support from loved ones when mental health deteriorates due to dermatological disease

- Results identifying outreach in the form of education and support of individuals in community forums. The vast majority of respondents sought knowledge about the dermatological disease from educational portals and acne patient portals. Additionally, support from other patients from online forums also proved to be a way of coping with mental deterioration. Detailed data are defined in Figure 9.

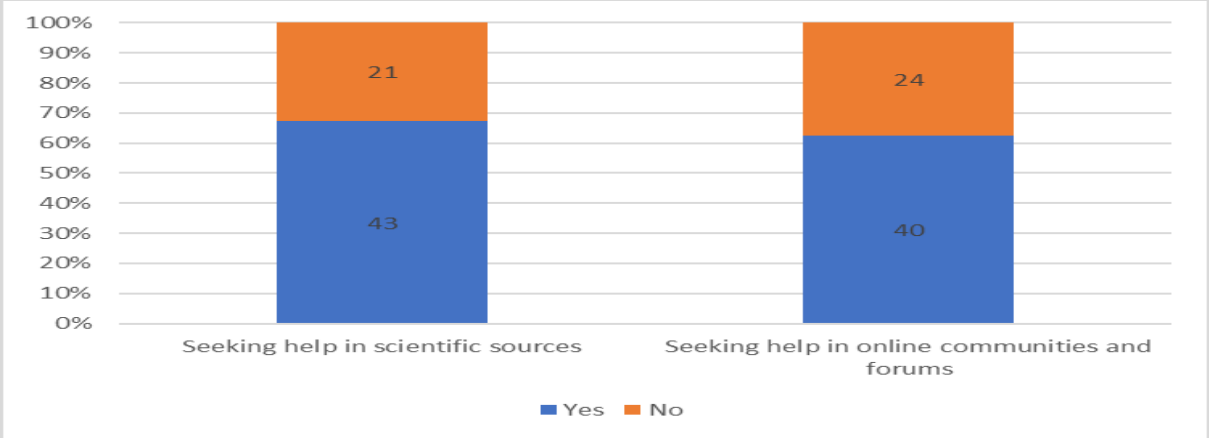

Figure 9. Outreach and education in scholarly sources and community forums

- Outcomes indicating the level of excessive covering of skin lesions as a result of mental deterioration due to dermatological disease. In the vast majority of subjects, excessive covering of skin lesions (e.g., thick layer of opaque makeup, clothing unsuitable for the weather) occurred in the situation of mental deterioration. Few individuals did not practice such behavior. Detailed data are presented in Figure 10.

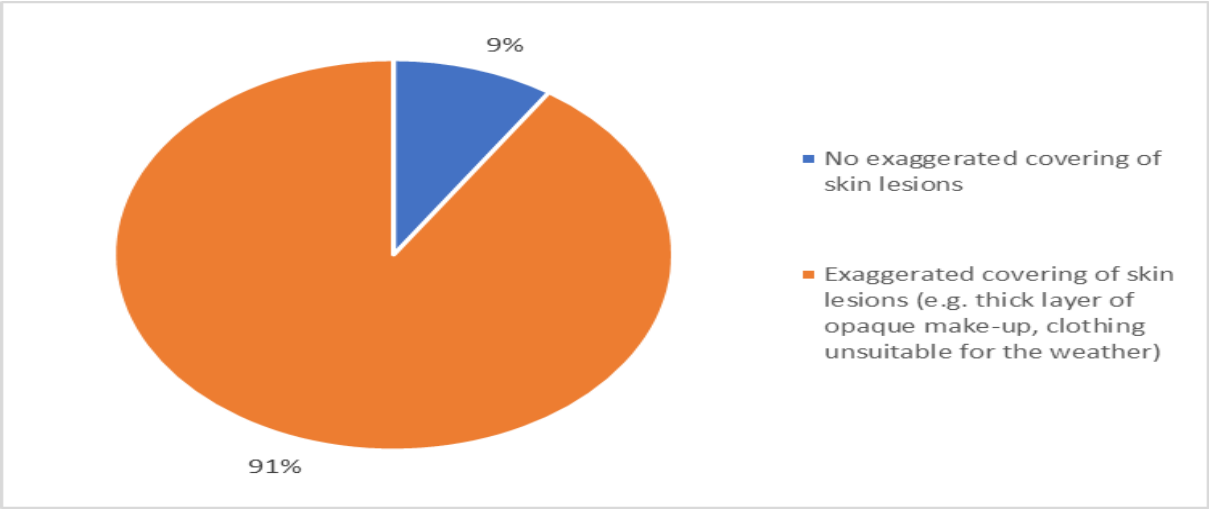

Figure 10. Excessive covering of skin lesions when mentally aggravated due to dermatological disease

- Outcomes that determine the long-term benefits obtained through specific forms of coping with mental deterioration caused by dermatological disease. The most frequently chosen form of coping with mental deterioration was covering skin lesions. In second place was the support of loved ones, then help from a specialist (mainly dermatologist). Individuals indicated education, help on social forums and scientific sources, and forms of coping defined as other or individual. The entire data is presented in Figure 11.

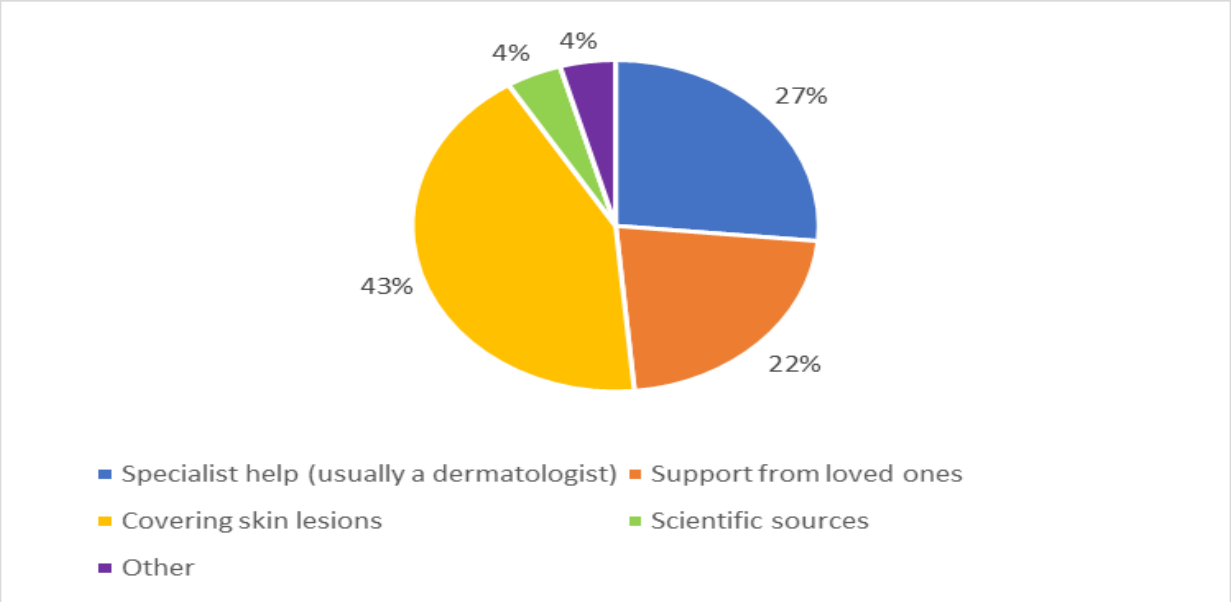

Figure 11. Declared most beneficial methods for improving mental health in the long term

DISCUSSION

In the 21st century, there are still harmful myths about acne in society that can cause mental deterioration for sufferers. One of them says that acne and its severe forms occur only in people whose diet is not one of the healthiest. Although there are indications that chocolate, fast food with high amounts of saturated fatty acids, and excess protein can aggravate acne, no evidence has been found of an effect of these dietary choices on the possibility of acne aggravation or appearance [4]. Another myth that unfairly categorizes acne sufferers is the belief that sufferers always have a problem with personal hygiene [5]. Such unfair treatment and perception of acne sufferers has a negative impact on patients. Therefore, according to the theory of the "butterfly effect", a significant increase in public awareness of issues related to

the causes and pathophysiology of acne, may bear fruit in the future and contribute to the elimination of circulating myths, which will reduce the level of stress in patients and improve their psychological state [5].

The most frequently chosen method of acne management, as shown in Figure 11., was covering skin lesions with cosmetics. Thus, cosmetic preparations containing benzoyl peroxide or salicylic or azelaic acid do indeed have a positive effect in acne therapy [6]. However, there are a large number of cosmetics on the market containing substances such as isopropyl palmitate, isopropyl isostearate or cocoa butter, which have proven comedogenic effects [7]. Therefore, unconscious use of cosmetics such as lipsticks, roses or foundations, which in their composition contain comedogenic substances, contributes to the aggravation of acne symptoms. Therefore, it is recommended to use appropriate cosmetics prescribed by a dermatologist, which, in addition to their aesthetic function, have a therapeutic effect [8].

Covering up skin lesions as the most common method of coping with acne indicates not only the choice of an inappropriate therapeutic method, but also addresses a deeper, more multidimensional problem. The results of the study conducted by Magdalena Kostyła and colleagues indicate that if the patient consciously chooses clothing or makeup to cover lesions in front of the environment, at the same time he experiences a higher intensity of certain psychopathological symptoms [9]. Acne impairs social functioning [10]. May impair interpersonal relationships, as a result of impaired self-esteem, social stigma or harmful stereotyping [11]. A recent study published by researchers at the University of Limerick in Ireland found that the social stigma of people with acne, reduces their quality of life [12]. Acne severity was significantly correlated with health-related quality of life and stigma was, according to this study, a significant reason for the association.

In the world of social media and mass culture, expectations for perfect, flawless skin are even higher. Editing photos and using photo filters that hide the natural appearance of skin only exacerbates the problem. In a survey we published, 40 out of 64 respondents sought psychological support for their skin lesions online (Figure 9) According to demographic data, one social media platform "Instagram" currently has 1.21 billion users, of which 30.1% are between the ages of18-24 (375 million people) [13]. Unfortunately, despite the unimaginable opportunities offered by such media, including finding factual help, joining support groups, these individuals may have also been exposed to the dangers of the virtual world. Juxtaposing one's image with artificially idealized faces may have caused feelings of inadequacy, alienation, otherness, illness, and exacerbated psychological problems associated with acne. Thus, there is

a real need to normalize people with acne online. Online 'acne-positive' movements encourage people to embrace and destigmatize acne. One of them is '#freethepimple' campaign founded by Lou Northcote in 2018 [14]. It is based on taking un-retouched, no make-up photos of oneself and sharing them with the others, which should encourage others to act in the same way. It is hoped that more social campaigns like this will be created in the future, helping to improve the mental state of acne patients.

Although acne is not a disease that can directly lead to death, it has been shown to have a significant impact on the occurrence of higher levels of stress, anxiety disorders, social phobias, depression or even suicidal thoughts [15]. More importantly, acne lesions occur in the vast majority of people under the age of 25 (Figure 4), that is, during the period of adolescence, broadly defined, when a person has not yet developed effective ways of coping with stress [10]. In addition, higher levels of stress were shown to exacerbate skin lesions by a mechanism involving CRH stimulating excessive lipid production by sweat glands [16]. Stress can also delay wound healing by up to 40%, which can prolong the time it takes for inflammatory changes in the course of acne to become visible on the face [16]. This creates a kind of "vicious circle" in which skin lesions adversely affect the psychological state and stress levels, contributing to the exacerbation of skin complaints [17]. It was also found that 55% of acne patients who developed red papules on their skin had a history of stressful situations up to 2 days prior to the appearance of skin lesions [18].

Depression and suicidal thoughts are another significant issue affecting patients with dermatologic diseases including acne. It is estimated that depression may occur in 8% to 60% of patients undergoing dermatologic treatment [19,20]. The literature also mentions that patients with acne represent one of the four groups of dermatology patients at highest risk for suicide [10].

According to the results of our questionnaire, the most noticeable mental deterioration occurred most often in the long-term patients who were using medications (Figure 6). Due to the exclusion of those taking oral medications from the study group, this was the group using topical treatment. This method of treatment correlates with the fact that the majority of the study group were subjects with moderate acne papulopustularis (Figure 4 and Figure 5), and topical treatment is the treatment of choice in this case. The recommended topical treatments for acne vulgaris are antibiotics (clindamycin and erythromycin) used for no longer than 12 weeks. Because of the risk of developing antibiotic resistance, combination treatment with benzoyl peroxide or topical retinoids is now recommended [21]. The effectiveness of the therapy is

estimated at 60-80% [22]. In addition, topical treatment of acne vulgaris is very rarely associated with the occurrence of adverse effects such as redness, flaking of the skin. On the contrary, in addition to the therapeutic effect, they exert a nurturing effect due to the bases contained in the ointments [23]. What, then, explains the deterioration of patients' psychological status despite the high efficacy of treatment and the low risk of adverse effects that may exacerbate skin lesions and psychological symptoms? This has to do with adherence and compliance in acne treatment. Recent studies show that adherence is responsible for a successful treatment plan and prevention of relapse or treatment failure. Additionally, it has been proven that there is a relationship between depression and treatment satisfaction among acne patients and the impact of satisfaction on adherence [24].

Patients with dermatologic diseases reported that family physicians and dermatologists often overlooked or underestimated the psychological aspect of skin lesions [25]. Additionally, recent research suggests that those working in medical settings should be aware of the links that exist between mental health problems and their higher prevalence in patients with skin conditions [25], so that early attention can be given to symptoms of mental disorders. Therefore, a holistic view of the patient and joint action of various specialists, including a psychologist in the aspect of stress management, a psychiatrist in the treatment of mental disorders and a dermatologist in the treatment of skin lesions, may facilitate and accelerate the therapeutic process [18].

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PAPA syndrome treatment as a challenge of the current medicine

Eliza Mędrek, Paulina Zegarska

3rd year medical students, Cardinal Stefan Wyszyński University in Warsaw, Faculty of Medicine, Collegium Medicum, Warsaw, Poland

INTRODUCTION

PAPA syndrome (pyogenic sterile arthritis, pyoderma gangrenosum and acne) (OMIM #604416), a rare autosomal-dominant disease caused by mutations in proline-serine-threonine phosphatase interacting protein 1 (*PSTPIP1*) gene. It is a disorder associated with disturbances in cytoskeleton formation [1]. It presents in the first decade of life with episodes of painful arthritis, severe cystic acne in early adolescence and pyoderma gangrenosum (PG). It is categorised as an autoinflammatory condition due to chronic or recurrent inflammation, which is correlated with dysregulation of the innate immune system [2,3,4.] The syndrome can be misdiagnosed as autoimmune or immunodeficiency conditions [5]. The syndrome is characterised by dysfunction of neutrophil cells and neutrophil extracellular traps (NETs). Enhanced formation and decreased clearance of NETs is a cause of macrophage activation and progression of inflammation [6]. PAPA syndrome manifests as severity of skin lesions [3,4,6]. It is observed that patients have elevated levels of neutrophil serine proteases and antimicrobial proteins, such as myeloperoxidase (MPO), neutrophil elastase (NE) and lactoferrin. That indicates neutrophil cell death and/or neutrophil activation [6,**7**]. The PAPA syndrome is one entity within *PSTPIP1*-associated inflammatory diseases (PAID).

CLINICAL FEATURES OF PAPA SYNDROME

The phenotype caused by single gene mutation is fever, sterile pyogenic arthritis, pyoderma gangrenosum (PG) and cystic acne, but it has heterogenous presentations [8]. Additional manifestations are splenomegaly [9,10-12,13] and inflammatory bowel disease [9, 10,14,15]. Arthritis includes mainly one joint such as elbow, knee and ankle, and is painful and recurrent [16,17]. It is characterised by neutrophilic infiltrate and usually occurs in childhood [17,18,19]. Involvement of shoulders, hips, and metacarpophalangeal, metatarsophalangeal

joints and cervical spine joints has also been described. Joint involvement manifests itself in radiographic patterns as an erosive arthritis, osteophyte formation, diffuse joint narrowing, subchondral sclerosis and cyst formation, reactive new bone formation, with significant bone overgrowth and joint deformity or destruction with ankylosis [20,21]. In young adults, cutaneous manifestations could have many phenotypes. Pathergy phenomenon can occur in PAPA syndrome and is characterised by the development of pustules and non-healing ulcers following minor injuries in childhood and early adolescence. Acne and PG start in adolescence and can last into adulthood. PG manifests as single or multiple painful skin ulcers. Patients with PAPA syndrome have varying degrees of acne vulgaris, usually a severe nodulocystic type involving the face and upper back [20]. In adult onset of the disease symptoms are mainly skin malformations and arthritis, which were seen in half of patients [9].

PATHOGENESIS

PAPA syndrome is an autosomal dominant disorder. It is caused by various mutations on chromosome 15q24-25.1 [9,22]. The most significant role in PAPA syndrome pathogenesis is in the proline-serine-threonine phosphatase interacting protein 1 (*PSTPIP1/CD2BP1*) gene [6,21]. Pathogenic mutations comprise p.A230T, p.E250Q, p.E256G, p.D246N, and p.D266N [23]. PAPA syndrome is caused by incomplete penetrance and variable expression of pathogenic variants [20]. Adult onset of the PAPA syndrome is more common in rare cases without genetic mutations [9]. The gene mutation is responsible for augmentation of the binding capacity of CD2-binding protein 1 (CD2BP1) with pyrin, which causes an increase of caspase 1 and production of IL-1 [24]. PAPA mutations were found in *PSTPIP1*, *A230T* and *E250Q* and *E250K* which are placed. in the F-BAR domain [17,22,25]. Hyperphosphorylation of *PSTPIP1* leads to activation of the inflammasome and IL-1B release, which eventually causes an inflammation [17,26,27]. Overproducing of IL-1β is not yet elucidated. Two possible explanations have been postulated. The first in which a hyperphosphorylated PSTPIP1-pyrin interaction triggers activation of the inflammasome. The second which comprises the same association, but it leads to activation of pyroptosome that triggers an increased pyroptosis, a caspase-1-dependent inflammatory form of programmed cell death [20].

PSTPIP1 is a cytoskeletal protein. It serves as a scaffold in purpose to bind cellular proteins, like pyrin, protein tyrosine phosphatases, c-Abl, CD2, and Wiskott– Aldrich syndrome protein (WASP). The role of PSTPIP1 is to regulate IL-1B release, cytoskeleton organisation,

cell migration and T cell activation [17,28,29]. Yet, pathogenesis is not understood completely. The severity of the disease is dependent on mutation location within the *PSTPIP1* gene. The spectrum is called PSTPIP1-associated inflammatory diseases (PAID) [13,28]. The inflammation can spread to various organ systems.

TREATMENT OF PAPA SYNDROME

PAPA syndrome is an inflammosomopathies which requires a cost-effective treatment for prolonged periods of time. The excessive activation of the inflammasome in PAPA syndrome finally leads to an increased production and release of IL-1. It is important cytokine crucial in the innate immunity response and the subsequent production of other downstream inflammatory mediators [29]. A patient needs are usually addressed by combine therapies, which can provide simultaneous inhibition of inflammatory mediators and the best quality of life to the patient with minimal adverse effects [30]. The early cases of PAPA syndrome were mostly treated with systemic or intra articular corticosteroids, non-steroidal anti-inflammatory drugs or antibiotics. But effects of treatment were variable [17,20]. It is confirmed that anakinra is an effective drug in treating PAPA syndrome. This drug reduces NETs formation and stands for a prominent role of IL-1 signalling in this syndrome [6]. Patients with milder onset of the disease may be treated with anakinra. More severe cases require a combination of anti-IL-1 and anti-TNF medication or triple therapy such as anti-IL-1, anti-TNF and glucocorticoid medication in order to control inflammation [6,7,13,28]. Due to the rare onset of PAPA syndrome and other PAID spectrum syndromes, guidelines of treatment have not been determined [5,13,17]. The available treatment is IL-1β antagonists and TNF-α inhibitors. Other anti-inflammatory medication is intended only for treatment failures. Dual therapy is reported rarely and in combination with steroids [5,13,31]. Case reports also indicate the possibility of safely using a combination of adalimumab with tacrolimus for PAPA syndrome [5]. A similar approach was used in the treatment of PG, acne, suppurativa hidradenitis (PASH) throughout the PAID spectrum. It comprises infliximab and cyclosporine. It may indicate that the combined use of TNF-α inhibitors and calcineurin inhibitors may lead to satisfactory treatment results of PAID spectrum symptoms [5,27]. According to other findings therapy of PAPA syndrome based on anti-TNF-a antagonists, like etanercept, adalimumab and infliximab is effective [17,23,32,33]. Whereas response to anakinra, anti IL-1 agent is variable, but better in joints manifestation of PAPA syndrome [17,22,34]. Joint type can be treated also by corticosteroids.

Yet in this case treatment could intensify acne [17]. Surgical procedure is also available for joint form of the disease. It can be drainage and /or intra-articular corticosteroid injections. If patient display joint destruction it is possible to apply joint replacement, synovectomy and arthroplasty [9]. It has been proven retinoids are effective for severe acne [17]. Kolios et al. [35] reported treatment with canakinumab of five patients with idiopathic, steroid-resistant PG. They applied a standard dose of 150 mg s.c. in two-to three injections. A clinical improvement was observed in four patients. According to them, canakinumab had good tolerability and was the cause of improvement of life quality. The good response to treatment with canakinumab in non-syndromic PG was validated in /other case-reports [29,36,37]. Other targeted therapies include therapies aiming at T-cell function (alefacept) and at the pathogenetic cytokines IL-6 (tocilizumab) and IL-23 (ustekinumab) [38-42].

PAPA syndrome can be treated with both systemic and intra-articular corticosteroids. Additionally, Sardana et al. notify a patient with PAPA syndrome who experienced a remission with a combination of minocycline, dapsone, deflazacort and methotrexate [20,42].

SUMMARY

On account of complicated pathogenesis of PAPA syndrome special caution should be taken during the course of diagnosis, especially in case of sterile areas of recurrent inflammation. PAPA syndrome could be easily misdiagnosed. It is difficult for physicians to identify PAPA syndrome, the most when it is the adult onset of the disease. The syndrome should definitely be considered if the patient presents one of the classical triad of symptoms (arthritis, PG, acne) [9]. In patients who present antibiotic-resistant arthritis and/or pyogenic skin manifestations, familial history and molecular analysis of the PSTPIP1 gene should be definitely obtained [27]. Because of the rarity of the disease, no controlled trials are available and there are no standardised treatments for PAPA syndrome [20]. That is why the PAPA syndrome is still a great challenge for current medicine.

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SELECTED PROBLEMS IN PSYCHIATRY

Borderline personality disorder – life prospects and suicide risk

Monika Nowak, Arkadiusz Jaworski, Dominika Ziółkowska, Wiktoria Lewicka, Katarzyna Skała, Julia Bilska

Student Research Group at the Chair and Clinic of Psychiatry, Faculty of Medicine, Wroclaw Medical University, Wrocław, Poland

INTRODUCTION

Borderline personality disorder (BPD) also known as emotionally unstable personality disorder (EUPD) is characterised by severe functional impairments, distorted sense of self, strong emotional reactions, a high risk of suicide, a negative effect on the course of depressive disorders, extensive use of treatment and high costs to society. BPD typically begins by early adulthood and occurs across a variety of situations [1]. The causes are not yet clear, but genetic factors and adverse life events seem to interact to lead to the disorder. Neurobiological research suggests that abnormalities in the frontolimbic networks are associated with many of the symptoms [2]. This disorder is associated with suicidal behaviors and self-harm. Up to 10% of BPD patients will die by suicide [3].

BPD is associated with a wide range of psychopathology, including unstable mood, impulsive behaviors and unstable interpersonal relationships [4]. Also self-harm behaviors (for example non-suicidal self-injury – NSSI) are common. NSSI usually presents as superficial cuts to the arms and wrists. Neverthless NSSI is not suicidal in intent. Patients with borderline personality disorder cut themselves because of problems with emotional regulation and they want to reduce painful inner states [5]. Cutting relieves emotional tension, but does not reflect a wish to die. What is very important - BPD patients have a mean of three lifetime suicide attempts, mostly by overdose. However, even when potentially fatal overdoses occur, patients with BPD often contact people who are in a position to intervene. While medications cannot cure BPD, they may be used to help with the associated symptoms (for example selective serotonin reuptake inhibitors and quetiapine). Severe cases of the disorder may require hospital care [3]. Since there is no evidence that hospitalization prevents completion, an ambulatory approach to the management of chronically suicidal patients may be most useful [6]. Borderline

personality disorder is a huge challenge of the current medicine and it is very important to treat the patients and to reduce the number of suicides and because of it to increase the life expectancy of them.

EPIDEMIOLOGY

Borderline personality disorder (BPD) is a relatively common condition - an estimated 1% of the general public suffers from it [7]. The prevalence of BPD varies between different populations. It depends on the country an individual hails from and their socio-economic status as well as other factors [8]. For example, it's significantly lower in some groups like the elderly and higher in others: psychiatric patients. BPD is diagnosed more commonly in female than male patients, with the female to male ratio being 3:1 in a clinical setting [9], however some studies show that the lifetime prevalence of BPD is not significantly different and occurs with similar frequency for both sexes and equals 5,9% [10].

The results of the clinical research conducted in the United States indicate that BPD is most frequently present among psychiatric patients (20%) [7] and around 6,4% of urban primary care patients, that number being significantly higher than the 1% estimated for the general population [8]. Findings from the same research show that half of BPD patients reported not receiving mental health treatment in the past year and around 40% of them were not recognized by their primary care physician as having emotional problems.

Diagnosis of BPD seems to be problematic for clinicians considering how widely prevalent it is. The reason for that might be that BPD frequently meets the criteria of many other personality disorders. Despite many efforts from the psychiatric community, this issue continues to significantly impact BPD patients' lives. Especially considering increased suicide rates compared to the general population. Worth mentioning is a fact that co-occurring psychiatric disorders are common in patients with BPD, which can lower their life expectancy and quality even further. Epidemiologic research aimed to estimate the population prevalence of DSM-IV personality disorders found that 84,5% of individuals with BPD have at least one comorbid mental disorder [10]. This comorbid disorder is often major depression, PTSD, or substance abuse [11].

Borderline Personality Disorder is linked to higher rates of self-harm and suicidal behavior when compared with the general population. Increased rates of substance abuse also lead to increased mortality rates in patients with BPD by causing accidental deaths i.e. overdoses. Furthermore, this risk also increases in cases where patients live in a highly stressful

environment or have trouble with self-regulation [3]. Meta-analysis of BPD linked suicides show that out of 1179 patients selected from eight different studies 94 of those committed suicide [12]. Based on various research up to 10% of patients suffering from BPD die by suicide and the most effective evidence-based treatment methods that could help prevent that are specifically designed psychotherapies rather than hospitalizations [3]. Many BPD patients have suicidal thoughts and attempt suicide a number of times before they take their life. Suicides in BPD occur later on in the course of the illness, usually around the age of 30 and after long courses of unsuccessful treatments [3]. Considering how early in a patient's life this condition develops correct diagnosis and holistic treatment are of the utmost importance.

ETIOPATHOGENESIS

There are several hypotheses of BPD etiology and pathogenesis, but it must be emphasized that the exact causes are not known yet. They can be grouped into: genetic, neurobiologic, psychosocial and environmental factors. The disease is due to a combination of those components [13].

Genetic twin studies, and other that included interviews, estimated a heritability of BPD approximate to 0,7. The disease also aggregates in families [14]. However, studies of genetic factors didn't find gene variants that would be specific enough for BPD, but the genome-wide association study concluded a genetic overlap with bipolar disorder, schizophrenia, and major depressive disorder. It referred to genes encoding proteins important in neural processing: myelination and neural cells adhesion, such as DPYD - encoding dihydropyrimidine dehydrogenase, PKP4 -encoding plakophilin 4 and SERINC5 - encoding serine incorporator 5. This genetic overlap raises a question of how relevant are transdiagnostic features in BPD [13,14,15]. Single candidate gene association studies results so far have not shown significant effect sizes, primarily because BPD is a complex disease [15]. However, several studies conclude that serotonin (5-HT)1A receptor alleles and MAO-A alleles are risk factors for BPD, due to changes in serotonin availability. Other important potential alterations include single nucleotide polymorphism (SNP) in the dopaminę transporter, polymorphisms in genes encoding μ-opioid receptors and CACNA1C (gene encoding calcium voltage-gated channel-Alpha1 C, which is important in proper mitochondrial functioning; alterations in their actions are associated with increased ROS which negatively impact on stress resilience and immune cells [16]. One study, which used an imaging-genetics approach, assessed the role of Brain Derived Neurotrophic Factor (BDNF) genetic variants in modulating amygdala habituation.

The results implicated that BDNF 66 Met allele was associated with impaired amygdala habituation (which is hypothesized to be an endophenotype for BPD) [15]. The interactions between psychosocial factors (especially traumatic childhood events such as sexual and physical abuse) and genetic factors are assumed to be crucial in developing BPD symptoms. Those include epigenetic alterations associated with early-life maltreatment, such as methylation of BDNF (encoding brain-derived neurotrophic factor) and MIR 124-3, where the latter is encoding a factor important in regulation of neural plasticity and function of amygdala [14]. Another alterations in gene variants, reported mostly in people who experienced adverse childhood events, include polymorphisms in stress response genes associated with HPA axis activity, such as FKBP5 (co-chaperone of the glucocorticoid receptor complex, which modulates intracellular glucocorticoid signaling) and the CRHR1 and CRHR2 (corticotropin releasing hormone (CRH) receptors). Changes in those genes were also reported as a risk factor for depression, which suggest overlapping pathophysiology of BPD and MDD. Impairment of HPA axis activity leads to alterations in amygdala-hypothalamus two-way interactions, rise of cortisol levels and finally problems with affect regulation [14,15]. A study examining gene-environment interactions as a predictor of the risk to develop the categorical, clinical diagnosis of BPD found that people with risk alleles of Tryptophan Hydroxylase I (TPH1) gene and history of abuse had higher risk of BPD [15]. Another studies concluded that polymorphisms of genes: catechol o-methyltransferase (COMT) and 5-HTTLPR ss/sl modulated the effect of stressful life events on impulsivity and aggression [15].

Neurobiologic mechanisms leading to BPD include many alterations in functioning of structures like amygdala, anterior cingulate cortex, prefrontal cortex and specific neural circuits, but also in hormone levels, neurotransmitters and their receptors, gut microbiota and prenatal events [14,16,17]. Various researches used imaging techniques to determine those variations. Volumetric MRI (Magnetic Resonance Imaging) revealed smaller volume of the frontal lobes, amygdala, hippocampus, gray matter in the cingulate cortex, medial PFC (prefrontal cortex), bilateral OFC (orbitofrontal cortex), bilateral middle temporal gyri, right inferior frontal gyrus and parietal cortex (including precuneus). Conversely – relatively a greater volume was observed in some regions which include: right basolateral nucleus of the amygdala (which is correlated with more severe BPD symptoms), right supplementary motor area, right cerebellum (lobules IV,V) and right middle frontal gyrus (including dorsolateral PFC) [17]. Microstructural abnormalities in white matter tracts in PFC, low prefrontal-limbic connectivity within the affect regulation circuit were also demonstrated. Alterations of specific brain circuits underlie the phenotypes of BPD [14]. DTI (Diffusion Tensor Imaging) reported lower fractional anisotropy

in the genus, anterior corpus callosum, orbitofrontal white matter tracts, anterior portion of the cingulum bundle and fornix. Fractional anisotropy measures the direction of water diffusion in white matter tracts [17]. Functional neuroimaging, like ERP (Event-Related Potentials) revealed a lower amplitude and longer latency of P300 wave, a smaller error-related negativity amplitude (which may represent the reduced ability to monitor impulsive actions) and lower amplitude feedback-related negativity (it reflects a reduced capacity to incorporate information about decisions to inform future choices). PET (Positron Emission Tomography) studies observed lower glucose metabolism in the medial OFC, cuneus and hippocampus, bilateral frontal regions, PFC, caudate nucleus, lenticular nucleus, thalamus, right frontal premotor cortex, right ventral striatum, temporal pole, fusiform gyrus, posterior cingulate cortex and higher metabolism in the ACC (anterior cingulate cortex) and superior and inferior frontal gyri. Some trials used PET to assess differences in activity of specific brain regions during tasks, like aggression provocation - patients with BPD were more aggressive and showed greater glucose metabolism in the OFC and amygdala. Tests including script-driven imagery of abandonment or trauma revealed less blood flow in ACC and OFC. Functional Magnetic Resonance Imaging (fMRI) showed that anterior neural centers can be more functionally interconnected with the amygdala during the perception of negative emotional stimuli; brain regions involved in cognitive control, especially the dorsal ACC, inferior frontal gyrus, and inferior parietal sulcus were less activated during cognitive reappraisal. Other studies including fMRI observed lower activity in frontal brain regions, involved in cognitive control, in the presence of negative emotions on trials requiring behavioral control. Dysfunction in brain networks involved in self-referential mental activity, like less connectivity between the PFC and cingulate cortex, may influence affective perceptions of pain, which is possibly responsible for physically self-injurious behavior [17]. Magnetic resonance spectroscopy revealed reduced NAA (N-acetylaspartate) and alterations in creatine concentration in amygdala (which can be responsible for neuronal necrosis due to inappropriate energy metabolism), higher total NAA and glutamate concentrations in the left ACC, and lower NAA in the bilateral DLPFC (dorsolateral prefrontal cortex). Those shifts in amygdala, ACC and DLPFC may contribute to problems with emotional and cognitive control [14,17]. More important abnormalities in hormone levels, in patients with BPD, include higher cortisol, decreased oxytocin and lowered melatonin. The first hormone is crucial in the „glucocorticoid cascade hypothesis", which says that early-life trauma leads to cortisol alterations which finally affects hippocampal volumes. This stress hormone may also affect the integrity of uncinate fasciculus and subregions of the corpus callosum. The levels of the second hormone are particularly lower in patients with a history of early-life maltreatment

and disorganized attachment representations. Oxytocin decreases cortisol's negative stress-related effects. Melatonin impacts the circadian cycle, inflammatory response and proper mitochondria functioning. It should be also mentioned that testosterone concentrations are increased, which is related to impulsive-aggression, and estrogen modulates BPD symptoms (inter alia via suppression of serotonin), which levels, as we know, change during menstrual cycle. Some data suggest higher comorbidity of BPD with endometriosis [14,16,17]. Major alterations in neurotransmitters comprise dopamine levels – which are linked to increased impulsivity, and serotonin levels – associated with comorbid depression, suicidal behaviors, mood symptoms, poor sleep and even increased risk of chronić migraine [16]. Reduced levels of endogenous opioids and opioid activity plays a role in chronic dysphoria, lack of a sense of well-being and self-injurious behavior [18]. Important aspects of BPD pathoetiology, which require further studies, are prenatal and maternal factors, as well as gut-microbiome and mucosal immune system. Prenatal stress, suboptimal prenatal factors and maternal dysbiosis may contribute to gut dysbiosis and increased gut permeability, which therefore provides increased circulating LPS, oxidative stress and pro-inflammatory cytokines. It should be pointed out that the gut has an influence on amygdala development. The latter drives the development of the cortex, brain reward system, and also plays a crucial role in BPD symptomatology [16]. Childhood trauma is most commonly mentioned psychosocial factor in BPD etiology, but it is not always present [13]. It should be pointed out that the importance of psychological aspects, especially childhood abusement, can be overvalued in BPD etiology and may mask the importance of biological factors [16]. Sleep dysfunction and drug abuse are also common features in BPD. Although they are presumably a result of BPD symptoms, dredging those factors may drive the self perpetuating cycle of BPD symptom dimensions [19].

Future research in BPD pathogenesis is urgently needed to provide novel and effective treatment options – especially targeted pharmaceuticals. From all aforementioned factors, trials on the role of gut microbiome and prenatal events are particularly under-explored and need large prospective randomized trials [16].

SYMPTOMS

The features of the disorder may be organized into three dimensions [20]: impaired relatedness (unstable relationships with others, identity disturbance, and chronic emptiness), affective dysregulation (affective lability, excessive anger, and efforts to avoid abandonment), behaviour dysregulation (impulsivity, suicidality, and self-injurious behaviour). BPD can also

present as multiple vague somatic complaints, high-risk sexual behaviors, binge eating, or chronic pain [21]. However, the core features of BPD are instability of interpersonal relationships, negative self-image, and affect, as well as marked impulsivity [13].

Patients with BPD can experience repeated and marked mood changes throughout the course of a single day. Periods of euthymia can alternate with episodic dysphoria (depression, anxiety, irritability). Angry outbursts are often followed by feelings of shame, guilt and worthlessness [13]. Moreover, patients often interpret neutral events, words, or faces as "negative" [22,23]. Thus, the patient is prone to misinterpret relatively minor disagreements or adverse events as a sign that the caretaker wants to terminate the relationship. The patient often reacts with anger or threats of self-harm, which can alienate the support person, who then may really want to end the relationship [13]. This is one of the reasons for stormy relationships between the patients and people who are close to them [24]. Additionally, patients with BPD rigidly classify people as all good or all bad. A friend may be viewed as an ideal person, and then can suddenly be seen as cruel and betraying. For example the patient can highly appreciate a clinician and then reverse this opinion when an appointment needs to be rescheduled or another perceived rejection occurs [25]. This phenomenon has been labeled "splitting" [26].

Self-injurious behaviour is characteristic of patients with BPD and is sometimes referred to as the borderline patient's "behavioral specialty" [27,28]. This type of behaviour includes impulsivity that is potentially dangerous (e.g., excessive drinking, high-risk sexual activity), deliberate self-injurious behaviour (e.g., superficial cutting or burning), suicide attempts, and completed suicide. In addition, patients can suddenly quit a job that they need or end a relationship that has the potential to last, thereby sabotaging their own success. Impulsivity in the sexual realm can have important utility or meaning to the patient (eg, helping to relieve inner tension or feeling loved following a recent real or perceived interpersonal rejection). Although the patient may be regretful of their behaviour afterwards and may even appreciate its potential dangerousness, they may find it very difficult, if not impossible to resist the urge to repeat the behaviour [13].

BPD is strongly associated with suicidal behaviours [29-31]. This risk increases during the course of the disorder [31], in the presence of psychiatric comorbidities [32]. In a study of inpatients with BPD, Soloff and colleagues reported that the comorbidity of borderline personality disorder and major depressive episode increased the number and seriousness of suicide attempts. They also identified impulsivity and hopelessness as independent risk factors for suicidal behavior in patients with comorbid BPD and major depressive episode [33].

DIAGNOSIS

For recognising Borderline Personality Disorders (BPD) are used criteria included in The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). At least five of nine following criteria need to be met for confirmed diagnosis of BPD.

1. Chronic feelings of emptiness.
2. Emotional instability in reaction to daily events (e.g., dysphoria, irritability, or anxiety usually lasting a few hours, rarely more than a few days).
3. Identity disturbance: markedly and persistently unstable self-image or sense of self.
4. Frantic efforts to avoid real or imagined abandonment.
5. Impulsivity in at least two areas that are potentially damaging for the patient (e.g., spending monay unreasonable, sex, substance abuse, reckless driving, binge eating) (Different than suicidal and self-inflicted injury behavior covered in criterion 6.)
6. Recurrent suicidal behavior, gestures, theatrical behaviour or threats, self-mutilating behavior.
7. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
8. Creating and maintaining unstable and intense interpersonal relationships characterized by extremes between idealization and devaluation.
9. Transient, stress-related paranoid ideas or severe dissociative symptoms [13].

Studies in which enrolled 201 patients, demonstrated frequency of each criterium. The efforts are shown in graph (Fig. 1).

One of the challenges of met diagnosis is to differentiate between Borderline Personality Disorder (BPD) and Bipolar Affective Disorder (BD). Depressive symptoms have an earlier onset in BPD than BD. BDP patients present less mixed or manic symptoms. Another distinctive criterion for Bipolar Affective Disorder is characteristic maniac symptoms. BPD patients more often are negative about others and self, more often have problems in relationships. Also oftenly they show lack of adaptation to regulating emotions and a sense of instability. Personal trait patients' with BPD is impulsivity, for BP patients impulsivity is one of state. Common items BPD and BP are for example depressive and anxious symptoms, suicidal ideation and various abnormal personality traits and traumatical memories from childchood [34].

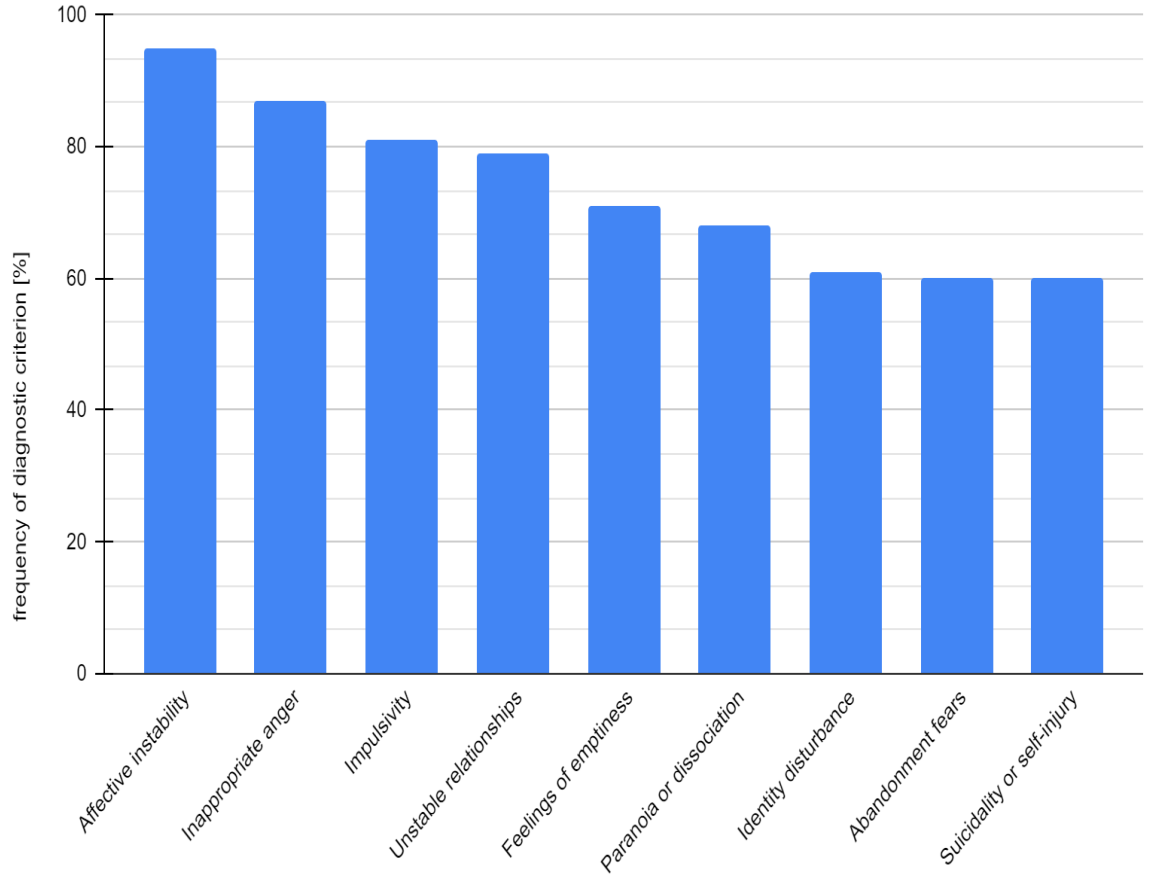

Figure 1. Graph created by authors, based on information from article [13]

TREATMENT

Treatment for people with borderline personality disorder involves psychotherapy, which is the first line of treatment, and pharmacotherapy as an adjunct. Treatment should be comprehensively developed and based on the needs of the individual, profit and loss assessment. The plan should be developed together with the patient.

Psychotherapy

Psychotherapy focuses on the ongoing functioning of the patient independently and in relationships in sociaty. Psychoeducation of both the patient and his family and relatives is an important element of treatment. We can distinguish several forms of psychotherapy used in working with BPD people

- Dialectical behavior therapy
- Mentalization-based therapy

- Transference-focused therapy
- "Good psychiatric management"
- Cognitive and behavioral therapies
- Systems Training for Emotional Predictability and Problem Solving (STEPPS)
- Schema-focused therapy [35].

Pharmacotherapy

The results of drug treatment studies in borderline personality disorder vary. Low doses of antipsychotics, mood stabilizers and antidepressants in some study groups gave positive results [36]. Studies are difficult to evaluate because there are few studies on each drug individually, which makes it difficult to draw firm conclusions [37]. Certain symptoms such as anger, anxiety, depression, and impulsivity can be treated with medication with positive results. However, there is a lack of research and results in the short and long term [37].

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What is Dissociative Identity Disorder?

Arkadiusz Jaworski, Zuzanna Marczyńska, Natalia Olesińska, Joanna Batko, Karolina Koszyczarek, Izabela Kudaj, Zuzanna Kuźniar

Faculty of Medicine, Students' Scientific Group at the Department of Psychiatry, Medical University Piastów Śląskich of Wroclaw, Wroclaw, Poland

INTRODUCTION

The International Statistical Classification of Diseases and Health Problems ICD-10 defines dissociation as "partial or complete loss of integration between memories, sense of identity, sensory impressions and motor control" [1]. An extreme example would be dissociative identity disorder, formerly known as multiple personality disorder. It is characterized by the presence of at least two different identities or personality states, each with its own established patterns of perceiving the world, establishing relationships, and thinking about itself [2]. The individual personalities are usually unaware of coexisting with others, and are also devoid of insight into information acquired when other personalities exercised control over the patient [3]. Interestingly, psychiatric,neurological and neuroimaging studies show differences in brain function depending on the currently dominant personality [2].

Dissociative disorders as a separate disease entity were first identified in 1980 with the creation of the Diagnostic and Statistical Manual of Mental Disorders (DSM) classification [4]. Currently, the prevalence of DID is put at 1% [5]. This diagnosis often co-occurs with depression, psychosomatic disorders, post-traumatic stress disorder, as well as in patients who enter into conflicts with the law and use psychoactive drugs [5,6].

HISTORY

According to Carlson (1986), the American physician, Benjamin Rush (1812), was probably the first author to use the concept of dissociation. He used it, however, for patients that Americans of that era called "flighty," "hairbrained," or "a little cracked;" patients who were probably suffering from manic attacks or schizophrenic excitement.

In France, Moreau de Tours (1845) was probably the first to use the concept of dissociation per se. In his experimental studies of the psychological effects of hashish, he concluded that „the action of hashish weakens the will-the mental power that rules ideas and associates and connects them together. Memory and imagination become dominant; present things become foreign to us, and we are concerned entirely with things of the past and the future." In France the concept of dissociation became linked with hysteria and hypnosis. Following the Marquis de Puységur (1751–1825), they observed patients who talked about themselves in the third person while in a state of induced or artificial somnambulism - as deep hypnosis was then known.

With regard to "natural" and induced somnambulism, Gros Jean (1855) remarked: We have seen in the same individual two simultaneous streams of thought: the one which formed the ordinary person, the other which occurred outside of him. We are in the presence of only the second person [in somnambulism]. The other remains asleep, exhausted. Because of this, it is impossible for the ordinary person to remember upon awakening anything of what has taken place during his attack (access). Such is the nature of the perfect somnambulism.

By 1887, the concept of dissociation was encountered in the work of Frederic Myers , in England, and of Charcot, Gilles de la Tourette and Pierre Janet, in France. Myers (1887) sought to show how far the dissociation of memories, faculties and sensibilities could go in multiple personalities without resulting in chaos. Charcot remarked that "by reason of the easy dissociation of mental unity, certain centers may be put into play without the other regions of the psychic organ being made aware of it and called upon to take part in the processes". Gilles de la Tourette (1887) used the concept to describe the abolition of certain senses in hysterical patients: they are dissociated from the patients' normal mental state.

Although the concept of dissociation had been described earlier, Pierre Janet was the first to show clearly and systematically how it is the most direct psychological defense against overwhelming traumatic experiences. He demonstrated that dissociative phenomena play an important role in widely divergent post-traumatic stress responses which he included under the 19th-century diagnosis of hysteria. His dissociation theory is outlined here as a background for Janet's specific studies of trauma, it is based on nine concepts developed or elaborated by Janet: psychological automatism, consciousness, subconsciousness, narrowed field of consciousness, dissociation, amnesia, suggestibility, fixed idea, and emotion [7].

Some new interest in the theory of dissociation appeared after the Second World War along with a restoration of interest in the study of hypnosis. A great interest in psychoanalysis after the First World War led to a forgetting of its origins at the French school in Salpetrière, where S. Freud studied in 1885–86 in J. M. Charcot. He saw the personality as composed of three parts, the id, ego and superego. According to Freud's vision, "dissociated states" are elicited by the repression of the libido energy which is of a sexual nature [8].

Paul Federn (1952), an Austrian-American psychologist saw the personality being composed of numerous parts. He called these parts, "ego states" because he observed that we take our ego with us when we change states. Federn shared his concepts of ego states with Edoardo Weiss, who likewise shared his understanding of ego states with John Goodrich Watkins. It was Watkins and his wife Helen who developed Federn's concept of multiplicity within the personality, into a therapeutic approach (Watkins & Watkins, 1997), which is known today as Ego State Therapy [9].

J.G. Watkins and H. Watkins emphasized that humans have an innate resolution of the mind into parts (divisibility), and the psyche is complex in many ways. The Watkins model emphasizes the horizontal nature of dissociation - the separated states of "Ego" are in relation to each other in the horizontal plane [10]. The authors believe that there is a continuum of dissociation. Normal development occurs at one end of the continuum, and dissociation is a natural adaptive phenomenon in which the child learns to segregate and differentiate experiences. This produces separated ego-states, i.e. organized systems of behavior and experience, the elements of which are linked together by a common principle, and which are separated from other states by borders that are more or less permeable. At the other end of the continuum, we can see the pathological outcome of trauma in dissociative personality disorders in which the ego states have developed separately and the boundaries between them are impervious [11].

Onno van der Hart, Ellert Nijenhuis, and Kathy Steele (2006) integrated Pierre Janet's concepts with subsequent trauma research and contemporary psychobiological knowledge and created a theory of the structural dissociation of personality. According to the authors, structural dissociation is a permanent division of the personality as a result of a traumatic situation, which results in the lack of integration between the psychobiological systems that make up the personality. An important element of this theory is the description of the internal dynamics between these systems (referred to as dissociative parts). These dynamics are largely

characterized by a tendency to avoid contact between these parts, which leads to the maintenance of structural dissociation [12].

The authors distinguish between two types of dissociated self states:

1. "Apparently Normal Personality" (ANP), which is focused on today's everyday life;
2. "Emotional Personality" (EP), which is fixated on the trauma in the past and is a defensive system aimed at the threat.

In simple PTSD there are only two dissociated self states - one ANP and one EP, the so-called primary structural dissociation. In complex PTSD, borderline and dissociative disorders, there is one ANP and more EPs (so-called secondary structural dissociation).

In dissociative identity disorder (DID), there are more than one ANP and more than one EP (so-called tertiary structural dissociation). Lowering the ability to integrate in dissociative identity disorders and the need to deal with everyday life causes the need for more dissociated self-states [10].

ETIOPATHOGENESIS

Multifactorial etiology of the disease leads to many conceptual models of pathogenesis of DID, but the exact way how disease is formed is not known. Those models include trauma model and fantasy model [13]. Developmental traumatization is a widely accepted primary etiologic factor [14]. Large-scale studies and clinical series confirmed a link between experienced child abuse and DID [15,16,17]. The most important contributors are early severe physical, sexual and emotional abuse, especially where a caregiver is a persecutor and attachment figure simultaneously [18]. Other etiological factors that occur in parallel with childhood trauma and may exacerbate the risk and contribute to development of DID, are genetic predispositions to dissociate, neurobiological alterations, cognitive disturbances and sociocultural factors [14,19,20]. The latter strongly influence the development and phenomenology of DID so clinical manifestations in different cultures can vary drastically [21]. Abuse and neglect from a relative lead to distorted attachment pattern, which can also entail alienation and loneliness. The proposed mechanism is that dissociative identities form as an adaptive reaction to repetitive traumas and isolation, as they may provide reduction of psychological pain [13,14]. Besides severe abuse, subtle forms of dysfunctional communication, such as parental emotional unresponsiveness, can lead to poor parent-infant attachment and promote development of DID [22].

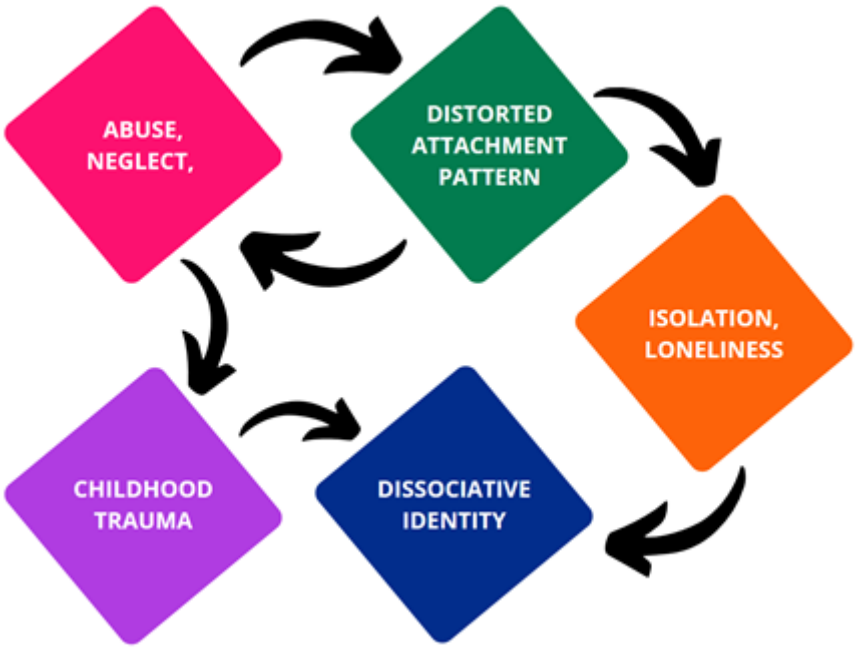

Figure 1. Possible pathomechanism leading to DID

Fantasy model assumes that symptoms of DID develop due to the patient's fantasy proneness, suggestion, enactment associated with social expectations and even iatrogenic, psychotherapeutic suggestions. This model can be detrimental for patients by increasing the risk of misdiagnosis and misdirected treatment, and can also hinder the research in the field of dissociative disorders [23]. Enormity of data support the trauma model and more important are neurobiologic differences between patients and healthy controls (e.g. lower hippocampal volume) [24,25,26].

SYMPTOMS

According to diagnostic criteria based on DSM-V, symptoms of DID include the presence of "two or more distinct personality states" as well as "recurrent gaps in the recall of everyday events, important personal information, and/ or traumatic events" [2]. The complete DSM-V criteria can be found in the "Diagnostics" section of this article.

In the course of DID, additional personalities called alternatives (Alter) are revealed. According to many researchers their formation is conditioned by a strong trauma in childhood and adolescence [27,28]. Their function is to protect the primary personality (Primary Person) from experiencing trauma, or later on from its memories. Thus, the main symptom of DID -

dissociation occurs. Dissociation is described as a self-hypnotic state in which current events and the thought process run separately from consciousness [28].

At the time of experiencing trauma the patient dissociates and leaves their consciousness, which allows the memory of it to be placed in the subconsciousness, which can later result in formation of a separate personality. Later on dissociation most often takes place in response to triggers, such as recalling the experienced trauma, but also the presence of factors that are associated with it. Those can be images, sounds or even colors. Therefore dissociation is a defense mechanism, allowing the Primary Person off of reliving painful memories, as it is replaced by an alternate personality [28]. During dissociation, the Primary Person may experience a gap in memory or time as the personalities may not have any access to each other.

There is no rule as to how many Alters can be created. Each personality evolves separately at different times. Typically each Alter is complex and has its own behavioral patterns. They can be of a different age, gender, and even race than the Primary Person [15,29].

Symptoms of dissociation may also occur in other mental diseases, according to the DSM-V diagnostic criteria they are borderline personality and PTSD [2,30]. Moreover, cases of dissociation in schizophrenia [31], eating disorders [32] and obsessive-compulsive disorders [33] have been described. In addition, these disorders may present other symptoms found in DID. These are among others:

- flashbacks
- insomnia
- nightmares
- headaches
- loss of time and space
- fragmented and/or missing memories
- mood swings and emotional instability [28].

DIAGNOSTICS

In this monograph criteria for diagnosis of DID are derived based on either The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or The International Classification of Disease, Eleventh Revision (ICD-11). Therefore, any further details are limited in its scope to derivatives of those two.

Criteria for the diagnosis of DID according to DSM-V:

A. "Disruption of identity characterized by two or more distinct personality states, which may be described in some cultures as an experience of possession. The disruption of marked discontinuity in sense of self and sense of agency, accompanied by related alterations in affect, behavior, consciousness, memory, perception, cognition, and/or sensory-motor functioning. These signs and symptoms may be observed by others or reported by the individual.
B. Recurrent gaps in the recall of everyday events, important personal information, and/or traumatic events that are inconsistent with ordinary forgetting.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The disturbance is not a normal part of a broadly accepted cultural or religious practice. Note: In children, the symptoms are not better explained by imaginary playmates or other fantasy play.
E. The symptoms are not attributable to the physiological effects of a substance (e.g., blackouts or chaotic behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures)" [2,6].

In order to diagnose DID according to ICD-11, it is necessary to confirm presence of:

1. "Disruption of identity characterized by the presence of two or more distinct personality states (dissociative identities), involving marked discontinuities in the sense of self and agency. Each personality state includes its own pattern of experiencing, perceiving, conceiving, and relating to self, the body, and the environment.
2. At least two distinct personality states recurrently take executive control of the individual's consciousness and functioning in interacting with others or with the environment, such as in the performance of specific aspects of daily life (e.g., parenting, work), or in response to specific situations (e.g., those that are perceived as threatening).
3. Changes in personality state are accompanied by related alterations in sensation, perception, affect, cognition, memory, motor control, and behaviour. There are typically episodes of amnesia inconsistent with ordinary forgetting, which may be severe.
4. The symptoms are not better accounted for by another mental disorder (e.g., Schizophrenia or Other Primary Psychotic Disorder).
5. The symptoms are not due to the effects of a substance or medication on the central nervous system, including withdrawal effects (e.g., blackouts or chaotic behaviour

during substance intoxication), and are not due to a Disease of the Nervous System (e.g., complex partial seizures) or to a Sleep-Wake disorder (e.g., symptoms occur during hypnagogic or hypnopompic states).

6. The symptoms result in significant impairment in personal, family, social, educational, occupational or other important areas of functioning. If functioning is maintained, it is only through significant additional effort" [34].

ICD-11 introduces several important changes as for DID compared with ICD-10. That includes recognizing each alter identity/dissociative part of a personality as a "subsystem of the personality" as a substitute than a complete personality. Some alters may be partially integrated with each other. They can have co-consciousness and share memories or emotions in the present. ICD-11 states that at least two identities need to function in daily life. The naming was also amended from a Multiple Personality [35].

Screening tools were invented but they cannot provide a definitive diagnosis of Dissociative Identity Disorder. We have a Dissociative Experiences Scale [36] or SDQ-20 [6]. They are designed to exclude individuals who are unlikely to suffer from a Dissociative Disorder and to highlight those who should have a clinical interview, like the Dissociative Disorders Interview Schedule or Structured Clinical Interview for Dissociative Disorders. A Dissociative Disorders Interview should confirm or deny a definitive diagnosis of Dissociative Identity Disorder or another Dissociative Disorder.

The Dissociative Experiences Scale measures different types of dissociation, including problematic and normal dissociation experiences. It is a screening tool for dissociative disorders: Multiple Personality Disorder and Other Specified Dissociative Disorder. The scale consists of 28 questions about inner experiences of a patient [36].

An example of another screening tool is The Somatoform Dissociation Questionnaire (SDQ-20) for Dissociative Identity Disorder and other Dissociative Disorders. It is a questionnaire that measures physical symptoms found to be common in people with Dissociative Disorders, including DID and Other Specified Dissociative Disorder. Symptoms like psychogenic blindness, insensitivity to pain, tunnel vision, auditory distancing [35,37].

TREATMENT

The treatment of Dissociative Identity Disease is multidisciplinary and is based on psychotherapy and pharmacological therapy. Both types of treatment should be combined and

customized depending on the patient's symptoms and needs. It is also very important to carefully plan the treatment.

Before discussing forms of therapy, goals of it should be highlighted. First of all it is important to establish safety, stabilization and the reduction of symptoms. That is beacuse many patients with DID present suicidal ideation and self-injurious behavior [38]. This goal can be achieved by educating patients about diagnosis and symptoms, and explaining the process of treatment [39]. It is also important to reframe the DID as a positive, rather than a negative, which might help establish trust in the therapist [40]. Then the treatment should focus on confronting and working through traumatic experiences which might be connected with alternate identities. The last goal of treatment is identity integration and rehabilitation [38].

The most common approach is psychodynamic psychotherapy with steps that help to achieve goals indicated above. Recent studies show that trauma-focused cognitive behavioral therapy and dialectical behavioral therapy are effective [38]. The cognitive behavioral therapy helps to communicate with the alters and find coping strategies other than switching between the personalities. The patient should be taught how to do relaxation exercises and how to gain control over cognitive distortions [41].

Another, less common approaches are hypnosis which allows access to alternate identities that are not present in the session and Eye Movement Desensitization and Reprocessing (EMDR) [41]. EMDR might change traumabased distortions in self-representation, increase linkages to adaptive materials, enhance the development of new behaviors by enabling the patient to process traumatic experiences and their triggers and facilitate the integration of processed traumatic material into alternate identities [39].

When it comes to pharmacological treatment it can be used to target certain symptoms that patients with DID have. The most common medications are those for post-traumatic stress disorder and mood disorders [41]. There are several drug groups that are used in DID treatment depending on the symptoms. As for now, there has not been any treatment preventing dissociation [40].

Antidepressants and anxiolytics, such as selective serotonin reuptake inhibitors, tricyclic antidepressants or monoamine oxidase inhibitors are used to stabilize a patient's mood, reduce hyperarousal and anxiety. Benzodiazepines might be used to reduce anxiety but they also might exacerbate dissociation, which is why they should be prescribed with particular caution. Beta blockers and clonidine have been found effective with stabilizing mood and reducing hyperarousal and anxiety as well as atypical antipsychotics. Reducing nightmares

might be achieved by using prazosin, while naltrexone can reduce the risk of self-injury behavior. Carbamazepine and other mood stabilizers can help with aggression, hyperarousal and intrusive symptoms [40].

CONCLUSIONS

Dissociative identity disorder is a rare psychiatric disorder, which definitely affects many aspects of a patient's life. As described by ICD-10 “partial or complete loss of integration between memories, sense of identity, sensory impressions and motor control” with an often coexistence of other mental disorders (such as schizophrenia, PTSD, depression) is a condition which needs a lot of attention. Psychotherapy, as one of the main ways of help, with an addition of psychiatric drugs (such as anxiolytics, antidepressants) can lead to improvement of a patient's condition. The pathophysiology of DID and its connection with abuse or traumas from the past can not be forgotten. It is often necessary for the person with dissociative identity disorder to face their own traumas from the past, manage to deal with them and cope with stress. Psychologists’, psychotherapists’ and psychiatrists’, teamwork can improve the quality of life of the patient.

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Current knowledge about amphetamine and its derivatives impact on mental health

Hubert Sawczuk, Julia Marschollek

Faculty of Medicine, Students' Scientific Group at the Department of Psychiatry, Medical University Piastów Śląskich of Wroclaw, Wroclaw, Poland

INTRODUCTION

Amphetamine was first identified more than a century ago. It was initially a medicine that was widely accessible without a prescription as a cure-all for a variety of diseases. Its therapeutic uses are now limited to attention deficit hyperactivity disorder (ADHD) and narcolepsy [1].

The use of amphetamines may have a variety of behavioral, hormonal or psychological effects. Both euphoria and an enhancement in memory and focus are brought on by it, along with psychosis and physical weariness that may even result in suicidal attempts. Regular use may result in increased heart rate, blood pressure and cortisol release, as well as an increase in locomotor activity and stereotyped behavior. The effects vary according to the frequency and dosage of drug use [2].

Additionally, a variety of amphetamine derivatives, including methamphetamine, 2,4,5-trimethoxyamphetamine (TMA), 2,4,5-trimethoxyamphe-tamine (TMA), and 3,4-methylenedioxyamphetamine (MDMA, ecstasy), are used for non-medical uses. After marijuana, amphetamine is the substance with the second-highest global consumption [3].

Poland is among the biggest importers and exporters of amphetamine and its derivatives [4].

The abuse of amphetamine and its derivatives is a widespread issue that has recently gotten worse due to the creation of ever-newer designer drugs and their sale on the black market. Therefore, it is important to pay attention to how it affects people's mental health [5].

RELATION BETWEEN INCREASED NUMBER OF MENTAL HEALTH ISSUES AND USE OF AMPHETAMINE AND ITS DERIVATIVES

It is commonly established that long-term usage of stimulants like amphetamine can lead to psychosis in people [6-13]. Moreover, research on amphetamine addicts has revealed that amphetamine can cause non-psychotic people to fall into psychosis [6,9,11]. Elevated risk of substance-induced psychosis is connected with frequency of stimulant use, as determined by a high number of years of daily stimulant use or a diagnosis of stimulant dependency [14].

McKetin et al. (2019) [15] conducted a meta-analysis that focused on amphetamine use and its effects on mental health. Due to their resemblance and the difficulties separating their self-reported use, both methamphetamine and amphetamine were included in the study. Accordingly, ecstasy and other stimulants were excluded. It was found that amphetamine use is a significant contributor to poor mental health. There is an increased risk of:

- psychosis (hallucinations, delusions, psychotic diseases),
- violence (perpetration only),
- suicidality (suicidal thoughts, attempts, and fatalities),
- depression

with any utilisation of amphetamines. Additionally, acute poisoning can trigger excitement and panic and it is conceivable that the sympathetic stimulation it causes may worsen anxiety.

In the study [16] that compared the frequency of mental health issues among young adults who take stimulants of the amphetamine kind and those who do not, researchers measured the 30-day presence of: post-traumatic stress disorder (PTSD), panic disorder, major depressive disorder (MDD), generalized anxiety disorder (GAD), mania. It was found that panic disorder and PTSD occurred more often in people who used amphetamine-type stimulants. Additionally, methamphetamine users were positively correlated with MDD and GAD appearance. On the other hand, ecstasy users were negatively correlated with panic disorder and GAD. Therefore, the association between amphetamine-type stimulants use and mental illnesses is complicated.

Amphetamine and methylphenidate are potent central nervous system stimulants used under prescription to treat attention deficit hyperactivity disorder (ADHD). An estimated 1 in 660 ADHD patients in their adolescence and early adulthood who were using prescription stimulants had new-onset psychosis. Additionally, the likelihood of psychosis was higher with

amphetamine usage than with methylphenidate. The following conditions met the criteria for psychosis:

- hallucinations,
- unspecified psychosis,
- delusional disorder,
- schizophrenia spectrum disorders,
- major depressive disorder (MDD),
- bipolar disorder with psychotic symptoms,
- other stimulant use disorders with psychosis [17].

Results of another study evidence that the connection values between the brain stem, striatal, and frontal cortex areas were shifting away from correlation as the outcome of amphetamine administration which significantly impaired brain activity [18].

Another paper provides paradoxical drowsiness and lowered electrical brain activity (CNV) as the result of the amphetamine administration [19].

THE RELATIONSHIP BETWEEN AMPHETAMINE USE AND SCHIZOPHRENIA

Animals exposed to discontinuous, increasing dose regimen of amphetamine develop sensitized states that resemble schizophrenia in terms of both behavior and neurochemistry. Amphetamine and other similar stimulants can trigger sensitization as well as psychosis in people when they are exposed to them repeatedly. Amphetamine sensitization can mimic some aspects of schizophrenia and is likely to modify behavior via affecting the function of the prefrontal cortex and mesolimbic dopamine pathways [20].

Amphetamine-induced sensitization is the phenomenon through which repeated exposure to the substance causes stronger behavioral and neurochemical reactions such as the capacity to induce striatal release of dopamine and motor skills improval [21-23].

Recent findings [24] show that long-term amphetamine usage effects and schizophrenia are not limited to just positive symptoms, patients present negative symptoms as well. A number of behavioral, physiological, and neurological modifications in animals that go beyond the striatal dopaminergic system have also been demonstrated [25-29].

The prospect that amphetamine sensitization can be utilized to represent conditions other than psychosis is suggested by these findings.

Association between schizophrenia and sensitization is supported by the facts that:

- both are long-lasting phenomena [30],
- stress may cause psychosis in susceptible patients through a process similar to sensitization [31], since amphetamine and stressors have been found to cross-sensitize [32],
- Hypothalamic-Pituitary-Adrenal (HPA) axis reaction to stressors after previous exposure to either amphetamine or stressful events can be elevated, indicating that amphetamine use could sensitize the HPA axis [33,34],
- prolonged amphetamine usage has been associated to psychotic symptoms occurrence [7,8,10, 3],
- in certain individuals with schizophrenia, amphetamine-induced dopamine production is increased [35-37].

Depending on this wealth of data, some researchers have hypothesized that a mechanism resembling sensitization that targets dopaminergic systems may be involved in the genesis of schizophrenia [38-42]. Numerous deficiencies associated with schizophrenia are reproduced when an amphetamine-sensitized state is induced, particularly those related to positive symptoms. Moreover, a number of the cognitive symptoms of schizophrenia, particularly those involving attention, seem to be repeated by inducing an amphetamine-sensitized state. Amphetamine along with other substances in polydrug use decreases the onset age of schizophrenia spectrum diseases [43]. It implies that the sensitization model is a viable way for investigating a variety of schizophrenia-related issues.

AMPHETAMINE-TYPE STIMULANTS (ATS) USERS PRESENCE IN EMERGENCY DEPARTMENT (ED)

The Australian scientists [44] reviewed patients who visited the emergency department's mental health team over the course of a year and had a history of using amphetamine-like medications. Most of the patients were male, with an average age of 32. The two most common complaints were psychosis and threats of suicide. Another issue that ATS users frequently had was aggression - in the ED, tranquilizers were utilized in at least 15.9% of cases. A psychiatric hospital admitted 34.4% of patients after discharge, while 32.8% were referred to community mental health teams.

Another group of Australian researchers [45] compared crystalline-methamphetamine users to other individuals who needed emergency room treatment for toxicology-related issues. The results were following:

- methamphetamine users displayed increased agitation, aggression, and violence,
- methamphetamine users exhibited lower levels of alertness, communication, and cooperation,
- more people who use methamphetamines than other drugs do so intravenously,
- users of methamphetamine were more likely to suffer from mental health issues,
- more methamphetamine users necessitated policy accompaniment,
- the Mental Health Act of 1990 required scheduling for 39% of methamphetamine presentations (39/100),
- methamphetamine users were more likely than other drug users to engage in street drug use.

CONCLUSIONS

Amphetamine-like stimulants are among the most potent psychostimulants. Dependence, both physical and psychological, develops quickly [46]. The stimulant, euphoric, and, in the case of MDMA, emphathogenic/entactogenic characteristics of these drugs contribute to their widespread usage. They have immediate effects on peripheral tissues as well as the central nervous system (CNS) [47]. The clinical outcome of chronic use includes anxiety, insomnia and depression with potential suicidal thoughts [46]. Given the correlation with ADHD and the comparable neurobiology and cognitive abnormalities with schizophrenia, vulnerability is likely to play a major role in the probability of developing psychosis following amphetamine use [48]. Obsessive delusions, paranoia, and hallucinations are examples of psychotic symptoms that might happen. The user's anxiety of being in immediate danger can manifest as aggressive and violent conduct [46]. The most often misused stimulant of the amphetamine class worldwide is methamphetamine. The growing need for patient care as well as the rising number of drug seizures globally serve as indicators of its expanding market. It is therefore a significant stressor on health resources [49].

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The importance of vitamin D3 in the pathogenesis, prevention and treatment of depression

Paulina Zegarska

Medical Faculty, Collegium Medicum. Cardinal Stefan Wyszyński University in Warsaw, Poland

INTRODUCTION

Depression is a common psychosomatic disorder that affects people all over the world, of all ages. According to the World Health Organisation (WHO), more than 350 million people worldwide suffer from depression, including approximately 1.5 million in Poland. Depression is most often diagnosed in people between the ages of 20 and 40. In addition, the disease is twice as common in women as in men. Among adults, certain professional groups are particularly vulnerable - two-thirds of doctors in the USA suffer from depression, while the average for the local population is 6.7 per cent. The predominant symptom of depression is mood disorder, especially a prolonged feeling of depression. It is not uncommon for patients to experience emotional indifference, anxiety, decision-making problems, impulsivity or sleep disturbances [1].

In addition to genetic, biological, environmental and psychological factors, nutritional deficiencies - one of which may be vitamin D3 deficiency - are important contributors to depression [2]. Receptors for calcitriol (the active form of vitamin D3) are found in almost all cells, suggesting that vitamin D3 has regulatory functions in many organs and is essential for the proper functioning of calcium-phosphate metabolism, endocrine glands, the immune system and the nervous system. Vitamin D3 deficiency has been shown to influence the development of various conditions, such as autoimmune diseases, cardiovascular diseases, infections, osteoporosis, obesity, diabetes, and some cancers [3]. A link has also been shown between insufficient vitamin D3 levels and neuropsychiatric diseases such as multiple sclerosis, Alzheimer's disease, Parkinson's disease, and between vitamin D3 levels and general impairment in cognitive functioning [4]. In 1982, the presence of receptors for vitamin D3 was discovered in brain structures that are involved in, among other things, emotion and mood regulation processes

(cingulate cortex, hippocampus, thalamus, hypothalamus) [5]. Vitamin D3 has been proven to significantly affect CNS function by participating in neuromodulation processes, regulating the secretion of brain neurotropic factors, neuroprotection and neuroplasticity.

Traditional treatments for depression are based on the monoamine deficiency theory, which posits that the pathophysiological basis of depression is a decrease in the levels of the neurotransmitters serotonin , noradrenaline and dopamine [6]. Localised in the brainstem, serotonergic and dopaminergic neurons have projection to extensive areas throughout the brain. This suggests that monoergic systems are involved in the regulation of a variety of brain functions such as mood, attention, reward-related information processing and cognitive processes. Any specification that inhibits the reuptake of monoamines while leading to an increase in their concentration at the synaptic gap has been shown to be clinically an antidepressant [7]. Classical antidepressants, however, have low efficacy, with only 50 per cent of patients experiencing improvement after treatment. Therefore, increasing attention is being paid to substances such as kappa receptor antagonists, cytokines and melatonin receptor agonists, which may find application as potential antidepressants [7].

THE ROLE OF VITAMIN D IN THE PATHOGENESIS OF DEPRESSION

The term vitamin D3 refers to a group of sterol derivatives that includes cholecalciferol, ergocalciferol and 25-hydroxycholecalciferol [8]. The standard recommended intake of vitamin D3 for children and adolescents in Poland and men and women up to 50 years of age is 5 ug/person/day, and for adult men and women >50 years of age 10-15 ug per person/day. On the basis of representative studies in each of the 9 European countries, an inadequate supply of vitamin D3 in daily rations was found. This shows that globally, including Poland and most EU countries, vitamin D3 deficiency is a widespread problem in every age group. The causes of population-based hypovitaminosis D can be traced to dietary errors, lack of supplementation in autumn and winter, and less sun exposure. Sources of vitamin D in the human body are food and 7-dehydroxycalciferol present in the skin. The amount of vitamin D synthesised when exposed to sunlight depends on the time spent in the sun, the degree of pigmentation, and individual differences [8]. In the diet, the main sources of vitamin D are fatty fish (5 μg -10 μg in 100 g),

meat, offal, poultry, dairy products (2 μg in 100 g). In addition, margarines and powdered milk for infants are often enriched in Poland. During autumn and winter periods, supplements are recommended in doses of: 100-500 IU cholecalciferol in multicomponent preparations, 1,000 IU in capsules, 15,000 and 300,000 IU/cm3.in combination with vitamin A in drops in so-called impact doses [8].

Vitamin D3 deficiency promotes the development of several psychosomatic diseases, including depression, bipolar disorder and schizophrenia. In addition, hypovitaminosis D3 causes an increase in serum parathyroid hormone (PTH) levels, which in turn leads to hyperparathyroidism. Primary hyperparathyroidism is often accompanied by depressive disorders, and disease symptoms normalise with appropriate treatment [9].

Vitamin D is essential for maintaining normal calcium-phosphate metabolism and bone mineralisation [10]. Its role is to enhance the absorption of phosphorus and calcium from food, to balance the abnormal ratio of these components, to stimulate the release of calcium from bone and to maintain constant plasma calcium levels [8]. In addition to the classic importance of vitamin D in maintaining mineral homeostasis, it plays an important role in neuroimmunomodulation, neuroprotection, cell proliferation in the developing brain and embryogenesis [2].

Vitamin D3 increases the levels of neurotropic growth factors such as: NGF, NT-3, GDNF [11]. Dysfunction of the above-mentioned factors may be important in the pathogenesis of depressive disorders and schizophrenia. It is worth mentioning that vitamin D increases the synthesis of gamma-glutamyl-transpeptidase-an enzyme that is involved in the synthesis of glutathione. which has an antioxidant function [12]. This suggests that vitamin D may have protective functions against free radicals in the central nervous system. It has been shown that animals exposed to prenatal vitamin D deficiency had morphological changes in the brain, impaired locomotion and learning and memory [13]. In humans early in life, hypovitaminosis D has been found to be a risk factor for the development of schizophrenia and a state of increased neuroticism, which is a common symptom of depression [14]. This suggests that vitamin D affects brain development, cognitive functioning, which may be related to the occurrence of depressive symptoms later in life. In addition, vitamin D is involved in the regulation of sleep and wakefulness rhythms, disturbances of which are observed in patients suffering from various

affective disorders. Vitamin D thus has many functions that overlap with the known pathophysiology of depression.

VITAMIN D RECEPTOR

Vitamin D functions are regulated by the Vitamin D Receptor (VDR), which belongs to the nuclear receptor family (NR1I1) and functions as a transcription factor [15]. The attachment of calcitriol causes activation of the receptor , which is associated with a change in its spatial conformation. VDR receptors are located in many tissues, where they have functions related to the regulation of calcium-phosphate metabolism, cell proliferation and immune system function [15]. In addition, their presence has been found in brain structures such as the prefrontal cortex, hippocampus, thalamus, hypothalamus and midbrain black matter [16]. Mice carrying a non-functional vitamin D receptor gene had anxiety disorders [17]. In contrast, in humans, dysfunction of this receptor was associated with mood and cognitive impairment, which may be related to depression [18]. This suggests that variants in the VDR gene may be associated with different behaviours in depression and susceptibility to cognitive impairment, which may be associated with early onset of depressive symptoms.

VITAMIN D3 DEFICIENCY AND THE OCCURRENCE OF DEPRESSIVE DISORDERS

Kjærgaard et al. in a population-based study conducted in Norway in 2007-2008 showed that low serum vitamin D3 levels are a predictor for the occurrence of depressive disorders. The SCL-10 scale (Hopkins Symptoms Check List 10) was used to assess mental status. A score of ≥ 1.85 on the SCL-10 scale was used as a criterion for the presence of depression. The association between low vitamin D3 levels and the presence of depressive disorders was statistically significant, also after taking into account factors such as gender, physical activity, chronic diseases, season, age, and BMI [19]. Similarly, a study by Berk et al. showed that individuals with low baseline vitamin D3 levels were more likely to have increased depressive symptoms compared to those with high serum vitamin D3 levels [2]. Patients in both groups underwent

supplementation with 40,000 IU of vitamin D3/week for 6 months, but no decrease in the severity of depressive symptoms was observed in either group. A study by US researchers examined the relationship between vitamin D3 levels and risk of depression in a group of people with cardiovascular disease. The study included 7358 patients with a history of myocardial infarction, congestive heart failure, stroke, transient ischaemic stroke and atrial fibrillation. The subjects had never suffered from depression. Patients participating in the study had their serum vitamin D3 and parathormone (PTH) levels assessed. The mean follow-up time was 1 year. Participants were divided into 4 groups according to their vitamin D3 levels: optimal (> 50 ng/ml, n = 367),normal (31-50 ng/ml, n = 2264), low (16-30 ng/ml, n = 3402) and very low (≤ 15 ng/ml, n = 1325). Vitamin D3 deficiency was found in 64.2% of patients. The highest incidence of depression was reported in the group of patients with very low vitamin D3 levels. The risk of depression was three times higher in patients with very low vitamin D3 levels and twice as high in patients with low vitamin D3 levels compared to patients with normal vitamin D3 levels. Vitamin D3 levels have also been shown to predict the occurrence of depressive disorders independently of PTH levels [20].

VITAMIN D3 SUPPLEMENTATION AND EFFECTS ON DEPRESSIVE DISORDERS

In a randomised trial, the use of vitamin D supplementation concurrently with standard treatments for depression was shown to be more effective than the use of antidepressants alone [21]. The study group received 20 mg of fluoxetine and 1500 IU of vitamin D3 for 8 weeks, while the control group received fluoxetine and placebo. Symptom severity was measured every 2 weeks using the Beck Depression Inventory (BDI). The Beck Depression Inventory is a popular psychological questionnaire used to measure the severity of depression. On the BDI, a score of 0-10 indicates no depression or depressed mood, 11-27 indicates moderate depression and 28 and above indicates severe depression. On the BDI scale, the group treated with fluoxetine alone had mean scores of 31.65 (BDI) at the start of the study and 17.95 (BDI) after eight weeks of pharmacotherapy.In the group in which vitamin D3 was included, mean questionnaire scores were 32.45 (BDI) at the start of the experiment and 13.2 (BDI) at the end [21]. Högberg et al. demonstrated the effect of supplementation on the alleviation of depressive

symptoms in a group of adolescents. Fifty-four adolescents with depression participated in the study. All participants were qualified for vitamin D3 supplementation for 3 months. The adolescents were orally administered 4000 IU of vitamin D3 per day for the first month, followed by 2000 IU for the next 2 months. A vitamin D3 deficiency scale was used to assess mental status before supplementation and after 3 months of supplementation. There was an improvement in mental status on the scale used-vitamin D3 levels averaged 41 at the start of the study and 91 nmol/l ($p < 0.001$) after 3 months of receiving the vitamin. There was an improvement in mood ($p < 0.001$), a reduction in feelings of depression, irritability, mood swings, normalisation of sleep, and increased ability to focus attention [22]. According to Jorde et al. vitamin D supplementation reduces depressive symptoms in overweight and obese individuals and lowers the risk of psychotic symptoms. The ongoing study involved 441 depressed patients (body mass index 28-47 kg m(-2), 159 men and 282 women aged 21-70 years) recruited from the outpatient clinic of a university hospital in Northern Norway. Participants were divided into 2 groups with low and high baseline serum vitamin D levels (25(OH)D < 40 nmol L(-1) and 25(OH)D > or = 40 nmol L(-1)). After one year of supplementation (20,000 IU cholecalciferol), a significant improvement in BDI scores was observed in both study groups compared to the control group taking placebo. In addition, there was a significant decrease in serum parathyroid hormone without a concomitant increase in calcium levels. High-dose vitamin D supplementation appears to alleviate depressive symptoms in overweight and obese patients, which may play a role in the prevention of depression in this patient group [23].

VITAMIN D3 SUPPLEMENTATION AS PREVENTION

Allen et al showed that vitamin D3 supplementation was effective in improving mood in healthy individuals. The randomised, double-blind study involved 44 volunteers who were divided into three groups. The first study group received a dose of 400 IU vitamin D3 and vitamin A, the second 800 IU vitamin D3 and vitamin A. The control group received only vitamin A. After 5 days of the experiment, participants' mood was assessed using the PANAS questionnaire, which measures both positive and negative affect and presents these two

components on separate subscales (referred to as PA and NA, respectively). Mean scores on the PA scale in the groups receiving vitamin D3 ranged between 35 and 37 points out of a possible 50, while the control sample's score was less than 29 points. However, no difference was shown with supplementation with doses of 400 IU versus 800 IU [24]. A meta-analysis published in 2013 in the British Journal of Psychiatry, however, recommended more studies to confirm the use of vitamin D3 supplementation in the prevention of depression in healthy individuals [25].

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The Impact of Loneliness on Medical Conditions

Arkadiusz Jaworski, Kamil Janosz, Zuzanna Lizoń, Julia Marschollek, Hubert Sawczuk, Paulina Typek

Faculty of Medicine, Students' Scientific Group at the Department of Psychiatry, Medical University Piastów Śląskich of Wroclaw, Wroclaw

INTRODUCTION

Loneliness is an important risk factor for many medical conditions and an important public health concern [1]. It can be considered as an independent disease entity - immunometabolic syndrome with a complex pathology [2]. Humans are social species and too long isolation is detrimental for health [3,4]. The COVID-19 pandemic exacerbated the problem in all age groups [5,6,7,8]. But actually what is loneliness? We can encounter different definitions and some can be not entirely accurate: “a state of solitude or being alone”, “perception of being alone and isolated”, “a subjective, negative feeling related to the deficient social relations” [1]. Taking into account the scale and intricacy of a problem we should look for a more complex definition. It is a distress that accompanies a perceived discrepancy between desired and actual social relationships [9]. An agonizing encounter, experienced when the need for human intimacy is not met adequately, or when a person’s social network does not match their preference, either in number or attributes [2]. It must be emphasized that solitude and loneliness are not the same concepts and they should not be confused. Solitude is a state of being alone, but not necessarily being lonely. It can be a positive and constructive state, which may enhance creativity and provide deeper reflection [10].

EPIDEMIOLOGY

Current research on loneliness revealed that its prevalence is related independently to some factors, such as female sex, being single and living alone (without partner or children), which demonstrate a positive correlation with reported loneliness level [11]. Findings vary

depending on the age of the participants with some study suggesting a possible but complex relationship between increasing loneliness and being in your late-20s, mid-50s or late-80s [12]. As for adolescents, the pooled prevalence was 8.2% and stable between 2006 and 2014 in the study conducted in the United Kingdom, examining the sample consisting of 11-, 13- and 15-year-olds. In adolescents aged 15 and individuals of lower socioeconomic status higher sense of loneliness was observed [13]. On DJGLS very severe loneliness was demonstrated for 6.7% of the surveyed Polish high-school students, severe loneliness for 7.7% and moderate loneliness for 42.3% [14].

Prevalence of loneliness amongst older people, that is aged 60 years and above, varies on account of using different measures and examining specific populations and age groups. Estimates range between 25 and 29% in the population of Americans aged 70 and older, and are quite similar to reports coming from European countries [15]. In meta-analysis examining observational studies from 29 high income countries 2008 to 2020 the estimates were 28.5% for overall loneliness, and including only the data, in which severity was reported - 25.9% for moderate loneliness and 7.9% for severe loneliness. No evidence of an increase in the prevalence of loneliness with age in the older population was found [16]. Estimates of prevalence among elderly persons living in residential and nursing care homes show significant variation, but overall, the mean prevalence was higher than in the general population [17].
Among both older adults and other adult age groups (young adults and middle-aged adults) variability in loneliness prevalence rates across Europe was observed, with the lowest rates consistently reported in northern European countries and the highest in eastern European countries [18].

Social distancing policy, implemented as a consequence of global spread of SARS-CoV-2, may lead to increasing loneliness rates. However, the study conducted right before the COVID-19 outbreak and then in the first months of the pandemic, between January and April 2020, showed resilience rather than significant increase in loneliness [19]. Similar results come from Norwegian research from the very beginning of the pandemic, which suggest slightly increased level of loneliness notable only in specific subgroups, such as older women or single individuals, with overall loneliness rates remaining the same or even lower during the lockdown [20].

On the contrary, in the sample consisting of 564 young adults loneliness level increased between January 2020 and April/May 2020 [21].

Nevertheless, the detrimental impacts of lockdown on loneliness may not be expressed straightaway, instead they may take some time to show up [22].

Further research, such as the study conducted in October 2020 in Poland during the second wave of the COVID-19 pandemic, showed a high sense of loneliness experienced by the participants. In the sample consisting of individuals aged 60 and over, almost two out of three participants, 58.8% specifically, declared moderate or moderately high sense of loneliness, and the correlation between that sense and depression symptoms was found [8].
A cohort study showed notable increase in loneliness among older adults with multimorbidity after the onset of the COVID-19 outbreak [23].

Comparison of predictors of loneliness before and during the COVID-19 pandemic identified the same sociodemographic groups (e.g. adults living alone, people with lower income, young adults) as being at risk of experiencing loneliness, with even greater risk for them in times of pandemic [24]. Younger people who tested positive for COVID-19 or experienced home quarantine had greater scores in UCLA Loneliness Scale [25]. Higher prevalence of loneliness among adult groups aged 18-59, especially those aged 18-29, compared to older adults (60-year-olds and above) was confirmed in other analysis conducted during the COVID-19 outbreak. Interesting gender by age association showed higher odds of loneliness among women in comparison to men, but was found only among those aged 18-29 and 60+ [26].

LONELINESS IN CHILDHOOD AND ADOLESCENCE

During adolescence as the social world changes quickly, there are many new experiences that can elevate the risk of physical isolation and therefore feelings of loneliness [27,28]. One way to describe childhood loneliness is as perceived discontent with some facets of their social relationships [29].

In 2018 in the UK, according to national surveys [30], 11,3% of children reported being „often” lonely and compared to those aged 13 to 15 (8,6%), younger children aged 10 to 12 years had a higher prevalence of loneliness (14,0%). In addition, when compared to kids who reported feeling "medium, high, or very high" satisfaction with their health (10%), "low" satisfaction respondents claimed they "frequently" felt lonely (28.3%). The other factor of increased loneliness is a place where a child lives. In comparison to children who live in small towns and countryside (5%), 19.5% of children who live in cities reported feeling „lonely"

often. Relationships between children and their parents and friends is also an important issue – children who felt lower connection were more likely to feel „lonely" [30]. Nowadays, computer- mediated – communication is also a great risk factor for feeling lonely among children. Loneliness is highly associated with lower mental health and self- esteem [31], depressive symptoms, suicidal thoughts, eating disorders and sleep issues [32].

The scientists from University of Jyväskylä in Finland took into consideration the association between loneliness and subjective health complaints (SHCs) among school-aged children. SHCs, which divide into somatic (headache, stomachache, backache) and psychological symptoms - feeling low, irritation and anxiousness, are described as signs of emotional distress, behavioral issues, and health concerns that cannot be directly linked to a specific medical or psychiatric diagnosis. Finnish students from grades 5,7 and 9 participated in a specific survey. They found out that girls were more likely than boys to experience loneliness and SHCs, and these rates rose with age. They also noticed that loneliness was a strong predictor of health complaints, especially mental ones and that it can really threaten children's health and well-being. Girls and ninth graders were most likely to experience it; among them, loneliness caused 28 and 30% of the difference in psychological symptoms [33].

Similar conclusions were acquired by Eccles et al. (2020). According to their study, higher levels of loneliness among adolescents were associated with lower self-rated health, troubles falling asleep, more sleep disturbances and morning fatigue. Teenagers who experience more loneliness frequently get headaches, stomachaches, and backaches [34]. Also the scientist from the UK [35] discovered diminished sleep quality among young people. Loneliness was connected with many components of sleep quality in adulthood: sleep latency, duration, subjective sleep quality, habitual sleep efficiency, interruptions in sleep, usage of sleep medications and daytime dysfunction.

The other instance of childhood loneliness is whether or not this condition will have any long-term effects that last into adolescence or adulthood. Researchers from University of Zurich [36] made a longitudinal study, in which they used eight CAPA interviews to evaluate participants' (age 9 to 16) childhood loneliness, difficulties and related mental diseases. Later, four times in adulthood—at years 19, 21, 25, and 30—participants were observed by researchers using the structured Young Adult Mental Assessment Interview to assess their psychiatric anxiety, depression, and drug use. They discovered a connection between childhood loneliness and adult self-reported anxiety and depressed outcomes, even after taking into account early adversity and psychiatric comorbidities, the relationships were still substantial. Children who

experienced moderate to high degrees of loneliness over an extended period of time displayed higher signs of anxiety and depression. On the other side there was no proof that childhood loneliness was linked to adult substance use disorders. It shows how important it is to intervene early to prevent long- term consequences of loneliness.

Another 8 year prospective study examined the relationship between childhood loneliness and adolescent depression symptoms [37]. Three tests were administered to children: once in primary school (age 5), once in upper primary (age 9), and once in secondary school (age 13). According to a SEM analysis, internalization in the infant school and reports of depressive symptoms at age 8 both predicted the onset of depressive symptoms in early adolescence. Depressive symptoms at the age of 13 were also predicted by the interaction effect of loneliness at ages 5 and 9, which indicated persistent loneliness in childhood. The scientist suppose that prolonged loneliness, as opposed to loneliness measured at a single time point, is more likely to predict later depressive feelings. Additionally, loneliness may lead children to developing unhealthy coping mechanisms and cognitive biases that put them at risk for depression.

There is a distinct group that is more likely to experience loneliness – long- term childhood cancer survivors (CCS). The primary contributing reasons are: spending a lot of time in the hospital, having fewer friends and being unable to play with the kids [38,39]. The German study, where The Patient Health Questionnaire was used to evaluate psychological symptoms. revealed that two years after the initial survey, 17.70% of CCS reported feeling lonely. These people also had a higher likelihood of persisting anxiety symptoms and suicidal ideation [38].

Different kinds of loneliness (trait and state ones) were examined in clinical histories of 645 kids affected by parental HIV/AIDS [40]. Moreover, participants delivered cortisol samples and sleep analyses. The correlations between trait and daily loneliness with HPA activity as well as loneliness and sleep analyses were significant. Although, after taking into account overlapping psychological constructs, some of the connections between sleep measurements and loneliness have vanished. One of the major processes explaining the correlation between loneliness and health has been identified as changes in the activity of the Hypothalamic-Pituitary-Adrenal (HPA) axis. Studies on teenagers demonstrated that loneliness was positively correlated with both sleep disruptions (such as the frequency of night awakenings) and difficulties going asleep. There are two outcomes from this study: it was discovered that high levels of trait loneliness predicted lower cortisol levels in the morning and there was a correlation between individual differences in daily loneliness and deviation in daily cortisol

profiles. As a result, those people who reported high levels of loneliness throughout the research days had a flatter diurnal slope. After adjusting for demographic variables and psychological concepts (depression, daily negative affect), these results still held significance. With regard to the sleep findings, children with high trait loneliness levels or daily loneliness predicted more nocturnal awakenings. Additionally, kids with trait loneliness reported worse sleep.

YOUNG ADULTS

Loneliness among people below 60 years of age is not properly researched. Most studies focus on seniors [3]. It may be caused by the fact that the older adults are more likely to report loneliness [41], although there is evidence that young adults report severe loneliness significantly (2-5 times) more often [42]. It leads to a common preconception that loneliness is especially a geriatric issue. In contrast to that, results of 2015 meta analysis demonstrate that loneliness is a stronger predictor of mortality in younger adults than inthe seniors [3]. This situation may be caused by the fact that loneliness among seniors causes mostly psychiatric issues [43] while among younger adults it has been shown to correlate with somatic issues as well [3,44].

LONELINESS AND SOMATIC CONDITIONS

Feeling lonely is a predictor of mortality [3]. There are multiple mechanisms in which loneliness affects one's somatic health. Lonely normotensive individuals have been shown to have higher total peripheral resistance and lower cardiac output than non-lonely normotensive population. This may, over the long term, lead to hypertension and associated cardiovascular incidents like stroke and myocardial infarction [45]. Lonely individuals have also been shown to have higher concentration of norepinephrine in urine, but their cortisol levels were comparable to the control group [46]. People with adequate social support have also been shown to have better functioning immune system than individuals without it. There are mixed results in research of the influence of loneliness on CD4+ cell count in individuals infected by HIV virus. It most likely does not affect early stages of disease but having high social support may have a positive effect in the long term, although it requires further research [46].

LONELINESS AND PSYCHIATRIC CONDITIONS

Loneliness increases the odds of many mental illnesses, especially depression and phobias. In one study the increase of risk of depression was found to be 11 fold, corrected for other potential depression risk factors [47]. Another study has shown that loneliness at the beginning of the semester was predictive of depression later in that semester. Lonely individuals also showed higher prevalence of suicidal ideation and parasuicide [48]. Loneliness has also been associated with higher risk of social anxiety and schizophrenia [48].There are mixed results of studies comparing alcohol consumption between lonely and non-lonely individuals, some of them show increased consumption among the lonely population but others do not. One of these studies did not find a difference in alcohol consumption but found increased drug consumption among the lonely population [48]. Loneliness has also been associated with dietary restraint, eating disorder and obesity [48].

LONELINESS IN THE ELDERLY

Social and demographic changes lead to an increased risk of loneliness and social isolation in modern societies [49]. The number of people over 60 years has tripled since 1950 because of the increased life expectancy [50]. According to a new report by Statistics Poland (GUS) around 40% of Poland's population is forecast to be aged over 60 by 2050 compared to 25.6% at the end of 2020 [51]. Older age is associated with reduced social interactions, longer periods of time living alone, and higher incidence of loneliness [50]. Worldwide, up to 50% of the elderly are at risk of social isolation and about a third of those aged 60 years and over experience loneliness in later life [52]. For these reasons the quality of social life has become one of the main challenges of aging societies and social isolation among the elderly has become a major problem for health and social policy [53].

Loneliness has social and emotional dimensions. Recent studies have shown that emotional loneliness is more common than social loneliness [54] and, in addition, is associated with greater health damage[55]. Emotional loneliness is connected with absence of a close emotional attachment figure. Social loneliness results from a lack of an engaging social network that can provide a sense of belonging and being part of a community. Emotional loneliness results in feelings of aloneness, anxiety, excessive vigilance, and a sense of abandonment. In contrast, social loneliness is associated with boredom, depression and pointlessness [56].

Social relations can also be considered in two different aspects: social relationships that contain structural features such as the number of close relationships, which may have a beneficial effect on health through influencing health behaviors as well as qualitative aspects such as the level of social support, which may benefit health through stress reduction, by providing psychological and material resources needed to deal with stress [57].

However, social isolation and loneliness are often not significantly correlated [58], suggesting that these may be independent constructs and that one may occur without the other.

Loneliness and social isolation have been associated with an increased risk of developing health problems such as:

- cardiovascular diseases [59],
- dementia [60],
- depression [61],
- disability [62],
- mortality [63].
- hospitalization [64],

LONELINESS AND MORTALITY IN ELDERLY

Social isolation and loneliness are associated with considerable morbidity and mortality, comparable to established risk factors such as smoking, alcohol consumption, obesity, and frailty [65]. A meta-analysis found that loneliness and social isolation are associated with an increased risk of death by 26% and 29%, respectively [66] . This increased mortality is in the same category as smoking fifteen cigarettes a day and alcohol abuse disorders. In addition, the health risk associated with loneliness are greater than the risks due to obesity and hypertension [66]. Moreover, loneliness and social isolation are associated with poorer health behaviors including smoking, physical inactivity, and poorer sleep [66]. Social isolation and loneliness are also common causes of chronic stress in adults [67].

CARDIOVASCULAR DISEASES IN ELDERLY

A systematic review found that loneliness and social isolation were associated with an increased risk of coronary heart disease by 29% and stroke by 32%, respectively. The relationship was comparable to anxiety and work stress [68]. There is also a link between

hypertension and loneliness in the elderly and middle-aged; this association strengthens with age [69]. This finding suggests that loneliness and social isolation can be considered as additional risk factors of cardiovascular disease [70].

Loneliness-related behaviors such as smoking, lack of exercise, poor sleep, and chronic stress are also risk factors of cardiovascular diseases.

LONELINESS AND DEPRESSION IN ELDERLY

Senile depressions along with dementia, visual and hearing impairment, mobility disorders and others are classified as the so-called “giants” of the geriatric problems [71]. Currently, the relation of loneliness to depression, and their impact on cognition in late life, are only partially understood. Depression in the elderly is not only somatogenic or endogenous, but also psychogenic. Often the etiology of disorders is mixed and difficult to assess [72]. Untreated depression affects the course and prognosis of somatic disease [73]. Chronic somatic diseases, especially those associated with persistent pain, worsen the course of depressive disorders. In case of coexistence of depression and chronic pain syndromes, the risk of suicide is six times greater [74].

Depressive syndromes among the elderly are largely ignored, because elderly people often view symptoms of depression as a normal part of the aging process [75]. In cross-sectional and longitudinal studies loneliness has been identified as a risk factor for depression symptoms [76]. Recent studies have shown that loneliness may be more common among older people in nursing homes than among those living at home [77].

LONELINESS AND DEMENTIA IN ELDELRY

Due to the lack of an effective treatment for dementia, identifying modifiable risk factors is important for delaying or preventing its onset [78]. One of the potentially important risk factors is the lack of good social relationships. Four studies [79,80,81,82] found a statistically significant relationship between low frequency of social contact and cases of dementia. Meta-analyzes show that people with less social participation, less social contact and a greater sense of loneliness have an increased risk of developing dementia [83].

Loneliness is a notable risk factor for mental and physical health problems [49]. It is not a condition that could be treated by pharmacotherapy but through psychosocial measures [84].

Potential causes and type of loneliness indicate which interventions would lead to the best response and outcome [85]. According to our present understanding from a therapeutic standpoint, O'Luanaigh & Lawlor (2008) [85] advise that any medical or psychiatric assessment should seek for loneliness, especially among depressed patients. Social interactions can aggravate or improve the feeling of being lonely [49]. The unexpectedly minor benefits of actions to improve social contact chances indicate that eliminating social isolation does not inevitably reduce loneliness as these two are not highly correlated with one another [49, 58]. Every patient's situation should be considered separately because there are plenty of reasons behind loneliness.

What is known about interventions to reduce loneliness is largely based on meta-analyses conducted by Masi et al. (2011) and Eccles & Qualter (2021) together with the findings of Hickin et al. (2021).

Masi et al. (2011) [49] explored interventions directly targeted at loneliness which involved a treatment group, not individual patients. The literature that was currently available evidence principally interventions among adults. Reviews have determined four strategies: improving social skills, enhancing social support, enhancing the likelihood of social interaction and dealing with dysfunctional social cognition. 50 articles included in review contained: 12 single group pre-post studies, 18 non-randomized group comparison studies and 20 randomized group comparison studies. Meta-analysis confirmed prior research findings that interventions were successful in all mentioned types of study designs. Due to the fact that randomized group comparison studies are superior to pre-post and non-randomized studies, authors mostly concentrated on these groups' results. They came to the key conclusion that for studies that utilised an RCT design, interventions focused on dysfunctional social cognition had a greater mean effect size than other intervention types. The outcome is in accordance with the regulatory loop hypothesis of loneliness suggested by Cacioppo & Hawkley (2009) [86] as that intervention type mostly relates to this loop.

Eccles & Qualter (2021) [87] conducted the first meta-analysis that focused on interventions which alleviate loneliness in young people. Previous work has almost entirely addressed the interventions among older adults which is a crucial restriction as loneliness affects people of all ages [88]. The review aimed for a population of people under 25 years of age. Studies included in quantitative synthesis were: 14 single groups and 25 randomised control trials. The authors discovered that youth-focused intervention programs are effective at

reducing loneliness. As shown in Table 1, there are differences and similarities in both mentioned publications.

Table 1 – A comparison of certain characteristics of meta-analyses conducted by different authors

Compared characteristic	Masi et al. (2011) [49]	Eccles & Qualter (2021) [87]
Targeted group	Mostly older adults despite there was not age group exclusion	Population of ≤25 years old
Interventions success	Confirmed	Confirmed
Intervention type moderating role in single-group study designs	Nonsignificant	Nonsignificant
Intervention type moderating role in Randomised Control Trial (RCT)	Interventions focused on dysfunctional social cognition had a greater mean effect size than other intervention types	Nonsignificant
Gender and age impact on effectiveness of interventions	Men responded to interventions better than women	Disproved (additionally, meta-analysis conducted by Maes et al. (2019) confirms that loneliness is the same throughout childhood and youth for both genders) [89]
Limitations	Most effective intervention type was present in four out of twenty RCTs. The researchers came to the conclusion that for it to be regarded as empirically substantiated, it needs to be independently repeated	Included studies pertain mostly youth considered to be at risk, such as people with health issues, and not those who reported loneliness as the clinical problem

Effect sizes of interventions to reduce loneliness were analogous and significant in both meta-analyses. RCTs showed average effect size of 0.198 at Masi et al.(2011) [49] and 0.316 at Eccles & Qualter (2021) [87], whereas single-group designs generated respectively 0.367 and 0.411. These effect sizes are indirectly comparable. For a single-group design results from both meta-analyses indicate that intervention type plays a non-significant moderating role.

Eccles & Qualter (2021) [87] state the same for RCTs. These findings are in contrast with previous results reported in the literature. Previous reviews focused on interventions to reduce loneliness in adults suggested that the intervention's focus could be crucial for its effectiveness [90,91,92]. Accordingly, Masi et al. (2011) [49] found one intervention type more effective than the others in RCTs.

Hickin et al. (2021) [88] meta-analysed psychological interventions for loneliness in RCT study design in order to determine their effectiveness. It was found that psychological therapies significantly decreased loneliness in contrast to control groups. Small to medium effect size was obtained (g=0.43). Speaking of different characteristics impact on interventions effectiveness (study quality, group or individual delivery, use of technology in interventions and type of intervention), there are two coherent conclusions from moderator analyses of the prior research: technological interventions and those that concentrate on social cognition show the greatest potential for alleviating loneliness.

A number of alternative approaches to reduce loneliness have been suggested, such as:

- Reminiscence therapy – which is a form of psychotherapy. A method of bringing back old memories to enhance satisfaction and to improve life quality. The addition of the word "therapy" indicates that it includes interaction between two or more people and the accomplishment of objectives depending on the requirements of each person. The discussion is open for participants so both happy and unpleasant memories may be brought forward. Reminiscence therapy is valuable because, by evoking previous experiences, it may facilitate regaining personal worth and identity among seniors. It can be performed while participating in daily activities in LTC (long-term care) as well. The literature defines three types of reminiscence therapy: simple reminiscence, life review and life review therapy. As there have been no negative side effects noted, it could be indeed regarded as a beneficial treatment, even though most of the research on group reminiscence therapy that were analysed were quasi-experimental and had modest participant counts [84].
- Meditation and mindfulness-based stress reduction (MBSR) - as the practices examined in a scoping review. There were just 13 suitable studies on this subject available; nevertheless, they all underlined favorable findings for at least one of their respective results. Eleven of the thirteen studies found benefits regarding loneliness [93].
- Internet-based Cognitive Behavioral Therapy (internet-based CBT) – as the promising path that was effectively applied to various psychiatric problems [94,95]. According to

the findings of the pilot randomized controlled trial, compared to the control group, the treatment group significantly reduced the amount of time they spent feeling lonely. However, authors point out limitations of the study: the study design does not clarify whether the outcome was a result of the treatment or nonspecific effects (e.g. contact with a therapist) due to the nature of loneliness; moreover, the provided data does not permit forming any conclusions about the treatment's long-term impact on loneliness or any of the other constructs. In conclusion, literature refers to the potential benefits of internet-based CBT in reducing loneliness, but further studies are required [96].

As outlined in the literature review a number of intervention approaches have been suggested but our understanding of the topic is still limited [85]. In order to treat loneliness efficiently we need a better understanding of its nature [49]. Creating personalized therapies might be the most valuable approach and is worth investigating in the future studies [88].

CONCLUSIONS

Contemporary medicine faces many complex issues, and modern research provides extensive data about associations with the above-mentioned. One of those major challenges is loneliness, especially during COVID-19 pandemic and in today's dynamic civilization. We should consider it in terms of serious risk factor, such as smoking, diet or habits. There is a necessity to provide appropriate care for all facing it, especially in the most vulnerable groups. The truth is that all of us can contribute to the reduction of loneliness. We must simply look around and act.

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SELECTED PROBLEMS IN REHABILITATION PHYSIOTHERAPY

Selected determinants of the acceptance of illness and life satisfaction in people with motor disabilities

Wiesława Kowalska[1], Renata Widziak[2], Małgorzata Struzik[3]

1. Faculty of Medicine, University of Technology, Zabrze, Poland,
2. Institute of Health Sciences, University of Opole, Opole, Poland
3. University Teaching Hospital, Urology Department, Opole, Poland

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INTRODUCTION

Congenital and acquired diseases causing skeletal, joint, muscular, nervous and vascular dysfunction lead to different degree of motor disability [1]. These diseases and disorders include: cerebral palsy [2], myelomeningocele [3], spinal cord injuries (hemiplegia, paraplegia, tetraplegia) [4], spinal muscular atrophy, congenital bone fragility, demyelizing diseases, rheumatoid diseases, peripheral nerve damage, myopathies, polymyositis and chronic extrapyramidal syndromes [1]. The diseases have various social, health and psychological effects for patients. The effects are influenced by age, development phase and previous lifestyle of the patient [1].

The acceptance of illness, which has an impact on the patient's functioning in the emotional, physical and professional sphere, plays an important role in adapting to the disease [5]. The acceptance of illness is one of the factors determining the effectiveness of physiotherapy [6], but it also has research and clinical significance [7]. The acceptance of illness is expressed in a positive attitude to the situation of living with a chronic disease. This attitude allows the patient to adapt to the restrictions imposed by the disease, to maintain a sense of self-efficacy, control and self-esteem [8]. Positive acceptance mobilizes the patient to battle against an illness and is expressed in a lower intensity of negative emotions and reactions [9].

A sense of well-being, which is part of health, covers the level of life satisfaction, the presence of positive feeling and the absence of negative emotions [9]. In Polish literature, life satisfaction is often referred to as the cognitive aspect of subjective well-being [10]. According to Juczynski, life satisfaction is the result of a comparison made by the patient between his/her own situation and standards set out by the patient, a satisfactory outcome of the comparison creates the feeling of satisfaction [9]. This category is useful in medical sciences [9,11].

An increasing number of chronic diseases and aging of the population increase the number of people with disabilities. According to the World Health Organization, over a billion people in the world suffer from disabilities [12]. In Poland, the disabled constitute 12.2% of the population [13], including about 10% with motor disabilities [14]. Wheelchairs are a technical solution supporting people with physical disabilities. The equipment fulfils rehabilitation and social functions, allows patients to be totally or partially self-reliant and independent [15]. The Foundation for Active Rehabilitation (FAR) is one of the institutions that show patients the possibilities of functioning in a wheelchair, help them to improve the functional efficiency and develop already acquired skills. The therapy implemented during the classes and camps organized by FAR is performed by instructors with disabilities, who set an example, a model for participants how to function in society, family and how to lead an active life despite disability [16]. Medical literature emphasizes the importance of sociodemographic and clinical factors to the acceptance of illness [17].

It is necessary to define these factors in order to develop and plan therapeutic activities to generate positive acceptance of illness and give greater life satisfaction to chronically ill and disabled people. Implementation of preventive programs will increase the effectiveness of rehabilitation and social integration of people with disabilities. The research into factors that determine life satisfaction of people in wheelchairs is still scarce and most often involves respondents with selected diseases. Studying life satisfaction and the acceptance of illness in people with motor disabilities allows to combine the subjective and medical perspective.

OBJECTIVE

The aim of the study was to analyze of the acceptance of illness and life satisfaction in people with motor disabilities and to define the relationship between the acceptance of illness and life satisfaction.

MATERIAL AND METHODS

The study included 67 people with mobility disabilities. The respondents were in wheelchairs. The research was conducted in the period from February to May 2018 among participants of the camps and regional classes conducted by the FAR in two voivodships: Opolskie and Małopolskie. The study was approved by the Bioethics Committee of the Opole Medical School (approval No. 4/91/2018). The subjects were selected in a targeted manner.

Inclusion criteria were as follows: age, voluntary consent to participate in the study, people with motor disabilities using wheelchairs, members of the Foundation for Active Rehabilitation, people in logical verbal contact with full capacity to act in law.

The study was conducted in accordance with the human research principles set out in the "Declaration of Helsinki". Prior to the study, informed consents were obtained from all respondents. The subjects were informed that participation in the study was voluntary and anonymous, and that they could withdraw from the trial at any stage.

The subjects were instructed on the objective of the study and how to complete the research tools. The respondents completed the questionnaires on their own, the time devoted to filling in the survey was adapted to their capabilities. Seventy questionnaires were distributed among the subjects, 67 of them were qualified for statistical analysis.

The study was based on the diagnostic survey method and the survey technique. Empirical material was collected using the original questionnaire and two standardized research tools: AIS, SWLS.

The Acceptance of Illness Scale (AIS) by Barbara J. Felton, Tracey A. Revenson and G. A. Hinrichsen (Polish adaptation by: Z. Juczynski) was used to measure a degree of the acceptance of illness. The questionnaire contained 8 statements about certain difficulties and limitations imposed by the disease. The subject determines the current state of health on a five-point scale. The respondent receives 1 point for strong consent which represents poor adaptation to the disease, and 5 points for the definite lack of consent – this reflect the acceptance of illness. The general acceptance of illness is determined by adding all points. The respondent can obtain from 8 to 40 points. The points are converted into disease acceptance levels: scores from 8 to 18 - no acceptance, from 19 to 29 points - average level, above 29 points - high level. The psychometric properties of the AIS scale are good. Cronbach's alpha is 0.85 [9]. Higher values of the AIS scale correspond to better adaptation to the disease and less sense of mental discomfort [9].

The Satisfaction with Life Scale (SWLS) by Ed. Diener, Robert A. Emmons, Randy J. Larsen and Sharon Griffin (Polish adaptation by: Z. Juczynski). It contains 5 statements, the respondent answers on a 7-point scale (from 1 - I completely disagree to 7 - I completely agree). The patient can obtain from 1 to 7 points. The general life satisfaction is determined by adding up points. The respondent can obtain from 5 to 35 points. The points are converted into sten scores. The results of 1-4 stens are defined as low, 5-6 stens as average and 7-10 stens as high. The psychometric properties of the SWLS are satisfactory. The reliability index (Cronbach's alpha) is 0.81 [9]. Life satisfaction measured on the SWLS scale is a global assessment of life satisfaction [9]. Our original questionnaire contained 18 items which were grouped into two research areas. The first area included sociodemographic data: sex, age, place and structure of residence, education and professional activity. The second area contained questions about the cause of disability, type of illness, frequency of participation in rehabilitation activities and health self-assessment.

Statistical analysis

Statistical analysis was performed using the Statistica 13.1 software by StatSoft Polska. Quantitative variables are presented by mean, standard deviation, median, minimum and maximum values, while qualitative variables are shown by numbers and percentages. The normality of distribution of quantitative variables was tested using the Shapiro-Wilk test. As the quantitative data distribution did not conform with normal distribution, in order to test differences in measurable parameters, we have used the non-parametric Mann–Whitney U test for two groups and the Kruskal–Wallis test for more than three groups with the post hoc test of multiple comparisons of average ranks for all groups. Because of asymmetry of the AIS scale distribution, the non-parametric Spearman's rank correlation coefficient was used to evaluate the relationship between the acceptance of illness and life satisfaction. Statistical significance was assumed at $p < 0.05$.

RESULTS

Characteristics of the respondents

The largest group of respondents (n=46;68.66%) were people aged 18 to 35, the average age was 32.42. Most of the respondents lived in the city (n=48;73.13), rural residents constitute 26.87% (Table1).

Table 1. Socio-demographic and clinical characteristics of the respondents (N = 67)

Variable	Category	Number	%
Gender	Female	26	38.81
	Male	41	61.19
Age	18- 25	23	34.33
	26-35	23	34.33
	36-57	21	31.43
Place of residence	Village	18	26.87
	City	49	73.13
Education	Higher	17	25.37
	Secondary	36	53.73
	Vocational, primary, junior high school	14	20.90
Professional status	I work	29	43.28
	I do not work	28	41.79
	I am a student	10	14.93
Structure of residence	With parents	38	56.72
	Alone	15	22.39
	With spouse/partner	14	20.90
Cause of disability	Congenital disorder/disease	38	56.72
	Result of the disease	16	23.88
	Result of the accident	13	19.40
Diseases	Myelomeningocele	20	29.85
	Spinal cord injury	17	25.37
	Cerebral palsy	14	20.90
	Neuromuscular diseases	5	7.46
	Other	11	16.42
Frequency of using rehabilitation	I do not use	33	49.25
	I use several times a week	21	31.34
	I use several times a month	10	14.93
	I use everyday	3	4.48
Health self-assessment	Good	30	44.78
	Average	17	25.37
	Very good	17	25.37
	Great	3	4.48
	Poor	0	0.00

Most respondents had secondary education (n=36;53.76%) and higher education (n=29;25.87%). Employment was (n = 29; 43.28%) of the respondents, a small group of students (n = 10; 14.93%). Over half of the respondents (n=38;56.72%) lived with their parents. Respondents with congenital disabilities (n=38;56.72%), myelomeningocele

(n=20;29.95%) and cerebral palsy (n=14;20.90%) dominated. The highest percentage of subjects assessed their health as good (n=30;44.78%), and none of them described their condition as bad. About half of the respondents do not use rehabilitation, only a small percentage of respondents (n=3;4.48%) used rehabilitation on a daily basis (Table1).

Acceptance of illness by people with motor disabilities

The number of points obtained by respondents on the Acceptance of Illness Scale ranged from 8 to 40. The maximum number was obtained by 3 people, and the minimum number by 1 subject. The value of general index obtained by 67 respondents was 27.69 ± 6.89 and it was at the average level. The distribution of AIS scale results expressed in descriptive statistics is presented in Table 2.

Table 2. Distribution of AIS results expressed in descriptive statistics

Parameters	Mean	Median	Minimum	Maximum	Lower quartile	Upper quartile	Standard deviation
AIS points	27.69	27.00	8.00	40	23	32.00	6.89

M mean, SD standard deviation

The points were converted to the level of acceptance of illness. Data is included in table 3. Most respondents showed medium (53.73%) and high (41.79%) level of acceptance of illness. A small percentage of respondents (3%) had a low level (Table 3).

Table 3. Level of acceptance of illness according to the AIS scale

Level of acceptance of illness	Points	N	%
Low	8-19	3	**4.48%**
Medium	20-30	36	**53.73%**
High	>30	28	**41.79%**

N number of respondents

Selected sociodemographic and clinical variables and the degree of acceptance of the disease

Statistical analysis showed that sex, place of residence, health self-assessment and structure of residence are variables that significantly statistically differentiate the acceptance of illness of people in wheelchairs (Table 4).

Table 4. Selected sociodemographic, clinical variables and the degree of acceptance of illness, statistical significance

Variable		Acceptance of Illness Scale (AIS)				
		MD	M	SD	Statistical analysis	p
Gender	Female	24.65	24	6.93	Z= 2.8177	0.004
	Male	29.61	30	6.20		
Place of residence	Village	24.44	23	7.79	Z=2.20661	0.026
	City	28.88	29	6.19		
Age	18-25	26.04	25	6.79	H=3.5375	0.170
	26- 35	29.34	29	7.44		
	>35	27.66	27	6.22		
Cause of disability	Congenital disorder/disease	26.66	27	6.77	H=1.9362	0.379
	Result of the disease	28.75		6.97		
	Result of the accident	29.38	29	7.15		
Education	Vocational, primary	25.07	24.5	9.60	H=3.1857	0.203
	Secondary	27.47	27.5	5.58		
	Higher	30.28	31	6.30		
Structure of residence	Alone (1)	32.13	32	5.84	H=8.5134	(1)>(2) 0.014
	With parents (2)	26.42	25.5	7.07		
	With spouse/partner (3)	26.36	26.5	5.68		
Professional status	I work	29.48	29	5.70	H=3.0692	0.215
	I do not work	26.46	27	7.21		
	I am a student	25.90	25.5	8.52		
Frequency of using rehabilitation	I do not use	28.45	29.00	7.22	H=5.7147	0.126
	I use several times a week	26.33	25	6.70		
	I use several times a month	25.70	26.50	5.14		
	I use everyday	35.33	36	5.03		
Diseases	Myelomeningocele	28.20	29.5	6.88	H=9.9236	0.0417
	Spinal cord injury	30.11	31	6.99		
	Cerebral palsy	24.78	26	4.95		
	Neuromuscular diseases	22.00	21	2.82		
	Other	29.27	26	6.63		
Health self-assessment	Great (1)	26.00	27	13.53	H=14.787	(2)>(3) (3)>(4) p=0.020
	Very good (2)	31.35	31	5.21		
	Good (3)	28.53	28	6.42		
	Average (4)	22.82	23	5.46		
	Poor	0.00	0.00	0.00		

Me – median, Z – result of the Mann–Whitney U tes *H - result of the Kruskal-Wallis test, p - significance level*

Men obtained a higher level of acceptance of illness (29.61 ± 6.29) than women (24.65 ± 6.93). People living in the city showed a higher level of acceptance of illness (28.88 ± 6.19) than rural residents (24.44 ± 7.79).

The structure of residence is a factor differentiating the acceptance of illness at the level of significance p=0.014.

The post hoc analysis using the test of multiple comparisons of average ranks for all groups showed that the subjects who live alone (Me = 32) show greater acceptance of illness (32.13 ± 5.84) than people living with their parents (Me = 25, 5), the difference turned out to be statistically significant (p = 0.016). The other differences in the acceptance of illness resulting from the structure of residence turned out to be statistically insignificant.

Health self-assessment is a variable that differentiates the acceptance of illness at the significance level p = 0.020.

The study results showed that the highest average value on the Acceptance of Illness Scale (31.35 ± 5.21) was obtained by respondents who rated their health as very good. Post hoc analysis using the test of multiple comparisons of average ranks showed a statistically significant difference (p = 0.001) between respondents who rated their health as very good (Me = 31) and as average (Me = 23).

Statistically significant differences (p=0.028) also occurred between respondents assessing their health as good (Me = 28) and as average (Me = 23). A type of disease differentiates the acceptance of illness at the level of statistical significance p = 0.041. Post hoc analysis using the test of multiple comparisons of average ranks demonstrated that these differences were not statistically significant (Table 4).

A summary of data contained in Table 4 shows that the variables, such as: age, education, professional status, frequency of using rehabilitation and the cause of disability do not significantly statistically differentiate the acceptance of illness

A summary of data contained in Table 4 shows that the variables, such as: age, education, professional status, frequency of using rehabilitation and the cause of disability do not significantly statistically differentiate the acceptance of illness

Life satisfaction by people with motor disabilities

The range of points obtained by the respondents on the Satisfaction with Life Scale was from 5 to 34.

The average SWLS value was 20.55 ± 6.19, it was within 5-6 sten, i.e. the average level of life satisfaction. 32.84% of respondents obtained the low score of 1-4, average outcome - 34.32% and high results - 32.84%. Detailed data are included in Table 6. The results obtained on the SWLS scale in descriptive statistics are contained in Table 5.

Table 5. Distribution of SWLS results expressed in descriptive statistics

Parameters	Mean	Median	Minimum	Maximum	Lower quartile	Upper quartile	Standard deviation
SWLS points	20.55	21	5	34	16	24	6.19

Table 6. Level of life satisfaction

Level of life satisfaction	Range of points	Sten	N	%
Low	5-17	1-4	22	32.84%
Medium	18-23	5-6	23	34.33%
High	24-35	7-10	22	32.84%

The impact of sociodemographic and clinical variables on life satisfaction

The analysis of data contained in Table 7 showed that the variables: gender, age, education, professional status, cause of disability and frequency of using rehabilitation do not statistically significantly differentiate life satisfaction of people with motor disabilities.

Table 7. Selected sociodemographic variables, life satisfaction, statistical significance

Variable	Index	Life satisfaction - raw score				
		MD	M	SD	Statistical analysis	p
Gender	Female	19.38	18.5	6.91	U= 425.00	0.167
	Male	21.29	22.00	5.66		
Place of residence	Village	18.33	18.50	7	U= 317.50	0.080
	City	21.37	22.00	5.72		
Age	18-25	20.83	21.00	6.68	H=0.053381	0.974
	26-35	20.00	21.00	6.45		
	>35	20.86	21.00	6.69		
Cause of disability	Congenital disorder/disease	20.63	22.00	6.54	H= 0.053381	0.911
	Result of the disease	20.32	19.50	6.1		
	Result of the accident	20.61	21.00	5.69		
Education	Vocational, primary	20.43	23.50	6.86	H= 1.571761	0.456
	Secondary	19.81	20.50	4.75		
	Higher	22.23	23.00	6.39		
Structure of residence	Alone	22.6	21.00	5.82	H=3.844882	0.146
	With parents	20.6	22.00	6.49		
	With spouse/partner	18.21	17.00	5.24		
Professional status	I work	21.14	21.00	5.77	H=0.3189268	0.852
	I do not work	19.96	21.00	6.78		
	I am a student	20.50	18.00	6.11		
Frequency of using	I do not use	20.70	21.00	6.48	H=7.131446	0.067
	I use several times a week	20.42	21.00	5.34		

rehabilitation	I use several times a month	17.8	16.00	6.03		
	I use everyday	28.00	29.00	4.58		
Diseases	Myelomeningocele	21.70	22.00	6.15	H=1.153277	0.885
	Spinal cord injury	20.88	21.00	5.45		
	Cerebral palsy	19.14	22.50	5.26		
	Neuromuscular diseases	19.80	20.00	3.03		
	Other	20.09	19.00	8.57		
Health self-assessment	Great (1)	28.67	29.00	5.5	H=17.249	(1)>(4) (2)>(4) 0.0006
	Very good (2)	24.05	24.00	5.82		
	Good (3)	20.23	21.00	5.11		
	Average (4)	16.17	16.000	5.21		

M - median, Z - result of the Mann–Whitney U test H - result of the Kruskal-Wallis test, p - significance level.

Health self-assessment is a variable that differentiates life satisfaction. The highest mean values were obtained by the respondents who rated their health as excellent (28.67 ± 5.5) and as very good (24.05 ± 5.82).

The post hoc analysis carried out using the test of multiple comparisons of average ranks revealed a statistically significant difference (p=0.018) between the subjects who evaluated their health as excellent (Me = 29) and as average (Me=16).

Statistically significant differences (p = 0.002) also occurred between the respondents assessing their health as very good (Me = 24) and as average Me = 16 (Table 7).

The correlation between the acceptance of illness and the level of life satisfaction of wheelchair users was determined by calculating the Spearman's rank correlation coefficient. The correlation is illustrated in Figure 1.

The value of Spearman's rank correlation coefficient R = 0.571353, p<0.05 allows to conclude about a moderate correlation between the analyzed features, i.e. the acceptance of illness and life satisfaction of people in wheelchairs.

The strength of this relationship is positive, i.e. the growth of one characteristic is accompanied by an increase of the other.

The significance of correlation was checked using a non-parametric test for significance of the correlation coefficient.

The value of t-statistic, which checks the significance of the Spearman's rank correlation coefficient t (N-2) = 5.612584 with the level p = 0.000001, indicates the connection between the acceptance of illness and life satisfaction.

The correlation result shows that the acceptance of illness is a factor associated with life satisfaction.

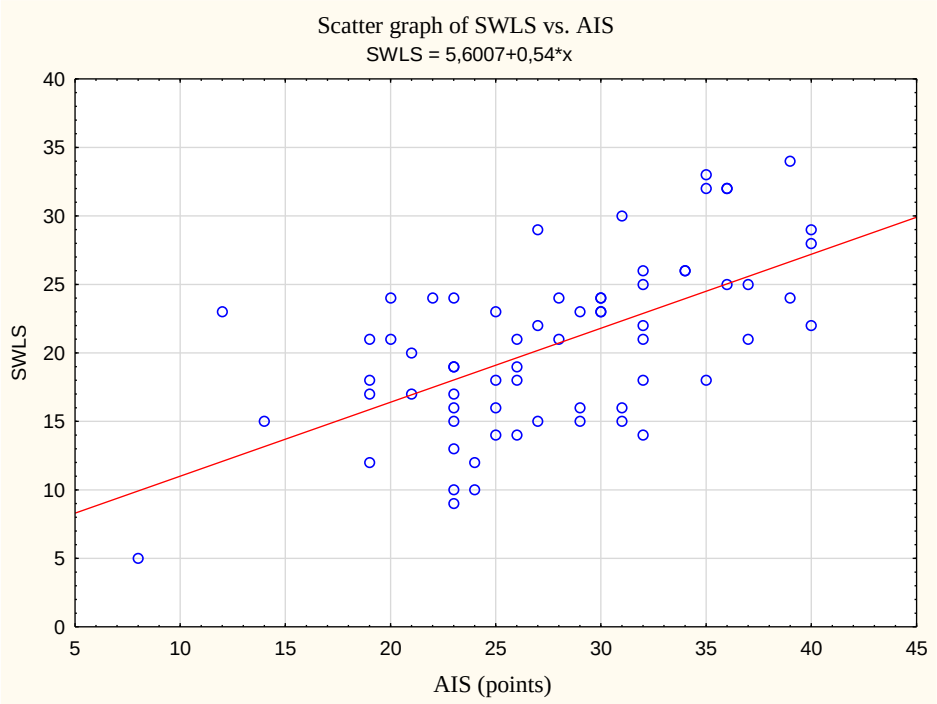

Figure. 1. The correlation between the acceptance of illness and life satisfaction

DISCUSSION

Medical and social literature describes numerous demographic, socio-economic, psychological and health factors having an impact on the acceptance of illness and life satisfaction of the disabled.

The research aimed at identifying selected determinants of the acceptance of illness and life satisfaction of people in wheelchairs. The results of our study showed that the respondents had a medium level (27.69 ± 6.89) of the acceptance of illness, and the type of disability did not differentiate the results. Men and city dwellers as well as those living alone demonstrated a higher level of the acceptance of illness.

Other researchers obtained comparable results i.e. within the average level of the acceptance of illness. In the Koszalkowska study, the respondents obtained lower results of the acceptance of illness, (23.04 ± 8.92) and (24.38 ± 10.38) for people with acquired and congenital disabilities, respectively. Type of disability did not differentiate a degree of the acceptance of illness [18]. According to Janowska-Matuszewska, disabled artists and authors showed the average level of acceptance of illness amounting to 26.03 [19]. The respondents after a stroke who participated in rehabilitation activities obtained low AIS scores, i.e. within

the lower limit of the average level (21.54 ± 9.42) [20]. Higher scores on the AIS scale, at the average level (25.75 ± 8.47) were obtained by people with osteoarthritis [21]. In patients with systemic connective tissue disease, the level of the acceptance of illness was 24.5 ± 7.5 [22]. Similarly, in patients with chronic diseases, the level of acceptance of illness was at an average level. For women with breast cancer, it was 26.53 ± 7.71, Me = 26. In this study, the highest percentage of respondents obtained the results at an average level (50.6%), differentiated by age and professional activity [23]. In patients with diabetes, the level of acceptance of illness was 27.61 ± 7.81) [24]. The results of the study conducted in people in wheelchairs are consistent in terms of acceptance of illness.

The analysis of the impact of sociodemographic variables showed that women achieved a lower level of acceptance of illness than men. The studies of patients with osteoarthritis carried out by Sochacka [25] did not reveal any statistically significant difference between women and men in terms of the level of acceptance of illness.

In our study, the age of respondents and type of disability did not differentiate the patients in terms of acceptance of illness. Opposite results were obtained by Sierakowska et al. [21] in the study of people with osteoarthritis who were found to have a negative correlation between the acceptance of illness and age, duration of the disease, pain felt during movements and the level of disability. Similarly, the results of a survey conducted in patients with systemic connective tissue diseases showed that the acceptance of illness was determined by age, marital status and source of income [22].

In our study, the mean life satisfaction index in wheelchair users was at an average level of 20.55 ± 6.19 points. Over a third of respondents described their life satisfaction as low (32.84%); a similar percentage of respondents rated the level of life satisfaction as high and average. Sociodemographic variables did not differentiate the results on the SWLS scale. Health self-assessment is a factor differentiating life satisfaction. Empirical results have shown a significant relationship between the acceptance of illness and life satisfaction.

Olszak-Winiarska studied life satisfaction of disabled people with various dysfunctions of the musculoskeletal system, including tetraplegia, paraplegia and hemiplegia. The study was conducted in three countries: Norway, Germany and Poland. The results showed that 60% of Norwegians, 30% of Germans and 23% of Poles achieved high results on the SWLS scale. On the other hand, 30% of Poles and 10% of Norwegians achieved low levels of life satisfaction, Germans did not achieve low results on the Satisfaction with Life Scale. On the Acceptance of Illness Scale, 30% of Germans and Poles achieved a high level,

the higher percentage - 40% - was obtained by Norwegians. The differences between the groups were not statistically significant. Life satisfaction was associated with the social and economic situation of the country. However, the country of residence did not have an impact on acceptance of illness [26].

In our study, similar low results on the Satisfaction with Life Scale were obtained by 32.84% of respondents, a larger percentage of respondents (32.84%) obtained high results.

The results obtained by Maarten J. Ficher and Fay-Lynn Asselman et al. confirmed that the country of residence has an impact on life satisfaction. The average results obtained in adults with spinal muscular atrophy on the SWLS scale were similar to the outcomes of healthy adults and amounted to 26.2 ± 6.5 points. 17% of respondents were dissatisfied with life. The results obtained on the SWLS scale did not show any correlation with sociodemographic data or features of the disease [27]. Similarly, the results of our research did not confirm the relationship between sociodemographic data and the level of life satisfaction.

Skalska studied a group of students with musculoskeletal disorders, chronic diseases and sensory disabilities [28]. The average level of life satisfaction was 20.96 ± 5.85 and it was related to the received social support. At the same time, a much higher percentage of respondents (70%) than in our research showed average life satisfaction. Fewer respondents obtained high (16%) and low (14%) results. Differences in the level of life satisfaction may result from the respondents' life cycle, because the time of studies is a period of social and professional rehabilitation for people with disabilities [26].

The research conducted by Scislo et al. [29] in the group of people with motor disabilities, including 60% of respondents in wheelchairs, did not reveal a relationship between the level of life satisfaction and a degree of disability. People with congenital disabilities showed greater independence and life satisfaction. Compared to our research, a smaller number of respondents (18%) obtained 15-19 points, a larger percentage of subjects (68%) obtained 20-30 points, with 6% having 31-35 points [29]. On the other hand, the low level of education was a factor significantly worsening life satisfaction. In our research, the level of education did not have a statistically significant impact on the level of life satisfaction.

The relationship between life satisfaction and physical activity was demonstrated in the research conducted by Pieszak [30]. People with physical disabilities (mainly with paraplegia and tetraplegia) practicing sports have a higher level of life satisfaction (24.17 ±

4.46) than disabled people not practicing sports (18.77 ± 3.57) [28]. Our study showed that the results obtained by disabled people practicing sport are higher than those obtained by the respondents. At the same time, life satisfaction of people who do not practice sport is lower than of FAR camp participants.

The research conducted by Janiszewska et al. [31] in women with osteoporosis who were rural residents showed that age and education differentiated the level of acceptance of illness and life satisfaction. Older people had lower levels of acceptance of illness and life satisfaction. Respondents with higher education showed greater acceptance of illness and life satisfaction. The average level of acceptance of illness was 22.2 ± 6.9, and life satisfaction - 14.7 ± 5.6) [31]. Our study demonstrated that respondents had a higher level of acceptance of illness and life satisfaction, and that education did not differentiate the results obtained on the AIS and SWLS scale.

In the study conducted by Kupcewicz in patients with lumbar, cervical and multilevel discopathy, the average life satisfaction score was 21.34 ± 6.17, and it was influenced by duration of the disease. There was a positive relationship between the acceptance of illness and life satisfaction ($r = 0.51$) which is statistically significant at $p<0.00001$ [32]. Our research also showed a statistically significant correlation $r = 0.571353$, $p <0.05$ between the acceptance of illness and life satisfaction.

Limitations

The study results should be interpreted with caution as there are some limitations resulting from the size of the study group and not taking into account all factors that may affect the acceptance of illness and life satisfaction. The study results have a practical dimension, because they give a subjective picture of life satisfaction of people in wheelchairs and the level of acceptance of illness which are important for the process of rehabilitation and social integration of people with motor disabilities. In practice, a nurse exercising holistic care by educating and preparing the patient for self-care should take into consideration the patient's acceptance of illness. The study results complement literature reports and may become an inspiration for further considerations.

CONCLUSIONS

1. People with motor disabilities show an average level of acceptance of illness depending on gender, place and structure of residence.

2. Respondents' life satisfaction is at an average level and is determined by health self-assessment.
3. A relationship was found between the acceptance of illness and life satisfaction. Higher level of acceptance of illness corresponds with greater life satisfaction. The acceptance of illness is a determinant of life satisfaction.

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Efficacy of oral collagen therapy in osteoarthritis

Joanna Gołda, Julia Mężyk

Wroclaw Medical University, Wrocław, Poland

List of abbreviations

CP - Collagen peptide

VAS - Visual analogue scale

WOMAC - Western Ontario and McMaster Universities Arthritis

OA - Osteoarthritis

MRI - Magnetic resonance imaging

HC - Hydrolysed collagen

TNF-α - Tumour necrosis factor alpha

MCP1 - Monocyte chemoattractant protein-1

CRP - C-reactive protein

CTX-II - C-telopeptide fragments of type II collagen

NSAIDs - Non-steroidal anti-inflammatory drugs

FACITs - Fibril-associated collagens with interrupted triple helices

MACITs - Membrane-associated collagens with interrupted triple helices

MULTIPLEXINs - Multiple triple-helix domains and interruptions

OP - Osteoporosis

LPS - Lipopolysaccharide

INTRODUCTION

Collagens are the most abundant group of both the organic macromolecules in organism and the proteins in the extracellular matrix of connective tissue [1]. Collagen is the key protein produced by the human body, consisting mainly of the amino acid glycine (33%), proline and hydroxyproline (22%) in a triple helix formed by three α chains. Almost 28 types of collagen have been identified, but type I is most commonly found in the skin, bones, teeth, tendons, ligaments and vascular ligaments [2]. They are also found in the interstitial tissue of the parenchymal organs, where they provide tissue stability and structural integrity [1]. Type II is

present in cartilage. The most common sources of type III are skin, muscle and blood vessels. Type IV occurs in the basal membrane and basal lamina separated by epithelium. Type V is one of the major components of the cell surface and placenta. This protein has been divided into different families, such as fibrillar and network-forming collagens, the FACITs (fibril-associated collagens with interrupted triple helices), MACITs (membrane-associated collagens with interrupted triple helices), and MULTIPLEXINs (multiple triple-helix domains and interruptions). Fibrillar collagen is the most abundant collagen in vertebrates and plays a structural role, contributing to the molecular structure, shape and mechanical properties of tissues, such as the tensile strength of the skin and the tensile strength of ligaments [2]. Collagens also have important functions in the cellular microenvironment and are involved in the storage and release of cellular mediators such as growth factors [1]. The body's loss of collagen starts between the ages of 18-29. After the age of 40 the human body can lose around 1% per year. Other factors such as free radicals in the body, poor diet, smoking, alcoholism and disease contribute to this. Collagen's role in the body is very important as it aids organ growth, wound and tissue healing, corneal, gum and scalp repair. It helps in the repair of bones and blood vessels. It is involved in cell biological functions such as proliferation, cell survival and differentiation. This is why collagen is found throughout the human body [2].

COLLAGEN SOURCES AND EXTRACTION

Native collagen can be extracted from a variety of sources, but the main source of extraction is bovine due to its availability and biocompatibility. Collagen extraction can be performed from a variety of tissues such as bone, tendons, lung tissue and connective tissue. Another common source is the by-products of porcine [2]. Collagen from this source is very similar to the human one. There are no allergic restrictions on its use, as it is widely used for: tendon reinforcement, hernia repairment, skin and wound healing as a material in plastic and reconstructive surgery. Alternative sources for obtaining native collagen that are not of bovine or porcine origin have been developed [2]. These sources are:

- sheep tendons and hides,
- fish tissues such as bones, skin and scales,
- by-products such as chicken, duck, rabbit or fish skin.

Denaturation of native collagen results in the formation of three α chains. This can be observed after heat treatment of collagen above 40 ◦C [2]. The separation of the chains is followed by hydrolysis under the action of proteolytic enzymes (alcalase, papain, pepsin and

others). The resulting product is commonly referred to as Hydrolysed Collagen (HC). Another type of hydrolysis is the use of chemical products in acidic (acetic acid, hydrochloric acid and phosphoric acid) or alkaline media. Alternative extraction methods include heat treatment or the application of high temperature and pressure to the protein [2].

One of the concerns regarding oral collagen supplementation is associated with oral tolerance. HC has been proposed to have higher bioavailability and solubility, due to its lower molecular weight [3]. Furthermore, lower molecular weight collagen peptides may be more easily absorbed in the small intestine. The resistance of collagen peptides to hydrolysis and digestion is primarily based on amino acid composition [3].

COLLAGEN IMPACT ON HUMAN CARTILAGES

Hydrolysed collagen can induce cartilage regeneration by increasing the synthesis of macromolecules in the extracellular matrix [4]. It has been shown to significantly increase type II collagen biosynthesis in chondrocytes in experiments with bovine cartilage cells. Experimental studies with collagen hydrolysate have shown that it accumulates in articular cartilage, where it stimulates the regeneration of type II collagen, the main type of collagen in cartilage. That results in increase of the proteoglycan biosynthesis and indicates that collagen hydrolysate can be used as an agent to stimulate regenerative effects in the cartilage of patients with damaged cartilage [5]. Moreover, collagen is able to reduce joint pain, as well as to reduce cross-linked C-telopeptide of type II collagen (CTX-II) concentrations in plasma and urine, a biomarker of cartilage degradation. Oral administration of hydrolysed collagen significantly increases the appearance of collagen-derived peptides in human blood, which influence the synthesis of hyaluronic acid from synovial cells [4]. Clinical studies show that collagen hydrolysate reduces pain and disability in some patients through its cartilage modification [5].

INDICATION

We can observe general indications in collagen supplementation, which are mentioned below.

1. The Elderly - It is known that among elderly people suffering from degenerative joint diseases, rest pain along with limited joint mobility are the predominant problems [6]. The main result in collagen hydrolysate intake is that it stimulates regeneration in the cartilage of patients with damaged cartilage [5].

2. Osteoporosis - Osteoporosis (OP) is a disease of the skeleton and is characterised by decrease in bone mass and deterioration of the anatomical or structural integrity of the bones. It leads to increased bone fragility and susceptibility to fracture. The group most affected by OP are older women, in whom reduced postmenopausal estrogen production accelerates bone loss [7]. Collagen intake has been shown to aid bone repair [2].
3. Osteoarthritis - Collagen disruption is one of the underlying causes of knee pain in patients with osteoarthritis (OA) [8]. Orally ingested collagen hydrolysate accumulates mainly in articular cartilage, where it stimulates the regeneration of the main type of collagen in cartilage - type II [5].
4. Athletes - Collagen supplements are willingly taken by athletes who expose their knee joints to a certain stress due to excessive sports [6]. The current study on young, physically active individuals demonstrated that the daily intake of 5 g of collagen peptides led to a statistically significant reduction in activity-related knee joint pain after a 12-week treatment compared [6].
5. Others - Collagen supplementation improves activity related knee joint discomfort [6].
6. Post-surgery - After arthroscopy or hip replacement, collagen may be beneficial for the recovery of the skin, especially scars. It influences in a great way the hip area and biomechanical properties [9].

OSTEOARTHRITIS

Ageing is a multifactorial and natural process that causes physiological changes in organs, tissues and cells over time. In the skin and cartilage, ageing leads to a decrease in the synthesis and changes in the proteoglycan and collagen systems, as well as a loss of glycosaminoglycans, which are responsible for the integrity and health of these tissues. This can be directly related to softening of the joint surface, a reduction in proteoglycan content and a loss of biomechanical matrix properties. Some evidence also suggests that the number of chondrocytes in the extracellular matrix decreases with age. Ageing and damaged cartilage is vulnerable to deformation during movement and is prone to develop osteoarthritis changes [10]. OA is the most common form of arthritis among the elderly and the leading cause of disability in this population. The disease accounts for 25% of visits to primary care physicians. OA causes more problems with stair climbing and walking than any other disease. The presence of arthritis and chronic joint symptoms increases with age. The incidence and prevalence of OA between the ages of 30 and 65 increased between two and ten times and increased even further after 65

[5]. There are two different forms of OA: primary and secondary. Primary OA has no clear causative factor, but may be related to ageing and lifestyle factors [5]. Secondary OA can result from various pathological conditions such as joint trauma, infection and developmental or metabolic disorders. Risk factors for OA include severe trauma and multiple joint use, obesity, systemic, metabolic or endocrine disorders, neurologic diseases, and dysplasia [5]. It manifests as persistent pain and loss of joint function, with gradual and progressive deterioration of cartilage and bone structure [11]. The disease affects one, two or more joints, such as the knees, hips, lower back, neck or finger joints. The knee is most commonly affected in approximately 83% of all OA patients [4]. OA affects the entire joint, including tissues such as cartilage, bone and synovium. These are connective tissues with an extracellular matrix in which the main structural proteins are collagens. In OA, the balance between extracellular matrix protein formation and degradation is disrupted due to increased levels of proinflammatory cytokines, cartilage-degrading proteases, cell activation and differentiation. These changes lead to progressive loss of cartilage, the formation of osteophytes in the subchondral bone layer, as well as fibrosis and vascularization of the synovial membrane [11].

Treatment

The current non-surgical treatment of OA focuses on relieving symptoms, minimising functional impairment and maintaining the quality of life [4]. The OA syndrome is not driven by a single pathogenic mechanism, but various factors including age, obesity, genetics, and injury should be included [9]. Various options are available for the treatment and include oral supplementation, intra-articular injections, exercises, pharmacotherapy, physiotherapy or surgical treatment [12]. Nevertheless, the strongest evidence-based recommendations are dietary modifications to achieve weight reduction where appropriate, along with increased physical activity [12]. The treatment of OA includes the following points that are written below.

1. Dietary modifications - Dietary modification should include moderate energy restriction without compromising micronutrient intake. It is important to reduce the intake of n-6 fatty acids by substituting oils rich in monounsaturates such as rapeseed, canola and olive oils. Moreover, cholesterol-lowering dietary portfolio should be advocated to patients with raised serum cholesterol. Vitamin supplementation: A, C, E, K and D also plays an important role [3].
2. Exercise-based rehabilitation - Exercises are the first line to treat OA and are very likely to support recovery before beginning long-term supplementation of CP. Studies provided evidence that exercise slightly improved pain and function and offered a range

of benefits on self-efficacy, depression and other psychosocial traits. These benefits may arise indirectly from a reduction in pain and improvement in function, or directly as a result of attending a rehabilitation program that developed positive attitudes toward living with OA [3].

3. Pharmacotherapy - Paracetamol, NSAIDs (non-steroidal anti-inflammatory drugs) and tramadol are prescribed to many patients with OA for symptom relief in clinical practice, supported by guidelines [13]. Nevertheless, pharmacological treatments are generally studied in short-term clinical trials, whereas the disease is chronic. Long intake duration can cause many side effects [13].
4. Intra-articular corticosteroid injections - Corticosteroid joint injections lead to pain relief that lasts for only a few months. It should be injected repeatedly over time for effective treatment, which can lead to serious adverse events such as local tissue atrophy, cartilage loss, long-term joint damage, infection, and systemic complications [12,13].
5. Collagen supplementation - Oral administration of hydrolysed collagen influences the synthesis of hyaluronic acid from synovial cells by increasing the appearance of collagen-derived peptides in human blood [4]. There have been reported several effects of collagen such as anti-inflammatory, antioxidant and reduced joint swelling in clinical trials [3]. Studies have demonstrated the positive efficacy of collagen peptides on skin and cartilage health and ageing as well [10].
6. Intra-articular collagen injections - Clinical evidence on knee OA suggests that intra-articular administration of collagen may be useful in the management of patients with persistent pain. Injections are usually administered to patients who fail to respond to physiotherapy and pharmacotherapy, especially in patients with OA, chondromalacia or other cartilage defects of the knee [12].
7. Additional supplementation - Nutraceutical supplements are orally administered, biologically active compounds that have been shown to slow down the progression of the signs of ageing [10]. These data are in accordance with other studies in which the combination of glucosamine, chondroitin sulphate, hyaluronic acid, vitamin D and other nutrients were shown to have promising benefits on joint cartilage, synovial fluid and overall clinical outcome in OA patients [10,14].
8. Surgical treatment - For end-stage hip or knee OA a joint replacement is an effective treatment option. However, joint replacements could fail after some time and needs a revision [13].

EXPLORATION OF ORAL COLLAGEN INTAKE

Many different studies while exploring oral CP supplementation in patients with OA, provided general orthopaedic scales and measured diverse times and doses of collagen. The clinical utility of both WOMAC and VAS scales makes them the most widely used tools for the evaluation of their effectiveness [4]. The WOMAC questionnaire was originally developed to measure the symptoms and physical disability of patients with OA. The subscore assesses the pain in five different activities. The VAS is one of the major methods to assess treatment efficacy which reflects the intensity of pain through a unidimensional measure [4]. The period of oral CP supplementation was diverse in different studies and lasted from 9 days until one year [14]. Moreover, the intake of collagen was also variable and considered from 5 grams to 10 grams [6]. Finally, in many studies the supplementation was well tolerated and did not induce significant side effects [14] beside individual cases of gastrointestinal complaints [15].

RESULTS

Oral Collagen supplementation

Both collagen hydrolysate and undenatured collagen exhibited a positive effect in the relief of OA symptoms which are described below [4].

1. Pain release - Joint pain was significantly reduced after oral supplementation and many factors: increased joint flexibility, mobility and reduction in joint stiffness were reported [10]. In addition supplementation with hydrolysed collagen reduced the number of additional treatments required to reduce activity-related knee pain [10] the need for additional therapies (physiotherapy, bandages, painkillers, ice packs and others) was statistically significantly reduced [6].
2. Cartilage improvement - Magnetic resonance imaging (MRI) enhanced gadolinium contrast confirms the improvement in the structure of the human cartilage due to collagen peptides supplementation. It is suggested that orally administrated collagen peptides have a potential protective function and might delay progression in patients with OA [10].
3. Inflammatory markers' concentration - In accordance with the concentration of applied HC, the plasma levels of glycine in one study increased, suggesting its ability to neutralise locally induced inflammation, according to reduction of the production of IL-6, and lipopolysaccharide (LPS) [4,7]. Nevertheless, no baseline differences of

inflammatory markers in serum such as TNF-α, MCP1 and CRP were found after oral supplementation of collagen [15].

4. Changes in microbiome - In the study examining microbiomes in patients with OA, collagen supplementation resulted in a higher concentration of Bacteroidetes/ Firmicutes. A low Bacteroidetes/Firmicutes ratio is associated with a proinflammatory state in organisms [3].

It is essential to emphasise that the formulation in which a nutraceutical is manufactured can have diverse impacts related to the pharmacokinetics, absorption, distribution, metabolism and excretion such as dose, half-life, and frequency of intake of the supplement that impacts bioactivities [3].

A wide variety of baseline lifestyle factors including nutritional status, background dietary and exercise habits could lead to variable interindividual responses to nutraceutical supplementation [3].

Intra-articular collagen injections

The novel injectable type I collagen formulation which is described to be a safe, well tolerated product, able to provide significant improvements in the scores such as VAS and WOMAC [16,17].

Histologically, one study described that intra-articular injection of collagen peptides significantly reduced cartilage degradation 10 weeks after surgery [17]. The complete mechanism is still unknown. One possible explanation says, it is probably due to the effect on chondrocytes in prompting them to produce more of the type II collagen which prevents proteoglycan loss and promotes matrix synthesis and reduce production of type I collagen which results in less fibrous tissue formation [16,17]. Furthermore, the deposition of newly synthesised collagen necessary for cartilage reorganisation may be enhanced by the availability of peptides [17].

The overall results are extremely promising but more studies should be investigated to discover whether intra-articular injection may be more beneficial than other non-pharmacological treatments already available in clinical practice [16].

PERSPECTIVES OF COLLAGEN SUPPLEMENTATION IN PATIENTS WITH OA

It is important to emphasise that firstly most patients with OA are treated in primary care with non-surgical treatments. Exercise therapy and physiotherapy typically delivered by

physical therapists, education and weight loss (if needed) are the first line universally recommended in treatment guidelines for OA [18]. Nevertheless, a significant improvement in functionality test and pain relief is found in patients with OA during both proper exercises and oral collagen supplementation (measured by WOMAC scales). However, a distinct advancement in pain relief was reported only in patients who included proper daily exercises which suggests the importance of appropriate and individual motion therapy [18,19].

CONCLUSION

The chronic pain associated with OA impacts on physical and psychosocial health and is often variable. It is essential to create a cooperative, multifunctional team of specialists which provides the patients an adjusted treatment and also offer a range of other therapies such as physiotherapy and psychotherapy. These benefits may arise indirectly from a reduction in pain and improvement in function or directly as a result of attending a rehabilitation programme that develops positive attitudes toward living with OA [9]. Given the potential of modifying cartilage degeneration and reduction of pain and disability in patients, it is reasonable for physicians to consider prescribing collagen supplements to older and active people as well as those who are overweight, have a sedentary lifestyle or have a family history of joint disease. However, further studies are needed to determine the pathogenic factors involved in osteoarthritis, its early diagnosis and from which stage of life it would be recommended to start supplementation, as well as the suitable dosage, in order to achieve significant therapeutic potential [7].

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The usage of doping in sport - challenges and hazard that come with it

Karolina Kędziora, Natalia Kałamarz, Maciej Dyda, Zuzanna Szczepaniak, Julia Błońska

Wroclaw Medical University, Wrocław, Poland

THE HISTORY OF DOPING

The history of using enhancing substances to improve performance reaches as far as the sport does.

Ancient times

There are reports of using special diets by athletes in 688 BC Ancient Olympic Games in Greece and extracts from various plants such as Ma Huang, which is an extract from Ephedra used in China about 5000 years ago [1].

Greek Olympic athletes used wine, dried figs, hallucinogenic mushrooms, coca leaves, and sesame seeds to overcome fatigue and injury [2,3].

To improve strength, vitality, and bravery athletes ate the organs of animals and humans, which wasn’t forbidden in the opposite of cheating [3].

19th century

The 19th century was a golden age for the usage of doping. The earlier-known performance-enhancing drug in American professional sports was the “Elixir of Life”, created by Charles-Édouard Brown-Sequard's. The famous Elixir was a fluid rich in testosterone, prepared from the testicles of guinea pigs and administered in subcutaneous injections [4].

In the 1880s cyclists often took nitroglycerin, caffeine, cardiac stimulants, and sugar cubes dipped in ether to improve their breathing. At the turn of the 19th and the 20th-century athletes used special “doping recipes” to gain a competitive edge against their opponents. Strychnine tablets, morphine, and mixtures of brandy and cocaine were popular among the boxers and runners until the 1920s [3].

20th century

During the Second World War a lot of sporting events took place to improve morale. These events were no exception when it comes to usage of enhancing - substances. Among the participants and soldiers, amphetamines were the most popular. From about 1946, substances, such as mentioned above, have become integrated into all varieties of sport. [3,4].

A few years later, the Soviet Olympic team experimented with testosterone supplements to increase strength and power. Since the 1960s, steroids have been extensively used by athletes in all strength sports. By 1968 runners joined this infamous group, and at the 1968 pre-Olympic training camp one third of the entire US track and field team had used steroids From 1974 the German Democratic Republic had a mandatory state doping policy. By 1978, East German athletes in every sport except sailing were receiving anabolic steroids. By the early 1980s and beyond, the usage of growth hormones was established among bodybuilders. In 1998 erythropoietin was found by the police among participants of Tour de France [1,2].

THE ESTABLISHMENT OF THE WORLD ANTI DOPING AGENCY

The main principle not only for the Olympics, but for all sportsmen is not only to conquer and win, but to maintain a healthy competition in every aspect of this sentence [1]. Since physical enhancement methods were becoming more and more prevalent among professional sportsmen, there became the need to establish a new foundation which would be responsible for regulations and rules concerning doping abuse [5].

This is the reason why in 1999 in Switzerland The World Anti- Doping Agency (WADA) was set up as a result of the “Declaration of Lausanne” to prevent the increasing performance of drugs and various enhancement methods [6]. WADA is a foundation created by the International Olympic Committee (IOC) as an international independent agency composed and funded by the sport movement and governments of the world. Its mission is to monitor the World Anti-Doping Code which harmonizes anti-doping policies in all sports and all countries [7].

Over the years the sport industry is developing rapidly and athletes are often pushed to the hard limits of their body's capabilities. Therefore it was expected from competitors to look for the way to make themself inhumanly strong or fast and the answer for their needs is doping. With the development of substances which can improve sportsmen capacity. The

World Anti-Doping Code every year updates the Prohibited List of drugs and methods which are forbidden in particular sports [8].

LIST OF PROHIBITED SUBSTANCES

Currently, there are many substances forbidden to be used among sportsmen, such as, but not limited to: anabolic-androgenic steroids, anabolic agents, aromatase inhibitors, anti-estrogenic substances, growth hormones, factors, and their modulators. Some of the doping products, on the other hand are commonly used medicaments, taken by millions of patients e.g. diuretics, β-2- agonists, and metabolic modulators (insulins, trimetazidine, and activators of the AMP-activated protein kinase (AMPK). On the sports' competitions prohibited list are not only the drugs but also the methods. Any manipulation with blood or its components is forbidden, no matter if it's intravascular manipulation, artificially enhanced uptake of oxygen with modified hemoglobin, or erythropoietin usage. All this makes doping one of the main problems in sports competitions as the variety of medications used to improve performance is unbelievably vast [8].

Anabolic Androgenic Steroids (AAS)

As follows: exogenous anabolic steroids like androstenediol and gestrinone; endogenous anabolic steroids with exogenous administration: dihydrotestosterone, testosterone; other anabolic agents: tibolone, zilpaterol, zeranol [9].

These are the most commonly used substances to improve exercise performance and/or body image of an athlete. The effects of testosterone on muscle mass is dose-dependent, which was proved in a study conducted by Bhasin and colleagues [10].

AAS are primarily used to increase muscle mass and as a consequence are associated with activities that require strength and high levels of peak power, such as weight lifting, throwing events and sprinting. They are also used by those seeking to increase muscle mass per se, which includes those seeking to attain a greater musculature and physical presence, as well as competitive bodybuilders. Additionally their use is known to extend to endurance athletes and cyclists who use AAS in smaller doses to increase red blood cell mass and haematocrit, which may augment oxygen delivery and utilization, as well as aiding recovery. Furthermore, the reported psychotropic effects of AAS include the elevation of mood, determination and aggression, all of which may aid in training and competition [11,12].

Side effects of AAS

AAS in supra-physiological doses are associated with cardiovascular complications. A study that investigated the cause of death among AAS users reported that around 35% of AAS users had chronic cardiac changes. The most common findings are concentric cardiac hypertrophy, dilated cardiomyopathy, fibrosis and myocytolysis; with significantly lower left ventricular ejection fraction and diastolic dysfunction. Left ventricular hypertrophy may persist even after AAS cessation. Finally, AAS abuse is linked to acute myocardial infarction and fatal ventricular arrhythmias. Other side effects relate to suppression of the hypothalamic-pituitary-testicular (HPT) axis. Although suppression of pituitary gonadotropin secretion is potentially reversible, largely depending on the duration of AAS abuse, hypogonadism may persist for prolonged periods of time after androgens are discontinued. AAS users may have reduction in testicular size, sperm count, sexual dysfunction, and other symptoms like gynecomastia that results from an increase in aromatised estrogen. In women, AAS abuse is associated with breast atrophy, hirsutism, clitoral enlargement, and menstrual irregularity. Other androgen-related side effects include acne, male pattern balding and an increase in hemoglobin. Hepatic dysfunction and neoplasms have been reported, mostly in relation to oral testosterone abuse. Muscle rupture, tendon and ligament injuries are also reported, which may result from disproportionate increase in muscle mass without an increase in strength of supporting tissue. Increased triglyceride levels, endothelial dysfunction, increased concentration of clotting factors, thrombosis, hyperinsulinemia and reduced glucose tolerance are also to be observed.

Special attention should be drawn to psychiatric side effects. Many studies have reported an association between AAS use and aggression, violent behavior, mood swings and mania. In AAS-dependent users the psychological/psychiatric symptoms are more prevalent and severe, with twice as many subjects reporting anxiety and major depression compared to AAS users without dependence. There is also an increased risk of other drug and alcohol abuse, and increased risk of suicidal and homicidal death [11,12,13].

Beta-2 adrenergic agonists

Their secretion increases at times of stress and facilitates a physiological response to a situation. In a sporting context this relates to increase in cardiac output, vasodilation, ventilation and the amount of circulating glucose, with the response being proportional to the intensity of the exercise. They are also used because of their bronchodilatory, anabolic and anti-inflammatory actions. Majority of studies however have demonstrated the limited effect of inhaled Beta-2 agonists on aerobic exercise performance despite an improvement in lung

function. Moreover, 6 weeks of salbutamol inhalation in male athletes did not result in significant improvement in endurance, strength or muscle power.. Beta-2 agonist drugs may be inhaled or taken orally and are commonly used as medications to treat and prevent asthma. WADA prohibits the use of Beta-2 agonists, including bronchodilators unless the participant has a 'therapeutic exemption', which must be applied for.

Side effects of Beta-2 adrenergic agonists

Clenbuterol and salbutamol are the most commonly reported doping agents in this class, with clenbuterol in particular being taken for its anabolic properties. Since Beta-2 agonist drugs bind to the ß2 androgen receptors in the heart they thereby elicit health risks such as supraventricular and ventricular arrhythmias, palpitations, myocardial ischemia, and even sudden cardiac failure. They are also reported to cause muscle tremor and may increase circulating glucose concentrations due to their action on the liver. Additionally clenbuterol has also been associated with reducing bone mineral content [11,12].

Human growth hormone (hGH)

Medically, exogenous hGH promotes muscle growth in people with growth hormone deficiency (GHD). This has led to its use as an anabolic doping agent by bodybuilders, weightlifters and people involved in sports requiring high levels of strength and power. It is also taken for its lipolytic effects that facilitate the loss of body fat, which also makes it attractive to bodybuilders. However the extent to which the increases in muscle mass translate into improved sports performance are unclear. Some authorities question whether there is strong evidence for its effectiveness if taken as a sole doping agent by those who are not GHD, although they do suggest that it could have a synergistic effect if taken in combination with AAS.

Side effects of hGH

The use of hGH in supra-physiological doses (which in athletes may be ten times higher than the therapeutic dose) is known to cause fluid retention due to its effects on increased sodium retention by the kidneys, with peripheral oedema resulting in swollen hands and feet as well as headaches and hypertension. It may also cause carpal tunnel syndrome and long term use can produce aspects of acromegaly. Human Growth Hormone abuse has also been reported to increase the risk of cardiomyopathy, possible arrhythmias, insulin resistance that can lead to

diabetes mellitus, bone abnormalities, adverse lipid profiles, acute renal failure and osteoarthritis [12].

Stimulants

Studies indicate that stimulants are responsible for around 6 – 18% of the positive samples detected in the sporting context. The potential ergogenic properties of stimulants primarily relate to their effects on the central nervous system and their capacity to:

- reduce the perception of fatigue,
- increase alertness,
- promote self-efficacy and confidence,
- in some cases stimulate cardiac output and blood flow to the exercising muscles.

Typically, they work via their pharmacological effects on increasing the release of neurotransmitters, blocking the reuptake of neurotransmitters, and the activation of receptors. Some mimic the responses of the sympathetic neuroendocrine system, notably adrenaline and noradrenaline, whilst others affect the dopamine and serotonin systems.

WADA lists over 60 specific drugs within this category and includes a general statement aimed at covering similar drugs with similar properties.

Side effects of stimulants

Evidence for the ergogenic efficacy of many stimulants on sport performance is often equivocal and the use of such drugs can entail serious health risks including hyperthermia, stroke, respiratory and cardiac arrest.

Aromatase inhibitors, selective estrogen receptor modulators (SERMs) and other anti-estrogenic substances

Estrogen blocker drugs include anti-estrogen drugs that block estrogen receptors and aromatase inhibitors that block the synthesis of estradiol.

Hence when males take these drugs the negative feedback process is interfered with, resulting in increased secretion of gonadotropins from the pituitary gland and a subsequent increase in circulating testosterone.

They may therefore convey an ergogenic benefit to men from the elevated levels of testosterone.

Side effects of Aromatase inhibitors, SERMs and other anti-estrogenic substances

When used inappropriately the health risks include cardiac arrhythmias, dizziness, osteoporosis and joint pain. Some can also result in breathlessness.

Metabolic modulators

Metabolic modulators include insulins, and Peroxisome Proliferator Activated Receptor δ (PPAR 3 δ) agonists. As a doping agent, insulins may increase the rate of glucose uptake into the muscles and thereby aid recovery by facilitating muscle glycogen replenishment. In addition to their hypoglycemic properties, insulins have an anabolic action, which makes them potential doping agents for increasing muscle mass. However, whilst there are some reports of insulin abuse it does not appear to be as widespread as other anabolic agents. PPAR δ agonists specifically mentioned in the WADA prohibited list are 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) and GW1516. Their inclusion on the prohibited list relates to their effect in augmenting the adaptations to endurance training, such as the enhancement of mitochondrial biogenesis, angiogenesis and insulin sensitivity, with the overall outcome being - muscle fibers with a greater aerobic capacity and greater fatigue resistance [12].

Other substances used for doping:

- diuretics and other masking agents: glycerols, plasma substitutes, acetazolamide, furosemide, indapamide
- autologous and allogeneic blood doping,
- narcotics: buprenorphine, fentanyl, methadone, morphine,
- cannabis extracts: cannabis, hashish, Tetrahydrocannabinol
- corticosteroids: cortizon, hydrocortisone, prednisone, methylprednisolone [9].

BLOOD DOPING

The World Anti-Doping Agency (WADA) defines blood doping as “the misuse of certain techniques and/or substances to increase one's red blood cell mass, which allows the body to transport more oxygen to muscles and therefore increase stamina and performance” [14]. We can differentiate between multiple prohibited procedures such as the use of synthetic oxygen carriers, the transfusion of red blood cells (RBCs), the infusion of hemoglobin(Hb), and the artificial stimulation of erythropoiesis.

Erythropoietin (EPO)

EPO is a peptide hormone secreted by kidneys and it is responsible for stimulating red blood cells production in bone marrow in response to hypoxia. EPO was initially produced synthetically by using DNA recombinant technologies in cell culture for treatment of such diseases as anemia, chronic kidney disease or myelodysplasia and as a post-chemotherapy treatment in cancer patients. The blood-forming properties of EPO triggered athletes to use its properties to increase their aerobic capacity by increasing the number of red blood cells which shuttle the oxygen to their muscle cells [15]. Subsequently other forms of using EPO such as drugs activating the endogenous Epo Gene, Epogene transfer and other erythropoietic hormones have been appearing [16].

Peptidic erythropoiesis-stimulating agents (ESAs)

Recombinant human erythropoietin- rhEpo preparations currently are available in Epo Complementary DNA (cDNA) transfected Chinese hamster ovary (CHO) or baby hamster kidney (BHK) cell cultures. There was a therapeutic rhEpo engineered in human cells (epoetins) but it has been off market since the beginning of 2009 because the patents of the originator epoetins have died, however biosimilar products have been approved in many parts of the world [17]. They were extremely desirable by athletes especially with a recent detection problem which has arisen with the addition of proteases to urinary samples, which destroys the erythropoietic proteins. The adulteration of urine with proteases is a prohibited method,1and there have been developed several techniques for the detection of their misuse [17]. There are also available Epo mimetic peptides EMPs, which are available as synthetic cyclic peptides of about 20 amino acids or constructed on human IgG1-based scaffolds by recombinant DNAtechnology and they are both proved to successfully increase capacity in healthy man [16].

Other erythropoietic hormones:

Some hormones may stimulate the Epo production such as prostanoids, thyroid hormone, angiotensin II, growth hormone (GH), and testosterone.

Drugs activating the endogenous Epo Gene:

Drugs activating endogenous Epo Gene stimulate endogenous EPO production based on activating the EPO promoter - GTA-inhibitors or enhancer-HIF-stabilizers. Primarily they were promising agents in anemia treatment but their major problem is teratogenous nature as

a side effect. With very difficult use detection they are encouraging athletes to be used as doping methods [18].

Epo gene transfer:

Epo Gene transfer using a viral gene delivery vector to carry the human Epo gene is under control of O2 dependent hypoxia response and was a very promising to use as prohibited way of doping but the technique has never been proceeded beyond animal trials [16].

NATURAL METHODS OF EPO STIMULATION

High altitude training

High altitude training is one of the legal types of doping. This method consists of the organism's physiological reaction to low availability of oxygen [19].

With increasing height, atmospheric pressure goes down and at 2000 - 2500 meters alveolar partial pressure of oxygen is significantly lower than on sea-level. That leads to reduction of hemoglobin-oxygen saturation and reduces total oxygen content of the blood [20,21].

This hypoxic stress activates lots of phenomenons, leads to increased erythrocyte mass and allows to achieve better scores in disciplines with high aerobic components. There are various types of taking advantage of the mountain conditions for example acclimatization in the higher part of the mountain and training lower, or living and training high [19,21].

Hypobaric chambers

Alternative for dwelling in mountain conditions are hypobaric chambers. Using these devices in preparation for competition is cheaper, more comfortable, and more affordable than mountain expedition In both of these methods, low oxygen availability affects adaptation by changes in organisms. Nowadays we know some of them, but it is still a complicated and complex process. Additionally impacts of individual variability cause a significant difference depending on the person's personal abilities and therefore advantages of using intermittent hypoxia are not the same in every case..The main role in this process plays hypoxia-inducible factor (HIF), which activates molecular cascade after hypoxic stress.

HIF causes increased transcription of target genes, including erythropoietin gene. As an effect of this stimulation level of red blood cells mass in the organism is increased. Another result of HIF stimulation is a ventilatory effect caused by changes in glial and neuronal cells in

the brainstem. Hypobaric hypoxia also causes favorable ventilatory, cardiovascular and skeletal muscle effects, which contribute to and bind together the spike of sport efficiency [19, 20].

NEURODOPING

Neuro-doping seems like a possible method consisting of stimulation of the brain using different techniques to achieve better scores in sport. It is still a novelty and not a wide-spread method among athletes. However, it shows an interesting approach to modern doping [22,23]. This idea is based on non-invasive techniques of neurostimulation used in recovery functionality of patients after a stroke. In this condition we can use transcranial magnetic stimulation (TMS) based on creating currents in the brain by using magnetic pulses from an electric coil over the patient's head. Stimuli of TMS interfere with neurons' networks and influence the activity of them [24].

Another method is transcranial direct current stimulation (tDCS) which is a method of using low continuous electric current delivered by electrodes perched on the scalp.

tDCS can modulate existing excitability of the brain through facilitating remodeling of neurosynaptic organization [22,25]. These phenomenons have positive influence on attention, object recognition and memory, reaction time, and motor skill acquisition, which makes them an option to be considered in many sorts of sport disciplines. Data also shows an increase in strength and lower detections of tiredness among professional athletes. Neurostimulation is safe and does not meet the World Anti-doping Agency (WADA) requirements to be presumed illegal, and therefore gives professional athletes a chance to increase their performance [23].

DOPING DETECTION METHODS

There are currently two types of anti-doping test: urine and blood. Once a sample is collected it is sent to a World Anti Doping Agency accredited laboratory to be analyzed. They never know whose sample they have, as it is anonymous. Trained and authorized Doping Control Officers (DCO) conduct testing. Sometimes athletes are notified by what’s known as a Chaperone, who can also observe sample provision too. The assigned workers always have to show identification when they notify athletes, and then they make sure the sportsmen are accompanied at all times until the process is finished. A Blood Collection Officer (BCO) is a trained and experienced phlebotomist, who carries out blood tests [26].

Examination methods allowing laboratories to detect doping vary depending on the substances that need to be detected, laboratory's possibilities and their advancement. The ones used regularly are as follows:

Gas Chromatography and Gas Chromatography-Mass Spectrometry

Gas chromatography was one of the first analytical techniques used to test doping back in the 1970s. It is a technique that separates thermally stable volatile compounds within a mixture. Compounds are separated using differential migration of the sample through a column containing a solid or a liquid stationary phase by a gaseous mobile phase [27].

Gas chromatography-mass spectrometry (GCMS) combines gas chromatography and mass spectrometry for qualitative and quantitative results. This technique works by separating the different chemical compounds in the sample (chromatography) followed by fragmentation of the chemicals in the sample in the mass spectrometer. The fragments of these molecules are weighed at the molecular level, and these data can be used to identify the original, intact compounds. The process allows the researchers to distinguish between naturally occurring steroids and synthetic, performance-enhancing substances [27,28].

Liquid Chromatography-Mass Spectrometry

Liquid chromatography-mass spectrometry (LCMS) combines liquid chromatography and mass spectrometry techniques. Unlike gas chromatography, liquid chromatography separates analytes in a mixture by using a liquid mobile phase and solid column stationary phase. LCMS has allowed for the detection of previously untraceable drugs as well as fast extraction and analysis procedures. It is used in drug doping to detect drugs such as diuretics, beta-blockers, and long-acting beta-2 agonists. LCMS can also be used to study metabolism pathways and EPO glycosylation pathways as well as peptide hormones such as cross-linked hemoglobins which are unable to be analyzed by techniques such as GCMS [27].

Isoform Differential Immunoassay Tests

Also known as Isoforms tests, they were first introduced in 2004. Since total levels of hGH in circulation are naturally variable and can fluctuate easily, it is difficult to use a test that solely measures increased total hGH concentrations for doping. The Isoform Test allows for the detection of the changes in the proportions of the hGH isoforms after a recombined growth hormone (recGH) injection [27].

RNA testing

Blood transfusions are one way that athletes managed to evade positive doping tests for many years. Autologous blood transfusion leads to an increase of selected circulating miRNAs in plasma of pulmonary and liver tissue [27,29]. The team at Duke University showed how microRNA (miRNA) testing could tell apart new and old red blood cells, due to the discovery of the 18-nucleotide miR-720 showing a predictable pattern as blood ages. The researchers at The University of Brighton are looking into the fingerprints that drugs leave behind in RNA. By analyzing the genetic markers in a sample, the banned substances can be detected weeks instead of hours or days after being taken. These methods can be very soon spread as the basic methods for blood transfusion detection [27]. Blood parameter analyses are performed using automated blood cell counters, and the resulting hematologic variables could be correlated to quantitative PCR measurements of circulating miRNA levels. PCR-based detection of miRNAs is a well-established, robust, and reproducible method with a number of key advantages, including its high sensitivity and specificity, potential for target multiplexing, and low RNA input requirements, all of which facilitate expression analyses, even in samples collected for anti-doping purposes with limited amounts of material [30].

Biomarker Tests

These are one of the simplest ways to detect steroids and hormones in samples. Biomarkers are measurable markers by which diseases can be identified. The Athlete Biological Passport is a common way of continually monitoring irregularities in biomarkers. Commonly used biomarker tests for drug abuse look for growth hormone (GH) and erythropoietin (EPO) abnormalities. The GH biomarker test looks at biological markers of GH activity, such as insulin-like growth factor 1 (IGF-I) and procollagen type III amino-terminal propeptide (P-III-NP). Testing for IGF-1 and P-III-NP allows for an increased detection time of seven days due to the longer serum half-lives. EPO biomarker tests look at hemoglobin, hematocrit, and reticulocyte levels [27].

Combination of biomarkers

Future research should explore complementary paths using mathematical methods for the combination of the multitude of markers that often display a good sensitivity but may lack specificity. Approaches such as support vector machines and other classification techniques that are in use in many other domains of science might be helpful. In this context, information from

different sources (e.g., urine tests, blood tests) should be combined, as also for urine test information, a longitudinal monitoring has been proposed [29].

A promising new method was developed to detect blood transfusion misuse, based on the measurement of the metabolites of the plasticizer diethylhexylphthalate (DEHP) in urine. The use of DEHP has been extended in medical devices, especially in the bags used to store blood products, which have been authorized for the last three decades. The good preservation conditions of blood and its components are the main benefits of using DEHP in the bags, although there is a high exposure to this chemical during the transfusion process, which allows to detect the above mentioned method of physical efficiency enhancement [31].

THE WORLD ANTI DOPING AGENCY TO FIGHT DOPING ABUSE AMONG SPORTSMEN

The World Anti-Doping Agency was established in order to monitor and promote the fight against doping in sport. It is also involved in education, which is why since then, as part of its activities, many campaigns to fight against doping have been created, including the famous anti-steroid campaign called Play Asterisk Free. This organization also approves substances that may be allowed for use by competitors and draws up a list of prohibited substances, the presence of which in the body is controlled [32]. The most commonly used are anabolic androgenic steroids, β2-agonists, hormone antagonists and modulators, diuretics, various peptide hormones, and growth factors. During competition, an additional wide range of compounds may also be prohibited such as stimulants, narcotics, cannabinoids, glucocorticosteroids, and beta-blockers [33]. WADA is also responsible for standardizing performance of examinations on detection of the prohibited substances and methods used by the people in sports performance [5].

ATHLETE BIOLOGICAL PASSPORT (ABP)

Due to doping, which is spreading among athletes, the "Athlete biological passport" was introduced to combat doping. This means that the athlete can be tested at any time and all tests are recorded in his history [34]. This is quite a controversial approach because it raises the problem of controlling private life and access to personal information.

The ABP Program is based on a combination of statistical analysis of laboratory results and human evaluation of Passport data in order to identify athletes or specific samples requiring further attention.

The ABP Program is currently composed of two modules:

- The Hematological Module, which aims to identify enhancement of oxygen transport, including use of erythropoiesis-stimulating agents (ESAs) and any form of blood transfusion or manipulation. This Module considers a panel of biomarkers of blood doping that are measured in an athlete's blood sample.
- The Steroidal Module, which aims to identify use of anabolic androgenic steroids (EAAS) when administered exogenously and other anabolic agents, such as selective androgen receptor modulators (SARMS). This Module considers a panel of biomarkers of steroid doping measured in an athlete's urine sample [35].

The ABP continues to be an essential tool with some significant potential for further development in order to protect clean athletes and clean sport, as well as a key strategic priority for WADA in terms of further research and development [35].

THE DOPING ABUSE

Despite the measures taken to combat doping, research conducted in 2003-2015 shows that the proportion of athletes using doping continues to increase. The important thing is that the use of particular substances differs depending on the sport discipline and whether it is an individual or team sport. These studies allowed us to narrow down the groups of athletes most suspected of using doping and to prepare appropriate tests to detect it [36]. The doping phenomenon in sports is increasing and diversifying, as are the drugs used for doping. There is a permanent race among those who invent new doping methods and sports ethics organizations that are searching for more performant methods to detect them. However, most of the time, those coming up with new doping methods are always one step ahead. Will this race ever stop? [37].

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The sexuality of people with disabilities

Maja Mielczarek[1], Jan Sroczyński[2], Paulina Wójcik[2]

1. Faculty of Medicine, Faculty of Medicine, Medical University in Wrocław, Wrocław, Poland
2. Faculty of Medical Sciences and Health Sciences, Faculty of Medicine, University of Technology and Humanities in Radom, Radom, Poland

List of abbreviations

ID- Intellectual disability

INTRODUCTION

Sexuality has always been and will be an indispensable part of human life. It is recognized as a human right by health organizations such as World Health Organisation [1]. It plays a major role in procreation, social relations, and pleasure. Although the interest in sexual health and rights has grown over the years as well as the concept of sexual education, the issues concerning sexual intimacy and disability have remained unaddressed [2].

Disability is defined as impairment due to an injury or disease that results in physical, mental, emotional, or functional limitations and difficulties [3]. According to WHO, there are more than 1 billion people living with disabilities in the world, which stands for 15% of the whole population. Disability concerns people of every race, sex, age, and ethnicity. The number of people with disabilities is growing every year due to multiple reasons like living longer with disabling diseases, increased incidence of chromosomal abnormalities or serious accidents [1].

SEXUAL ACTIVITY OF PEOPLE WITH DISABILITIES

People with disabilities have to perceive many environmental and psychological barriers that may influence their sexual lives, such as experiencing emotional issues about their

self image, having walking/movement problems, visual or self-care disabilities, having to use physical devices, and to receive assistance and care in the home environment [4].

People with disabilities form a large, heterogeneous population with many specific sexual needs that differ from the general population [1]. Though the details of sexual relations and intercourses of individuals with disabilities may be distinct from those of the general population, they are nevertheless as important.

Findings from researchers confirm that people with intellectual disabilities are less likely to have had sexual intercourse by age 19/20 than their peers. 75% of men and 72% of women with an intellectual disability never had sexual intercourse (89% and 88% for the control group) [5]. People with intellectual disabilities are less likely to have had sexual experiences than disabled people or young people from the general population. This also held true for all forms of sexual contact such as kissing or hugging [6]. According to the National Survey of Family Growth performed in 2003, individuals with disabilities are more likely to report more than 10 sexual partners over a lifetime, to identify other than heterosexual and to have more same-sex sexual partners than people without disabilities [7]. Besides that fact, boys and girls with intellectual disabilities are significantly more likely to commonly have unsafe sex than their peers [5]. Because of that, they were also noted to acquire an increased number of sexually transmitted diseases, unintended pregnancies as well as sexual violence [8]. Alarmingly it is noted that individuals with disabilities have smaller chances of obtaining police intervention, sexually transmitted infection prophylaxis, and legal protection. Increased health risks mentioned above ale contributed to poverty, illiteracy, lack of access to sexual education, and lack of power when negotiating safe sex [9]. Sexual health clinics need to be equipped to deal with people with mild/moderate intellectual disabilities [5] .

It is also important to acknowledge that apart from facing limitations such as social exclusion and stereotyping, individuals with disabilities often face barriers solely due to their medical condition. They are reported to have significantly higher rates of female sexual dysfunction, erectile dysfunction, and low desire [10]. The physical limitations pose difficulties to physical as well as emotional aspects of the sexual lives of both a person with a disability and their partner. There may be problems and pain experienced during positioning and the sexual act itself. Severe physical impairments are associated with lower levels of self-esteem and sexual satisfaction. People with severe physical disabilities experience higher levels of sadness about their sexual life than individuals with mild or no physical disabilities [10]. They were also found to be less engaged in sexual relations than those with milder impairments. Evaluating the differences in perception of their sexuality according to sex, women often had

more positive feelings and significantly more sexual experiences than men with similar levels of disability. The same research has also proved that people who had a physical disability for a longer period of time are also more positive about their sexuality with it, which shows a huge hope, especially for individuals with acquired disabilities [10]. In some cases, sexual barriers are caused by the treatment of secondary conditions like depression and heart conditions [11].

Nevertheless, there are ways to deal with those limitations, that should be advised by the healthcare providers. For people experiencing pain during intercourse, it is suggested to use analgesics before, and for limitations in positioning, it is possible to take muscle relaxants. Another option is using sexual enhancement devices. Consulting sexologists and sex therapists can also prove helpful in those situations [12]. For people who are unable to have conventional sexual intercourse, it is advised to try other sexual activities such as mutual masturbation, oral sex, and nongenital touching [1].

PSYCHOLOGICAL IMPACT

False assumptions circulating around society about sexuality of people with disabilities creates a downward spiral of asexuality that may influence an individual to internalise such behaviours to for example consider himself/herself asexual or hypersexual. These people often experience anxiety and question their sexual performances. Stereotyping and stigma affects confidence and renders it difficult to find a partner [13]. People with intellectual disabilities experience bullying more often than their peers. Both men and women with intellectual disabilities who were bullied were more likely to report unsafe sex on 50% + of occasions [6]. Rescent studies show that restoring and improving sexual lives of poeple with acquired physical disability has a significant psychological impact and plays an important role in patients rehabilitation process [14].

SOCIETY PERCEPTION

There are many incorrect assumptions shared among people in society about the sexual lives of people with disabilities. There used to be an supposition that people with disabilities experience a “relative absence or insufficiency of sexual interest, biologically and socially described function, and interpersonal sexual engagement”. People on wheelchairs, for example, are believed to be incapable of having sex and are assumed to be asexual individuals [15]. Another common misconception is that when a non-disabled person is in a relationship with

an individual with a disability, he/she has a duty to take care of the one with disability [16]. In history, disabilities were considered defects that are abnormal and should be avoided, which even led to sterilization of people with physical disabilities [17]. Even though those practices are no longer performed there are still beliefs held by some parts of society that people with disabilities should not have sex and should not have children [18]. In 2017 research was performed on non-disabled people of South Africa, concerning their opinion on the sexuality of people with disabilities. Participants of this research were given a questionnaire with particular statements and asked whether or not they apply to people with and to people without disabilities. In the findings, participants believed that 61,47% of people with disabilities are capable of expressing sexuality when in comparison they agreed with this statement applying to 72,49% of the general population. There were similar results concerning sexuality being a basic human right, benefiting from sexual and reproductive health services and sexual education. In the same research, respondents were asked to indicate the percentage of people who identify as asexual believed it true for 29.97% of people with disabilities and 25.23% of people without them [19].

Disabled people are often excluded as potential sexual partners. One British poll found that 70% of adults surveyed would not consider having sex with a disabled person [20]. Images of disability and sexuality either tend to be absent or disabled people being presented as asexual, perverse and hypersexual. Furthermore the population of people with intellectual disabilities is commonly perceived as vulnerable to sexual abuse and exploitation [21].

SEXUAL EDUCATION

Sexuality is often overlooked in the development of social-skill learning plans during their education [21]. Young people with intellectual disabilities have significantly lower levels of sexual knowledge compared with their peers from the general population [22]. According to an research performed on caregivers of individuals with disbilities, many caretakers consider people they take care of as child-like and incapable of sexual needs and feelings [21]. McCabe's research published in 2000 stated that around 50% of people with disabilities do not receive any form of sexual education. Moreover, it has shown that when usually non-disabled people receive their basic sexual education from parents and friends, in the case of people with disabilities it usually comes from other sources [23]. People with intellectual disabilities are less likely to discuss sexual issues with family or friends leading to a lack of normalisation and consolidation of knowledge [22]. It is not common for the caregivers to leave individuals with

intellectual disabilities during social gatherings, which could allow them to explore and develop their sexual identities. Learning how to react and behave independently is vital for growing future relationships and friendships. It is also important for people with intellectual disabilities to learn how to define their personal space boundaries and to recognize behaviors that violate this boundaries [21].

Individuals with disabilities are at significantly higher risk of sexual victimization than people without disabilities, and that is why proper sexual education should play essential part in their schooling [4]. According to research performed on 60 people with intellectual disabilities and 60 young people from the age of 16-18, only 25% of questioned people with disabilities were aware of the legal age of consent in a heterosexual relationship. 72% of participants with disabilities could realize that being threatened with a knife to have sex means it is not consented. More than half of individuals with intellectual disabilities either thought that people with IDs were not allowed to have sex by law, or they did not know if they were allowed to have sex by law. Similar opinions were held concerning people with IDs being able to get married. A lot of adults with IDs were not aware that the laws about rape, abusive sex, and sexual assaults were also applying to them [24].

CONCLUSIONS

People with disabilities are sexual beings and have the same needs as people without disabilities, though they are forced to face psychosocial disadvantages and barriers that include discrimination, stereotyping, prejudice, and stigma [2,25]. Unfortunately they are often not seen as fully sexual by community members and are excluded as potential sexual partners. Apart from that, there are many sexual and reproductive healthcare barriers among people with disabilities. Researches also show that people with disabilities have a higher tendency to engage in risky sexual intercourses. It can be related to possessing a lower level of knowledge about safe sex than their peers. That is closely related to multiple barriers of accessing proper sexual education. What is disturbing in research's results is that people with disabilities, particularly women, children, or individuals with intellectual disabilities, are be more vulnerable to sexual abuse, exploitation, and violence [15].

They also tend to be marginalized in relation to systems of care, including healthcare. That is why society should pay attention to treating people with disabilities on an equal footing with others in case of sexuality and emphasize their sexual education.

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SELECTED PROBLEMS CONNECTED WITH CORONAVIRUS INFECTION

Neurological manifestations associated with COVID-19

Julia Mężyk[1], Joanna Gołda[1], Aleksandra Snopkowska[1], Marta Nowakowska-Kotas[2]

1. Student Science Association of Neurology, Wroclaw Medical University, Wrocław, Poland
2. Department of Neurology, Wroclaw Medical University, Wrocław, Poland

List of abbreviations

CNS - Central Nervous System

SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2

WHO – World Health Organization

COVID-19 - Coronavirus Disease 19

PNS - Peripheral Nervous System

TNF-α – Tumor Necrosis Factor-alpha

IL – Interleukin

ACE – Angiotensin-converting Enzyme-2

BBB – Blood-brain Barrier

CRP – C Reactive Protein

CK – Creatine Kinase

IFN γ – Interferon gamma

MRI – Magnetic Resonance Imaging

CT – Computerized Tomography

EEG – Electroencephalogram

PET – Positron Emission Tomography

PCR-Ct – Polymerase Chain Reaction – Cycle Threshold

GBS – Guillain-Barré syndrome

IVIG- Intravenous Immunoglobulins

LMWH - Low Molecular Weight Heparin

DWI – Diffusion-Weighted Image

FLAIR- Fluid attenuated inversion image

ADC- Apparent diffusion coefficient

CSF- Cerebrospinal Fluid

NCS- Nerve Conduction Study

EMG - Electromyography

INTRODUCTION

Viral neurotropism

Neurotropic viruses can cause devastating central nervous system (CNS) infections in all age groups. Viral CNS infections are almost as common as bacterial infections, with an incidence of 20–30/100.000 per year [1]. Many of them, including Coronaviruses, H1N1 influenza virus, Herpesviruses, Orthomyxoviruses, and Parvoviruses, represents similar neurological symptoms that causes problems with proper diagnosis and adjustment treatment [2,3,4]. Despite the diversity of viruses that invade the CNS, many infections induce common pathogenic cascades such as the breakdown of CNS barriers and the release of detrimental mediators that can cause neurotoxicity [5]. It is essential to understand interrelated inflammatory mechanisms and identify universal mediators promoting CNS inflammation to develop new diagnostic and treatment strategies [1].

CNS symptoms in viral infections

Previous coronavirus epidemics have reported 10-15% of cases with similar symptomatology [4]. Headache and dizziness have been largely present in most studies conducted across the globe and often occur as a symptom of other viral meningitis, encephalitis or infectious encephalopathy or could be a temporal association with a systemic viral infection [4,6,7]. More than a third of patients experience impaired consciousness or delirium during the acute course of the disease [8]. Signs of impaired corticospinal tract involvement could also be induced by other factors like metabolic imbalances, acute toxic or hypoxic encephalopathies, strokes or seizures with postictal confusion [4].

SARS-CoV-2 INFECTION

In December 2019, a new respiratory virus, later named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first detected in the Chinese city of Wuhan

[2, 9]. WHO declared a coronavirus disease 19 (COVID-19) pandemic in March 2020, caused by SARS-CoV-2 infection [10]. SARS-CoV-2 primarily causes upper and lower respiratory tract infections, manifested by cough and fever. Extrapulmonary symptoms are also common, such as gastrointestinal and neurological symptoms [11]. The condition can lead to severe pneumonia, respiratory failure, sepsis, and multiple organ failure [10]. The clinical course of the disease can vary from asymptomatic cases to those requiring intensive therapy [11]. A higher infection rate is observed in neonates, the elderly and people with comorbidities [9]. Approximately one-third of patients infected with the SARS-COV-2 develop neurological symptoms [2,9].

The neuro-invasive nature of the SARS-COV-2 has been suggested in histopathological studies. The virus is capable of directly infecting central (CNS) and peripheral nervous system (PNS) cells [10]. However, it should not be assumed that all neurological symptoms are due to direct infection of the cells of the central nervous system of the CNS [12]. Hypoxemia, hypoperfusion, dehydration, glucose dysregulation and sedation may also influence the development of neurological symptoms [10].

Transmission of SARS-CoV-2

According to the available literature, SARS-CoV-2 can spread between people differently [13,14,15].

Current evidence suggests that SARS-CoV-2 is primarily transmitted between people directly via respiratory droplets. The virus spreads mainly when people are in close contact with an infected person with respiratory symptoms such as coughing or sneezing. However, infectious particles' droplets can also be released while speaking or even quiet breathing. Inhalation of air carrying contaminated droplets may spread infection [16,17].

The virus can also easily spread in crowded indoor settings, crowded spaces with poor ventilation, or prolonged contact with an infected person. It happens because aerosol particles can remain suspended in the air for minutes to hours [16,17].

Besides that, some data confirm that SARS-CoV-2 can be transmitted into the human body indirectly via contact with surfaces contaminated by the virus [15]. People become infected when they first touch contaminated objects or surfaces, and then their hands come into direct contact with mucous membranes such as the eyes, nose or mouth [16,17].

Recent studies also suggest that transmission of SARS-CoV-2 can be affected by environmental factors such as temperature, humidity, precipitation, air currents, pH and radiation [18].

ROUTES OF ENTERING THE NERVOUS SYSTEM BY SARS-CoV-2

It is supposed that SARS-CoV-2 can attack the nervous system in several different ways and through various mechanisms. First, the virus can directly enter and damage nerve cells. Second, the virus can enter the central nervous system through blood circulation. Third, the virus can transmit through neural pathways, infecting sensory or motor nerve endings.

Hematogenous route

SARS-CoV-2 may infect the endothelial cells of the blood-brain barrier and cause an increase in the permeability of the vascular endothelium. This will allow the virus to penetrate the blood-brain barrier and lead to the induction of local inflammation by increasing the production of chemokines and cytokines. At the same time, the migration of inflammatory cells to the brain parenchyma will be facilitated [14,19,20].

Neuronal route

SARS-CoV-2 can also enter the nervous system by infecting peripheral nerves and then entering the CNS retrograde via active axonal transport. The transport via olfactory pathways can be a great example of that. The unique anatomic [19] construction of the olfactory nerves and olfactory bulb in the nasal cavity and forebrain makes it work as a transport channel between the nasal epithelium and the brain. It is believed that SARS-Cov-2 can reach from the nasal cavity the entire brain and cerebrospinal fluid within days. Further neurodegeneration can be caused by misdirected host immune responses against SARS-CoV-2 or direct damage to neuronal cells by replicating viral particles [14,19,20].

PATHOPHYSIOLOGY

Neurological symptoms of SARS-CoV-2 infection not only can be caused by the direct viral attack on structures such as neurons, glial cells, cerebral vessels and the blood-brain barrier but also secondary due to immune response against the virus. The virus can have an impact both on the central and peripheral nervous systems. There are a few possible mechanisms of neurovirulence of SARS-CoV-2, which are further described below.

Hypoxia

A lot of patients with a severe COVID-19 infection suffer from hypoxia due to shortness of breath and dyspnea. Impaired breathing mechanisms can lead to a build-up of acids in the

brain which contributes to cerebral oedema. As a result the intracranial pressure increases, which can cause drowsiness and sometimes even coma [14].

Infection induced cytokine storm

It is observed that the SARS-CoV-2 may also trigger a systemic inflammatory response syndrome that can contribute to the blood-brain barrier dysfunction. Hyperactivation of the immune system results in activation of glial cells, and afterwards excessive increase of levels of inflammatory factors, such as cytokines, chemokines, and other signals of inflammation. The production of interleukins (ILs) such as IL-6, IL-12, IL-15 and Tumor Necrosis Factor-alpha (TNF-α) is most often observed. Recent studies report that there is a positive correlation between IL-6 and the severity of COVID-19 symptoms. The production of pro-inflammatory cytokines then may lead to significant damage to the blood-brain barrier, which can induce and magnify the neuroinflammatory process [14,19,20].

Angiotensin-converting enzyme-2 (ACE-2) binding related neurovirulence

The angiotensin-converting enzyme-2 is said to be one of the most important targets of SARS-CoV-2. This enzyme has a huge impact on blood pressure regulation and anti-atherosclerosis mechanisms. A lot of receptors for ACE-2 are present in the glial cells and neurons, particularly in the brainstem and also in the regions, which are responsible for the regulation of cardiovascular function. They are also expressed by endothelium. The endothelium also prevents thrombosis and is responsible for hemostasis, therefore endothelial cell dysfunction, induced by COVID-19 infection, can be an important driver of coagulopathy and increased thrombotic burden. To the prothrombotic state contributes factors such as disruption of the antithrombotic endothelial surface caused by endothelial cell activation by infection, excess thrombin generation and early termination of fibrinolysis. It is reported that SARS-CoV-2 in the endothelium is accompanied by inflammatory cells and evidence of endothelial cell death, which suggests an endothelitis and can explain microcirculatory injury and failure or injury of organs. For instance, there has been case report of severely ill patient with COVID19, ARDS, acute renal failure, and altered mental status in whom von Willebrand factor, a marker of endothelial stimulation and damage, was massively elevated at 500% of normal. -It has been also noticed that the most frequent comorbidities of COVID-19 patients are hypertension, diabetes, and cardiovascular disease, which share endothelial dysfunction as a common feature. That is why it is suggested that the vascular endothelium may be a key organ in COVID-19 infection [20,21].

SARS-CoV-2 uses spike proteins present on its surface to bind with ACE-2. This can badly affect the blood pressure regulating mechanism and predispose infected patients to cerebrovascular events. Especially older people or those with treatment-resistant conditions are concerned [19,20].

Demyelination of nerves

There is also some evidence of SARS-CoV-2 involvement in demyelination. Current studies show that COVID-19 infection can be a risk factor for demyelination both in the peripheral and central nervous systems. The demolition of the myelin sheath is mostly provoked by a complex autoimmune reaction [14,22].

EPIDEMIOLOGY OF NEUROLOGICAL AND PSYCHIATRIC MANIFESTATIONS OF SARS-CoV-2

In retrospective studies, it is emphasized that respiratory and gastrointestinal symptoms are the most commonly observed symptoms among patients diagnosed with COVID-19, but the central nervous system may also be affected after the damage of the blood-brain barrier through the blood vessel-rich meninges [23]. Many researchers inform about 36.4% of patients who had neurological involvement more in the CNS than in the peripheral nervous system [4,6] . In the retrospective study from Wuhan, patients developed acute cerebrovascular events during COVID-19 infection. Several other studies have shown neurologic involvement as the presenting feature of SARS-CoV-2 infection or have reported post-infectious neurologic complications [4].

Central nervous system (CNS) manifestations of SARS-CoV-2

Although mostly considered a rather non-specific symptoms of any viral infection, headache has been largely present in most studies conducted across the globe, ranging from 3% to as high as 13% in some studies [25]. Peripheral nervous system (PNS) manifestations of SARS-CoV-2

The SARS-CoV-2 infection may affect cranial nerves (i.e. olfactory and gustatory dysfunction, oculomotor nerve palsy), peripheral nerves (polyradiculopathy, neuropathy, Guillain Barre Syndrome), neuromuscular junction (causing myasthenic crisis in patients with history of myasthenia gravis) and muscles (myopathies) [7].

Table 1. The most common symptoms and disease reported as the manifestation of SARS-CoV-2 infection in central nervous system (based on [7,23,24]) are listed in table below

SYMPTOMES	DISEASES
- Headaches **- Anosmia, Hypogeusia** **- Spasms** **- Confusion** **- Dizziness** **- Conscience problems** **- Nausea, Vomiting** **- Ataxia** **- Seizures**	- Encephalitis , Meningoencephalitis - Encephalopathy - Atypical postpartum reversible encephalopathy syndrome - Stroke - Cerebral hemorrhage - Cerebral venous thrombosis

Epidemiology and symptoms of psychiatric incidents

The estimated cumulative incidence of psychiatric sequelae concurrent with SARS-CoV-2 is about 59% [26]. In this group decreased levels of consciousness and encephalopathy were reported in about 31% of the patients [7]. Possible mechanisms are complex and should include many different issues, caused by infections, immunological response, parenchymal damages, electrolyte imbalance, hypoxic, toxic and metabolic encephalopathy or medical interventions [3,7].

In various studies, a large group of patients was affected by both neurological and psychiatric diagnoses and was identified with altered mental status - defined as an acute alteration in personality, behavior, cognition, or consciousness and peripheral neurology [2,7, 23,24,27]. Other psychiatric findings were dementia-like syndrome, chronic fatigue syndrome, depression, catatonia, mania or anxiety [2]. Moreover, in SARS-CoV-2, after recovery from the infection, sleep disorder, emotional lability, impaired concentration or memory were reported in more than 15% of patients at a follow-up period ranging between 6 weeks and 39 months [3]. Both neurological symptoms (especially cerebrovascular events) and psychiatric impairment such as altered mental status, were identified across all age groups. Moreover, acute alterations in mental status were disproportionately overrepresented in younger patients [2]. The suspected reason for these symptoms is systemic hyperinflammation provoked by innate immunity that may impair neurovascular endothelial function, disrupt BBB and induce para-infectious autoimmunity, potentially contributing to the CNS complications associated with SARS-CoV-2 infection [26]. Many of the cytokines known to be induced in COVID-19 patients, including IL-1β, IL-6 and TNF-α, have been associated with major depression and anxiety disorders [28].

Post-Covid neurological syndrome

The number of case reports of patients having protracted neurologic manifestation after the acute phase of COVID-19 is growing [28]. The relationship between the appearance of complications in mental health is seen in the first 45–60 days after infection (occurs even in young people without specific risk factors) [6]. It constitutes symptoms such as chronic fatigue, dyspnea, or tiredness. It also represents a high-risk period where there is silent target organ damage [6,28]. Stress was identified as the most common mental health consequence (48.1%) of the COVID-19 pandemic, along with depression (26.9%) and anxiety (21.8%) [23]. It is still unknown whether there is greater activation of immune complexes and neurological inflammatory activity after infection or the persistence of symptoms long after the onset of the first sign [6]. In large research, it was found that more than half of the infected patients experienced new or deteriorating behavioural disturbances, including aggression, apathy and depression. Moreover, the researchers determined that COVID-19 indirectly affects the clinical conditions of patients with dementia and other cognitive disturbances [28].

METHODS OF EXAMINATION OF NEUROLOGICAL SYMPTOMS

Blood examination

Specific and non-specific markers should be assessed in suspicion of COVID-19 positive patients, including CBC with differential inflammation markers: CRP, CK, D-dimer, lactate dehydrogenase, transaminase, and azotemia (uremia), creatinine, IL-6 and IL-7. Peripheral cytokines involved in antiviral responses may elicit neuropsychiatric symptoms and neuroinflammatory responses. Increased secretion of proinflammatory cytokines and chemokines such as IL-6, IFNγ are found in the blood of COVID-19 patients [7,29].

Cerebrospinal Fluid (CSF)

An increased level of inflammatory precursors in CSF was described in patients whose either CNS was affected during Sars-CoV-2 infection or in those without neurological manifestations. Infection induces a high level of GM-CSF that stimulates cells to produce granulocytes (neutrophils, eosinophils, and basophils) and monocytes. Because of that peripheral cell, monocyte, and neutrophil counts were significantly higher in patients with COVID-CNS infection than in patients with COVID-respiratory infection and healthy controls. Furthermore, it was observed that such inflammatory chemokines: IL-6, IL-8, and MCP-1 were significantly accumulated in the CSF of patients with neurological symptoms [6].

Neuroimaging

Magnetic resonance imaging (MRI) especially with use of Diffusion weighted image (DWI), Fluid attenuated inversion image (FLAIR) and Apparent diffusion coefficient (ADC) [7] reveals reversible lesions or multiple white matter lesions of the brain and spinal cord, with frequent involvement of the subcortical grey matter structures [26]. Cerebrovascular symptoms (manifested as ischemic stroke or haemorrhagic stroke) were much more common in patients with severe SARS-CoV-2 infection [24,30]. The risk of stroke was directly associated with advanced age and comorbidities. Moreover, ischemic stroke happens not only in the early stages of convalescence, but it can also appear later [23].

In one publication, which describes a brain CT scan in infected patients, it is mentioned evidence of irregular hypodensities in the periventricular deep white matter, bilateral basal ganglia, thalami, pons, cerebellum, and cerebellar pedicles and corpus callosum. MRI revealed multiple areas of signal abnormality in the periventricular deep white matter, subcortical area, corpus callosum, pons, mesencephalon, cerebellum, and upper cervical cord [6].

Although nonspecific symptoms of encephalopathy are common in COVID-19 patients, cerebral neuroimaging evaluation is performed in less than 15% of the patients [30]. This raises a probable selection of underreporting cases with presumable neuroimaging findings but mild clinical symptoms, where a brain MRI or CT was considered unnecessary. Furthermore, neuroimaging findings are also found in many other constellations such as sepsis-associated encephalopathy. Carefully planned and more systematic studies are needed to clarify if observed imaging patterns are attributed to direct COVID-19 pathophysiology [7].

Other examinations

Electroencephalography of infected patients in 21% cases was indicative of encephalopathy and the ratio increased to 74% in critical ill patients. The most common abnormality was the diffuse slowing of wave frequency, especially in the frontal region [28].

Nerve Conduction Study (NCS) and Electromyography (EMG) tests defined dysfunction in the peripheral nervous system. Myopathy is assessed on the basis of NCS or EMG findings. In Covid- positive patients the EMG findings of short motor unit action potentials, with decreased amplitude and duration, along with normal sensory and motor NCS were seen. However, in some of the patients, low compound muscle action potentials are also noted. In addition, these methods are used as well as to define GBS and its variants or other peripheral nervous system abnormalities [22].

In some patients, the brain PET scan highlighted hypometabolism of the left orbitofrontal cortex, which is involved (together with the limbic system) in the chemosensory process [31] as well as hypermetabolism in the cerebellar vermis [32].

Subsequent psychological testing reveals a significant episodic memory decrement both in symptomatic and asymptomatic patients who do not report long-COVID symptoms [33]. COVID-19 survivors are significantly impaired in their ability to sustain attention and motivation on a demanding task up to nine months after COVID-19 infection, along with significantly worse episodic memory [33].

PROPOSED TREATMENT AND THERAPEUTIC OPTIONS

Preventing infections

In preventing infection, it is essential to avoid close contact with infected people, stay at home when symptoms occur, wash your hands frequently, and disinfect regularly used items. Reducing the risk of COVID-19 transmission can be achieved by wearing masks in public, not only by symptomatic people or healthcare workers [34]. Vaccination has been reported to reduce the number of symptomatic cases of COVID-19. As measured by the PCR-Ct value, a reduction in viral load was observed among vaccinated infected [35]. Lower viral load is associated with decreased further transmission, suggesting that vaccination may reduce transmission [35].

General management

The primary clinical treatment includes symptomatic management and oxygen therapy with mechanical ventilation in patients with respiratory failure [36]. The nonspecific neurological symptoms of COVID-19 often resolve with treatment of respiratory symptoms. There is no specific treatment for neurological symptoms in patients with COVID-19 [10]. Decreased platelet levels or increased ferritin levels in patients with severe COVID-19 may signify cytokine storm syndrome. Existing approved therapies for the treatment of hyperinflammation should be used to reduce increasing mortality [36]. Steroids may be considered for post-infectious / para-infective complications in all phases of the disease. The exception is GBS, which should be treated according to protocols using intravenous immunoglobin therapy (IVIG). However, there is a risk that these immune interventions may interfere with the host's protective immune response against SARS-CoV-2 [10].

Delirium

The pathophysiology of delirium in COVID-19 patients is not completely clear, so treatment decisions should be made based on presenting symptoms and comorbidities. Potential drug interaction should also be considered. The first line of treatment for delirium is behavioral modification. If this is not sufficient and the patient is a danger to himself or the medical staff, pharmacological agents are necessary [11]. In the treatment of delirium, there is a growing interest in the use of melatonin and melatonin receptor agonists due to their sleep-regulating, immunomodulatory, and neuroprotective factors. It is recommended that the addition of melatonin be considered in all patients with COVID-19 [11]. Alpha-2 agonists are effective in preventing delirium and treating agitation associated with delirium. Dexmedetomidine may improve delirium and shorten recovery time and should be considered in ICU patients. Clonidine is effective in delirium, alcohol and opioid withdrawal and may also be an appropriate first-line drug for COVID-19 delirium. Antipsychotics are an option for the treatment of behavioral dysregulation or perceptual disturbances [11]. To minimize the risk of extrapyramidal side effects and catatonia, starting treatment with low-potency antipsychotics is recommended. Psychiatrists should be cautious in treating elderly patients with antipsychotic drugs because of the increased risk of death and stroke in patients with dementia. Patients with chronic obstructive pulmonary disease should be closely monitored because they are at increased risk of respiratory failure. The use of valproic acid should be considered if additional medications are required or if antipsychotics are relatively contraindicated. Valproic acid therapy is associated with a reduction in agitation, delirium, and the concomitant use of neuroleptics. It is useful in the treatment of behavioral dysregulation in delirium patients. Trazodone may be effective for daytime impulsivity and restlessness in elderly patients who cannot tolerate antipsychotics. Amantadine and methylphenidate, may be used in patients with akinetic mutism or catatonia. All dopamine agonists can increase delirium and impaired perception [11].

Stroke

Among the critical situations faced by neurologists in the COVID-19 pandemic is the management of acute stroke. The ability to provide prompt and effective care should be considered in the risk of exposure to infection. This becomes particularly important in patients with acute stroke. It should be noted that specifically timed reperfusion therapies, such as thrombolysis and mechanical thrombectomy affect recovery and long-term outcomes in patients with COVID-19 [4]. In addition to stroke evaluation, the attending health care

professional should pay attention to other comorbidities, damage to other organs and general condition that may worsen the prognosis in such patients. Post-stroke care must be then modified according to the patient's condition [4]. The management of ischemic stroke associated with COVID-19 is the early therapeutic anticoagulation of Low Molecular Weight Heparin (LMWH), which may also be beneficial in reducing thromboembolism in these patients. However, the risk of intracranial haemorrhage, including the haemorrhagic transformation of acute myocardial infarction with anticoagulant LMWH therapy, should be considered [37]. Mechanical thrombectomy, which is an invasive procedure, is more challenging. If the patient meets all inclusion criteria, thrombectomy should always be considered a therapeutic option, as it can be performed with appropriate safety precautions, assuming the patient is a COVID-19 case [4]. Ischemic stroke patients with COVID-19 perform worse outcomes after acute revascularization treatments than contemporaneous non-COVID-19 treated patients [38].

Cerebral venous thrombosis

Cerebral venous thrombosis is a rare complication of COVID-19. Patients without risk factors for cerebral venous thrombosis may develop such neurological sequelae due to prothrombotic state induced by COVID-19 [22]. The risk of thrombosis in COVID-19 patients has increased significantly compared to the risk of thrombosis in the general population before the pandemic [38]. Initial symptoms may include signs of increased intracranial pressure such as progressive headache, visual disturbances, optic disc edema, focal neurological deficits, impaired consciousness and seizures. Venous sinus thrombosis is diagnosed based on clinical and radiological criteria. Anticoagulation therapy with heparin is preferred, using therapeutic doses of low molecular weight heparin or unfractionated heparin. Low molecular weight heparin therapy appears to be more effective than unfractionated heparin and is, therefore, a first-line treatment [22].

Post-COVID

Patients require multidisciplinary care, including long-term monitoring of persistent symptoms, to identify the need for physical rehabilitation, mental health, and support for social services. Appropriate rehabilitation is recommended to prevent muscle weakness, deconditioning, myopathies and neuropathies begin in the intensive care unit as soon as sedation and clinical stability permit. Non-hospitalized patients with long-COVID may also require physical rehabilitation [39].

In addition to physical pathologies, the COVID-19 pandemic has placed a strain on the mental health of the world's population. Appropriate mental health support should be provided for patients who require it. Patients found to require additional support were referred to specialist management. Due to persistent symptoms, a significant number of long-COVID patients are unable to return to work and may require financial support from the government. Some patients are unable to cope with daily life, especially if they suffer from social isolation or stigmatization. These groups of patients would benefit from the support of social services [39].

CONCLUSIONS

Many advances in our understanding of neurotropic viruses have been made thus far, but more research is required to improve our ability to diagnose and then treat CNS infections rapidly. Viral diseases of the CNS represent a significant burden to the global community, especially during the COVID-19 pandemic [1].

The virus constantly evolves and spreads through asymptomatic carriers, suggesting a high international health threat [34].

The complexity of COVID-19's pathology and the impact on the brain requires appropriate screening that has to go beyond the psychosocial impact, taking into account how stress and neuroinflammation affect the brain [12].

A thorough understanding of the complex and interrelated inflammatory mechanisms and identifying universal mediators promoting CNS inflammation is essential for developing new diagnostic and treatment strategies [5].

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Review of selected immunological aspects of COVID-19 complications

Sven Solisch[1], Anna Susłow[1], Adam Szwed[1], Krzysztof Gomułka[2]

1. Student Science Association of Adult Allergology, Wroclaw Medical University, Wrocław, Poland
2. Department of Internal Medicine, Pneumology and Allergology, Wroclaw Medical University, Wrocław, Poland

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes coronavirus disease 2019 (COVID-19), has afflicted hundreds of millions of people in a worldwide pandemic [1]. Aside from the symptoms and complications patients experience during the disease period, there is an accumulating body of evidence regarding the late-onset COVID-19 complications, many of which involve SARS-CoV-2 affecting and destabilizing the immunological system [1,2]. As studies continue to unveil the pathophysiology behind those disorders, understanding these mechanisms is vital for employing appropriate diagnostic and therapeutic procedures. In this article selected immunological aspects of COVID-19 complications are reviewed, focusing on the post-COVID-19 syndrome, pediatric inflammatory multisystem syndrome (PIMS), and the role of neutrophils in severe COVID-19.

POST–COVID-19 SYNDROME

Many patients suffering from COVID-19 and presenting different levels of its severity, have reported prolonged symptoms and complications, often affecting patients' quality of life, that continue to occur beyond four weeks after recovering from the infection. The residual effects of SARS-CoV-2 infection may concern various organs and systems leading to manifestations such as i.a., fatigue, dyspnea, chest pain, cognitive dysfunction, diarrhea, and arthralgia [3]. These observations led to the recognition of post-COVID-19 syndrome, also referred to as post-COVID-

19 conditions, post-acute sequelae of SARS-CoV-2 infections or long COVID-19 [4]. There is limited literature concerning post-COVID-19 syndrome, its epidemiology and exact pathophysiological mechanisms behind the disorder.

Although initially there were no uniformly accepted diagnostic criteria, most researchers agreed upon defining post-COVID-19 syndrome as symptoms that persist or develop ≥4 weeks after recovering from initial SARS-CoV-2 infection and cannot be explained by other causes [5,6,7,8,9].

Later in October 2021, World Health Organization (WHO) developed a clinical case definition for post COVID-19 condition based on Delphi consensus that reads as follows: "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time" [10].

The incidence of symptoms that may be attributable to post-COVID-19 syndrome is estimated to be about 20% for COVID-19 survivors aged 18–64 years, 25% for those aged ≥65 years and up to 85% for hospitalized patients [11]. The most frequently observed symptoms are breathing difficulties and/or breathlessness, fatigue and or malaise, chest and/or throat pain, headaches, gastrointestinal symptoms, myalgia, arthralgia, cognitive abnormalities (sometimes referred to as 'brain fog'), anxiety and/or depression [12]. Patients aged 65 or above are observed to be at an elevated risk of neurological and mental health complications [13].

Possible explanations of the mechanisms involved in post-COVID-19 include virus-specific pathophysiological variations, inflammatory injury, oxidative stress and abnormal immune response. SARS-CoV-2 is observed to cause cellular damage through inflammatory cytokines, ACE2 pathway maladaptation and procoagulant activity [7]. Reportedly, similar patterns of symptoms were observed in SARS-CoV patients in 2003 and MERS patients in 2012 [3]. Oxidative stress observed in post-COVID-19 syndrome is thought to be a consequence of mitochondrial damage that follows SARS-CoV-2 infecting type II pneumocytes. Moreover, excessive ROS production is also a known consequence of oxygen treatment that is administered in COVID-19 patients suffering from ARDS during the acute disease phase. Mitochondrial-targeted antioxidants

are proposed as a potential approach in treatment, however, this solution requires further research. The presence of SARS-CoV-2 in alveolar epithelial and endothelial cells causes a cascade of neutrophils, monocytes, and T-cells resulting in diffuse alveolar injury. Patients with severe pneumonia or ARDS in acute COVID-19 are observed to present decreased lymphocyte counts and elevated levels of cytokines, in particular, tumor necrosis factor and pro-inflammatory interleukins, e.g. IL-6 [7].

There are ongoing clinical trials investigating possible therapies for the post-COVID-19 syndrome, including i.a., hyperbaric oxygen therapy, nebulized platelet lysate, and C1-esterase inhibitor recombinant. However, as of May 2022, the only generally accepted and recommended treatment was through rehabilitation exercises that rely on gradual increases in intensity. Breathing exercises aiming to strengthen the respiratory muscles accompanied by a light regimen of aerobic training is proposed as a treatment for patients presenting impairment in physical performance. Cognitive behavioral support combined with psychological support and therapy is also indicated [9,14].

More research is needed to deepen the understanding of mechanisms behind post-COVID-19 syndrome and to form appropriate strategies for dealing with this condition, which came to be recognized as one of the most prominent COVID-19 complications.

PIMS

One of the complications of SARS-CoV-2 infection in children is pediatric inflammatory multisystem syndrome associated with coronavirus disease - PIMS. This is a new disease because the first descriptions appeared in the second quarter of 2020 [15,16]. The prevalence is estimated at about 1: 1000 children infected with SARS-CoV-2, and the mortality rate is around 2% [17]. The pathogenesis of PIMS is associated with a pathological reaction of the immune system, which results from infection with COVID-19 2-4 weeks earlier - often the SARS-CoV-2 infection itself could be mildly symptomatic or even without any clinical symptoms [18].

The main causes of the pathomechanism of PIMS are seen in the increased activity of the NF-κB pathway and the action of IL-6. Increased activity of the NF-κB pathway implies the formation of large amounts of pro-inflammatory cytokines, in particular TNF-α, which in turn causes a significant increase in the concentration of chemokines such as CCL2, CCL3, CCL20,

CXCL10, and CX3CL, whose task is to increase the migration of immunocompetent cells to the sites of inflammation. IL-6 is a pro-inflammatory cytokine whose activity increases mainly due to the activation of Toll-like-4 receptors (TLR4). The mechanism of action of IL-6 is based on the phosphorylation of the STAT3 factor, which directly influences the expression of genes encoding a number of key proteins in maintaining inflammation, including: IL-17, IL-23, IFN-γ, TNF-α, CRP or VEGF. All the above-mentioned occurrences are responsible for the control of the immune response, the initiation of angiogenesis and the activation of fibroblasts [19,20].

The clinical criteria for the diagnosis of PIMS are (1) age below 18 years with a median of 9 years, (2) fever above 38.5°C for at least 3 days, (3) increase in inflammatory markers such as: CRP, procalcitonin, fibrinogen, D-dimers or ferritin, (4) clinical picture indicating the involvement of at least two systems - e.g. severe abdominal pain or vomiting indicating gastrointestinal involvement or features of myocarditis or arrhythmias as a manifestation of cardiovascular system, (5) exclusion of other possible causes - including systemic connective tissue diseases, acute appendicitis and other toxic or infectious agents, (6) connection with COVID-19 - e.g. with a documented infection in the past or positive results of RT-PCR or antigen tests. Criteria 1-5 should always be met, while criterion 6 is not necessary for the diagnosis [21]. Laboratory tests reveal characteristic deviations from the reference ranges: very high CRP, elevated BNP or troponin I levels, and lowered levels of lymphocytes, hemoglobin, albumin and serum sodium levels [17,18].

PIMS should be differentiated from another disease entity seen in children - Kawasaki disease. Although both disorders are associated with autoimmune vasculitis, there are several differences, including PIMS most often affects older children while Kawasaki disease younger, the level of thrombocytes in the blood serum in PIMS is often lowered, in Kawasaki disease it is elevated. Complaints on the part of the digestive system are relatively common in the course of PIMS, while in Kawasaki disease they appear sporadically. Finally, the features of dysfunction of myocardial contractility or acute left ventricular failure often appear in PIMS and rarely in Kawasaki disease [22].

Treatment of PIMS is multidirectional and includes symptomatic (general) and essential (specific) treatment. Symptomatic treatment consists in supporting vital functions and monitoring the patient's haemodynamic status - blood pressure, pulse and saturation. The basic treatment has three levels and its essence is to reduce the activity of the immune system. Intravenous

immunoglobulin infusion (IVIG) is recommended as the first-line treatment. The second-line treatment is the administration of intravenous glucocorticosteroids (GCS) - most often methylprednisolone, and the third-line treatment is biological treatment in the form of preparations containing infliximab or tocilizumab [23,24]. Antiviral treatment should be reserved only for patients with positive RT-PCR results and saturation below 95% [25]. Empirical antibiotic therapy is not recommended in PIMS - it should be implemented only in severely ill patients with symptoms of sepsis or bacterial superinfections. Whereas, antiplatelet therapy in patients with PIMS should be continued until no coronary artery lesions are confirmed in the ECHO study [21,23].

Vaccination against COVID-19 should be recommended to all children over the age of five, because the disease, and above all complications in the form of PIMS, pose a real threat to the health and life of children.

ROLE OF NEUTROPHILS IN COVID-19 COMPLICATIONS

SARS-CoV-2 infection can cause mild or sometimes subclinical symptoms, but it can also lead to serious complications, presenting as severe pneumonia and ARDS. ARDS is an uncontrolled systematic inflammatory reaction associated with a tremendous amount of pro-inflammatory cytokines being released into the bloodstream and tissues, called cytokine storm. Cytokine storm drives severe and poorly understood host response, but little do we know about what actually triggers the whole cascade of hyper-inflammation in COVID-19 patients. Recent studies showed significant role of neutrophils in aggravated host response in patients with severe COVID-19. Neutrophils are first line fighters in battle against microorganisms, especially bacteria and fungi. They use many mechanisms that allow them to kill pathogens attacking our organism such as oxidative burst and phagocytosis [26]. One particular method called NETs is especially interesting considering SARS-CoV-2 infection.

Neutrophil extracellular traps (NETs) are comprised of DNA, histones and granule proteins - lactoferrin, cathepsins, neutrophil elastase (NE) and myeloperoxidase (MPO), as well as cytoplasmic and cytoskeletal proteins [27]. In general NETs entrap pathogens by its web-like structure. This mechanism is not considered as a critical immune function, but apart from its benefits, excessive NET formation can be responsible for inflammatory reactions that destroy surrounding tissues, facilitates microthrombosis, and results in permanent organ damage [26].

Unrestrained NET release has been already associated with numerous diseases, such as small-vessel vasculitis [28] and systematic lupus erythematosus [29].

Veras et al. in their cohort studies found that viable SARS-CoV-2 can directly induce the release of NETs by healthy neutrophils [30]. SARS-CoV-2 binds to ACE2 and enters epithelial cells. As a result, ACE2 expression decreases and neutrophil recruitment is stimulated. NETs produced by neutrophils, induce necrosis in epithelial cell. This leads to the release of associated molecular patterns and sets up a self-perpetuating loop of inflammation-causing exacerbating severity during COVID-19 [31]. What is more, intravascular NETs have been shown to play a vital role in initiating and congregating thrombosis in arteries and veins, what may explain hyperactive coagulation in severe COVID-19 [32]. NETs activate the contact pathway of coagulation by interacting with platelet phospholipids. In conclusion, high blood levels of circulating NETs can trigger the occlusion of small vessels, leading to damage to the lungs, heart and kidneys [26].

Analyzing the role of neutrophils in severe cases of COVID-19, another clinical consequence must be taken under consideration. The severe cases of COVID-19 were likely to present higher neutrophil count but lower lymphocyte count compared with non-severe patients [33]. As a result neutrophil-to-lymphocyte ratio (NLR) is also increased and it is found to be an independent risk factor of the in-hospital mortality for COVID-19 patients, in particular male. NLR can be quickly calculated based on a routine blood test taken on admission, allowing early identification of high-risk individuals. NLR is a valuable predictor of overall inflammatory status, up to now it was used in other than COVID-19 infectious disease, in malignancy, acute coronary syndrome, intracerebral haemorrhage, polymyositis and dermatomyositis [34].

Crucial, although not yet clarified, neutrophil role in COVID-19 pathogenesis, may imply potential treatment strategies. Thus far, systemic glucocorticoids and heparin are well-established medications used in COVID-19 patients. Heparin neutralizes histones forming NETs and accelerate DNAse I, an enzyme that degrades NETs mediated clots. Glucocorticoids, including dexamethasone, have been reported to reduce NET formation most likely by suppressing the expression of inflammatory mediators that activates neutrophils [27]. In contrast to universal immunosuppression, the specific inflammatory pathways can be targeted. Inhibitors of NETs synthesis or promotors of NETs fragmentation, as well as inhibitors of neutrophil recruitment, are suggested as future therapeutics [31,34,35,36].

CONCLUSIONS

The disease caused by SARS-CoV-2 should definitely be seen through the prism of events at the level of immune mechanisms. This applies to both the infection itself and its complications, such as PIMS. Due to the high mortality rate, not only of COVID-19, but also the above-mentioned complications resulting directly from the primary infection, we are convinced that preventive vaccination can save not only health but also life on several occasions.

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Seasonality of COVID-19

Sven Solisch[1], Anna Susłow[1], Adam Szwed[1], Krzysztof Gomułka[2]

1. Student Science Association of Adult Allergology, Wroclaw Medical University, Wrocław, Poland
2. Department of Internal Medicine, Pneumology and Allergology, Wroclaw Medical University, Wrocław, Poland

INTRODUCTION

As SARS-CoV-2, the novel coronavirus that causes coronavirus disease 2019 (COVID-19), continues to circulate around the world, patterns indicating an influence of environmental factors on its transmission have been observed.

Since there is a number of other determinants of current development of the pandemic (including social distancing, lockdowns, and vaccination campaigns), it is challenging to analyze the seasonal components having to separate their impact from that of remaining circumstances [1]. Modelling seasonal variation of COVID-19 transmission, leading to more accurate predictions, is a valuable tool in managing the pandemic [2].

SEASONALITY OF INFECTIOUS DISEASES

The role of the seasonality of infectious diseases is one of the key elements in understanding the impact of particular infections on the biological variability of the human population. Undoubtedly, the cyclical nature of infectious diseases is associated with many environmental factors, which include: weather changes, such as heavy rainfall or fluctuations in atmospheric air temperature, development cycles of vectors or pathogens themselves, fluctuations in social behavior of people (e.g., intensive contacts of children in kindergarten), but also changes in human immunity status in given populations. Many infectious diseases are characterized by a well-known seasonality [3,4].

The best-described vector-borne diseases associated with cyclical incidence are malaria, West Nile fever, and Dengue fever. All of the above-mentioned disease entities share the fact that they have the highest incidence in hot and relatively humid conditions. The most common infections occur in summer and early fall, when many people travel to tropical countries. Heavy rains of zenith along with the accompanying high temperature are responsible for the increase in the number of vectors and enable the development of microorganisms in the body of vectors [3,5,6,7].

Studies on bloodstream infections caused by Gram-negative bacilli infections have shown that they occur much more frequently in the warmer months. It was found that high temperature positively influences the colonization of the human body by *Acinetobacter spp.*, *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella spp.*, and *Pseudomonas aeruginosa* - the latter microorganism tolerates the increased level of humidity equally well [8,9].

The well-documented seasonality of the disease also applies to infectious diarrhea [3]. A bacterial disease with intense and watery diarrhea is cholera caused by *Vibrio cholerae* (most often strains O1 and O139) [4,10]. It has been proven that rains combined with a moderate ambient temperature help in the spread and survival of microorganisms. Therefore, the most frequent increase in cholera cases occurs in spring and autumn [11]. In turn, *Rotavirus* infection is one of the most common viral diseases characterized by the seasonality of infections linked with diarrhea [4]. The peak of incidence occurs in the autumn and winter period and is associated mainly with intensive contact between children in school and kindergarten, and a natural decrease in immunity during the cold months [3,12].

The most common infectious diseases concern the upper and lower respiratory tract. Diseases affecting the respiratory system are characterized by various etiologies - viral or bacterial [13]. It is the influenza virus, RSV and *Streptococcus pneumoniae* that are responsible for a significant number of respiratory ailments in adults and children. The greatest number of cases is usually recorded in winter when the effectiveness of the immune system to fight pathogens decreases and due to persistent low temperatures, we use less leisure time outdoors, crowding inside buildings. It is conducive to the transmission of infections [14,15,16]. Measles, on the other hand, was characterized by a cyclical increase in infections, on average, every 2.5 years, most often in spring or autumn. The increased incidence in these periods corresponds to the children's return to school, and hence - to increased contact between the children, which has helped spread the disease.

Fortunately, the introduction of vaccination against measles has significantly reduced the incidence of this disease [4,17]. In the last three years, we have also observed the seasonality of a new disease entity – COVID-19 [18].

The above examples show that infectious diseases constitute a heterogeneous group in terms of the seasonality of their occurrence.

COVID-19 SEASONALITY BEFORE VACCINES (2020)

"Will COVID-19 become a seasonal disease?" is one of the most important questions nowadays, considering the economical, political and social aspects of the pandemic. Predictions about seasonal outbreaks will help to prepare sufficient amount of vaccines and healthcare system resources.

Considering seasonality, we must take a memory lane and acknowledge what we already know about other human coronaviruses. Four known seasonal coronaviruses (sCoVs) circulate in human populations, including two alpha-coronaviruses (NL63 and 229E) and two beta-coronaviruses (OC43 and HKU1). In temperate climate sCoVs occurred mainly in winter months. In China and tropical climate less seasonality was observed. Winter outbreaks were similar for all species of sCoVs in the temperate climate, which suggests that SARS-CoV-2 may follow the example [19]. Furthermore, interactions between SARS-CoV-2 and sCoVs can cause cross-reactive T-cell recognition that may modulate our immune response and impact the dynamics of the COVID-19 epidemiology [20]. Tedijanto and Kissler predict that if duration of immunity to SARS-CoV-2 mimics that to other related coronaviruses, recurrent outbreaks are likely to occur [21].

Understanding what drives the seasonality of disease is essential to control it. Before launch of COVID-19 vaccines, three types of factors were mainly associated with the disease seasonality: environmental factors, viral characteristic and host features. Bukhari and Jameel claim that the novel COVID-19 pandemic has affected more seriously countries within a temperature range of 3°C to 17°C with absolute humidity between 3 g/m^3 and 9 g/m^3 [22,23], concluding that moderate temperature and dry environment are the most optimal for spreading of SARS-CoV-2 and present higher morbidity [18,24]. Cold weather increase in-door activity of humans and enhance person-to-person contact. In addition, in autumn and winter we are influenced by greater temperature

fluctuations between indoor and outdoor. When temperature in the nose drops by 5ºC, our antiviral defence weakens and we are more prone to infections [18]. Moreover, temperature has larger effects when containment measures are lifted and people mobility is higher [25].

On the contrary, other studies indicate that the most critical feature of seasonality is the day length period. Seasonal conditions with constantly changing day length and UV levels may modulate virus spread and host immune system. Correlation between UV levels and COVID-19 is not fully examined, yet promising and needs further study. UV radiation also correlates with vitamin D levels [26]. Vitamin D has a positive effect on the immune system and stimulates antimicrobial activity [27]. Seasonal changes of vitamin D levels can also influence host sensitivity to COVID-19 infection. What is more, there are also other immune system related factors. Enzyme called Furin, causes conformational changes separating the S1 and S2 domains of SARS-Co-V2 spike glycoprotein allowing viral endocytosis [18]. Dopico et al., detected that Furin transcripts in human leukocytes exhibit seasonal rhythmicity in children, with higher expression in summer and low in winter [18,28].

Another protein related to host response to viral infections including SARS-CoV-2 is ANTX1. Transcriptome analyses of human leukocytes showed that ANTXR2 expression is seasonally dependant [18,28]. These lead to a conclusion that there might be an endogenous seasonal change in immune defence against SARS-CoV-2, although further studies are needed to establish the importance of this finding.

Analysing viral features is as important as other two indicators of possible seasonality of COVID-19. Researches point out that SARS-CoV-2 stability in the air and on surface is influenced by humidity, temperature and sunlight. The virus is stable at low-temperature and low-humidity conditions, on the other hand warmer temperature and higher humidity shorten its half-life [1]. Furthermore, viral ability to spread is measured as a basic reproduction number (R_0). For SARS-CoV-2 R_0 is estimated to be about 3 (3.32 or between 2 and 3 depending on source) [29,30]. For comparison, seasonal influenza virus R_0 is estimated to be 1,27 and for SARS-CoV is between 2 and 3. Basic reproduction number briefly is the number of secondary cases resulting from one infected person and describes the transmissibility of the pathogen within a specific population and setting [30]. R_0 indicates needed mitigation efforts and mitigation reduces the effective transmission rate, also called effective R_0. It is proposed that virus will follow a seasonal pattern if its effective R_0 drops below 1 [29]. In the early pandemic times high R_0, high stability of SARS-

Cov-2 and the fact that global population was immunologically naïve against SARS-CoV-2, it was unlikely to drop R_0 in summer. Nevertheless, studies showed that a 1ºC increase in temperature and a 1% increase in relative humidity can lower the daily effective reproductive number (re) by 0,0383 and 0,0224 [22]. Nowadays, in light of gaining natural immunity and through vaccinations, we shall assume that R_0 might drop and the virus will more likely enter seasonal occurrence [30].

COVID-19 SEASONALITY AFTER VACCINES (2021 – PRESENT)

Overall, vaccines against SARS-CoV-2 are observed to prevent severe infection and COVID-19-related hospitalizations, also reducing the mortality [2,31,32].

According to recent studies by D'Amico et al. (2021), and Coccia (2022) COVID-19 seasonality in countries and regions of temperate climate, being expressed there more sharply [1], in general presented no significant alteration caused by the vaccines [33]. In comparison to the period preceding introduction of the vaccines, daily reported deaths attributed to COVID-19 manifest similar trends, reaching peak values during the winter months and subsequently decreasing throughout late spring and summer months. Likewise, the decrease in mortality observed during the warmer months was comparable across countries that presented varied vaccination rates in population [2].

Interestingly, the beneficial effect of the vaccines on reducing the mortality was observed to be stronger during the colder months. According to models and estimations for certain temperate American states presented by D'Amico et al. one percent increase of fully vaccinated citizens results in a drop of about 27 COVID-19 deaths per million on a yearly basis. When calculating the vaccination effect independently for high temperature months and low temperature months, the mortality reduction is estimated to reach about 22 and 46 deaths less respectively [2].

CONCLUSIONS

SARS-CoV-2 infection can undoubtedly be classified as an infectious disease characterized by a kind of seasonality. It has been proven that environmental factors such as the temperature or the length of the day have an impact on the course of the disorder. However, there have been no significant changes resulting from the introduction of vaccines that specifically address the

seasonality of COVID-19. Further observation of seasonality patterns can be an advantageous tool in predicting future pandemic waves which facilitates adjusting containment as needed [2].

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Impact of COVID-19 pandemic on suicide rate among various demographics

Natalia Nowak, Klaudia Włodarczyk, Weronika Biziorek, Mikołaj Palczewski, Haytham Al Hamaydeh

Faculty of Medicine, Students' Scientific Group at the Department of Psychiatry, Medical University Piastów Śląskich of Wroclaw, Wroclaw, Poland

List of abbreviations

PTSD – ang. post-traumatic stress disorder

PASC – ang. post-acute sequelae of SARS CoV-2 infection

ARDS – ang. acute respiratory distress syndrome

NGO – ang. non-governmental organization

INTRODUCTION

From the very beginning COVID-19 pandemic and its' global consequences caused a tremendous effect on lives and mental wellbeing of millions of people all around the world. The unprecedented scale of socioeconomic changes resulted in deprivation of sense of safety and demanded an abrupt and total modification of the way of living. The impact of the pandemic was particularly devastating for specific groups of people. Lack of social help for elderly resulted in them being deprived of the possibility to safely take care of their essential daily duties like grocery shopping. Shutting down of workplaces of many low-income individuals resulted in lots of people suddenly being unable to earn money needed to fulfill their existential needs. Schoolchildren were unable to have regular social contacts with their peers and were forced to spend most of the time indoors attending online classes. Due to the shutdown of face-to-face classes in most of the universities many college students had to return to their family houses. Medical staff was forced to adapt to the new reality and work under entirely different circumstances with problems they have never dealt with before and risking their own health in order to do their job. Data indicates that contraction of COVID-19 may also lead to severe psychiatric problems. Isolation and physical weakness combined with cognitive and

psychological malfunction may result in long lasting trauma and psychological function impairment.

These circumstances have led to such a significant increase in mental health issues, that some experts call it psychiatric epidemics. The prevalence of psychological problems in general population varied depending on many factors but overall an upward tendency was observed in many different age and social groups all around the world. There are many psychological problems experienced by patients in the COVID era. Some of them are depression, anxiety disorders, panic disorders, anger, impulsivity, somatization disorder, sleep disorder, PTSD, and emotional disturbances. Apart from those, probably the most severe consequence of psychological suffering - suicide [1], which is the most complicated issue related to mental health in this pandemic. Although there is strong evidence on mental health problems rising due to COVID-19, the data concerning suicidal ideations, suicidal behavior and general suicide rate presents conflicting results. Before first statistics appeared, many researchers feared of a huge spike in suicide rate. Surprisingly, the data seems not to support the idea that the general suicide rate increased during the COVID pandemic. There are significant differences in suicidal thoughts and attempts between different age groups, genders and countries of origin [2]. Early predictions projected a sharp increase in suicides in developed countries like Norway. Surprisingly, the statistics seem to suggest that it did not happen. An increase in suicide rate could be observed outside the COVID outbreak, while during the outbreak itself the number of suicides decreased [3]. On the other hand, some studies underline an increase in suicide ideation, suicide attempts and self-harm numbers especially in groups of risk, such as young people, women and individuals from democratic countries when compared to pre-pandemic levels [4]. The conflicting results emphasize the need to conduct more long-term studies. In our work, we try to focus on suicide related health issues in several groups of risk and review available data to learn more about the complex topic of suicidal behavior related to the coronavirus pandemic.

COVID-19 SUICIDE IN MEDICAL STAFF

Although the pandemic affected everyone’s lives, some groups were struck more than others. From the very beginning of it, the COVID-19 outbreak forced medical care workers to adapt to a new reality. Due to the sudden influx of new patients, many of whom were in life-threatening conditions, medics had to quickly learn new skills that were necessary to help them.

Prolonged shifts reduced the amount of time that could be devoted to their friends and families. Perpetual exposure to highly contagious patients triggered a feeling of constant tension. Even before the pandemic, health care professionals were in high risk of committing suicide compared to general population. COVID-19 exacerbated the difficult conditions faced by the medics. One of the studies conducted in Poland among health care professionals including doctors, nurses and paramedics stated that while all of the groups experienced elevated stress levels, nurses were the ones with the highest level of pressure, which lead to psychopathological symptoms, such as insomnia and depression. In the researched group, many coping mechanisms could be observed including adaptive and non-adaptive ones. One of the most frequent non-adaptive coping mechanisms was the use of psychoactive substances that ultimately resulted in deterioration of mental health [5]. Another study was conducted among Australian paramedics. Almost two-third of them reported experiencing professional burnout. When asked about concerns about their job, most frequent answers were concerning risk and safety in the workplace, uncertainty, and upheaval both at work and at home and lack of crisis preparedness. The results confirmed the lack of mental health support and wide range of psychopathological symptoms associated with COVID-19 pandemic [6].

Yet again in terms of suicide rate, the problem is more complicated than in other manifestations of psychological disturbances. Suicide can be regarded as occupational hazard in health industry. The pandemic deteriorated a situation that has already been difficult. The risk factors during COVID-19 era included increased workload, burnout, fatigue, multifaceted challenges and substance abuse [7]. As a recent Brazilian study report the suicide rate of doctors in the pandemic era seemed to be influenced by age, gender and race. Overall, the suicide rate increased in white male physicians and black male physicians but decreased in white female physicians. Among the various health occupations, the suicide rates varied depending on ethnicity. Overall, white males and females had highest suicide rates in most health occupations compared with general population. Black and white male physicians' suicide rate both increased significantly. There is little data to compare suicide among physicians in different countries [8].

The common expectation in the society is that health care professionals would put their patients' interest first before themselves in terms of their physical and mental health needs. The social support for medics struggling with psychiatric issues is insufficient. Various factors lead to burnout and suicidal behavior among physicians at work, including a lack of flexibility, lack of meaning, no sense of community, and scarce resource availability [9]. Analysis of the health

care workers' suicides reported by the press found that the most common reason for committing suicide was being infected with COVID-19, followed by work-related stress, fear concerning a COVID-19 infection, fear of transmitting the virus to others, anxiety caused by witnessing an overwhelming amount of death and mental suffering. The findings differed slightly from those found in the general population, in which the COVID-19 infection was the most common reason, but the second most common reason was economic distress [10]. Another meta-analysis of precursory literature concluded that main risk factors for suicide among physicians were loneliness, not having children and personal history of mental disorders [11].

A study conducted after the first year of the pandemic underscored the importance of moral injury which led many health professionals to suicidal ideations and suicidal behavior. Moral injury is described as a psychological consequence of transgressing moral values and witnessing such transgressions. The difficult choices the medics had to make every day, especially during early months of the pandemic caused some health care workers to have a sense of betraying their moral obligations and neglecting patients' needs. Many of them had to risk their families' health by being exposed to COVID-19 every day, which resulted in many existential dilemmas. Moral injury was described as a sense of betrayal, guilt, shame, moral concerns, loss of trust, loss of meaning, difficulty forgiving, self-condemnation, faith struggle and loss of faith. It is found to be strongly correlated with high risk of significant PTSD symptoms and suicidal behavior [12].

Another suicide risk factor was change of workplace for many physicians that were not experienced in handling of the critically ill patients. Many doctors that were not accustomed to extreme levels of pain and suffering were redeployed to unfamiliar wards due to staff shortages. Depressive symptoms were found to be disproportionately elevated among medics redeployed to intensive care units [13]. Recent study conducted among healthcare workers in United Kingdom reported that 3,4% of them experienced thoughts of suicide or self-harm in the 2 preceding weeks. When asked about the difficulties that they had to struggle with, they reported that the pandemic exacerbated many pre-existing life challenges, such as living with mental illness, working in an unsupportive environment, and experiencing personal difficulties such as relationship violence and illness of family members [14].

One of the recently published case studies blames the culture of medicine for a toxic working environment. The COVID-19 pandemic added pressure to the system that has already been a huge burden for health care workers. The article describes the gradual deterioration of mental health of an emergency medicine doctor that struggled with staff shortages, deteriorating

working conditions which resulted in him eventually committing suicide. His pleas directed to the management for more help or physician coverage were declined. Even when he admitted to his wife about his mental health problems, he insisted on keeping it secret from his colleagues because of fear of being unable to work again. Lack of support from the management, sense of ostracism from workmates ultimately caused the physician to eventually commit suicide, a situation that perhaps could have been avoided if needed support was given earlier [15].

The concerning data about mental health issues faced by health care professionals and high suicide risk demands taking action immediately to reduce psychological damage experienced by millions of medics all around the world. Some of the solutions include periodic mental health assessment, easily accessible professional psychological consultation in the workplace, peer support groups, case consultation groups, where staff could openly discuss challenging cases and increased availability to convalescent leave or mental health treatment in case of decreased functioning over several weeks. Those are some of the proposals that could possibly decrease the prevalence of burnout, depression, suicidal ideations, and suicidal behavior in health care professionals [16].

The virus that causes COVID-19 can have long-lasting symptoms in certain affected individuals. These effects are referred to as post-COVID conditions (PCC) or extended COVID long COVID, long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS CoV-2 infection (PASC), long-term consequences of COVID, and chronic COVID.

Numerous persistent health issues included in post COVID-syndrome can continue for weeks, months, or years and anyone who has been infected with the virus that causes COVID-19, even those who had minor illness or no symptoms from coronavirus, can have post-COVID syndrome but it is more frequently detected in individuals who had severe COVID-19. Also, people who have not been vaccinated may be at higher risk of developing post COVID syndrome than those vaccinated [17]. Common symptoms of long COVID include: fatigue, shortness of breath, problems with memory and concentration ("brain fog"), dizziness, heart palpitations, joint pain, depression and anxiety, chest pain or tightness, insomnia, a high temperature, cough, headaches, sore throat, changes to sense of smell or taste, pins and needles, tinnitus, earaches, rashes, feeling sick, diarrhea, stomach aches, loss of appetite [18].

In the aftermath of COVID-19 infection incresed risk of suicide may have many origins: social (for eg. losing loved ones due to ARDS or other severe complications of the infection), economical (for eg. higher psychological burden caused by decreased earnings due to changes in workforce during and after pandemic) and biological which we aim to discuss here further.

According to studies, the COVID-19 pandemic is linked to worry, anxiety, fear of spreading the disease, depression, and insomnia in both the general public and among medical professionals. In vulnerable populations, such as those with pre-existing psychiatric disorders and people who live in high COVID-19 prevalence areas, social isolation, anxiety, fear of contracting an illness, uncertainty, chronic stress, and financial difficulties may cause the development or exacerbation of depressive, anxiety, substance use, and other psychiatric disorders [19]. Research suggests that in the six months after COVID-19, around 34% of patients who survive receive a diagnosis of a mental illness.

Psychological aspects and neurobiological damage may be linked to COVID-19 survivors' persistent mental problems like sadness, anxiety, post-traumatic symptoms, and cognitive impairment. Anosmia, ageusia, headaches, dizziness and seizures are some neurological symptoms of COVID-19 that may last for a very long time after the acute sickness. Suicidal ideation and behavior are likely to be more prevalent in this patient population as a result of the signs and symptoms of psychiatric, neurological and physical disorders as well as inflammatory brain damage. Additionally, the direct biological effects of the virus, such as its signature pathology - hyperinflammation, may have contributed to the rise in suicide risk during the pandemic's later phases, which may have increased among COVID-19 survivors [20]. There’ve been also reports of COVID-induced psychosis and even Cottard syndrome occurring in patients after acute COVID-19 infection [21].

In other instances that have been reported COVID-19 first appears in otherwise asymptomatic, SARS-CoV-2 positive patients, it causes severely disordered behavior, including homicidal and suicidal thoughts [22].

As psychotic disorders are typically linked to significant premature mortality and morbidity, this case demonstrates how acute psychiatric complications in COVID-19 patients can be a serious concern [21].

Although at this point the data to sufficiently examine the problem of suicide in post-COVID syndrome is not present due to not sufficient amount of case. The problem should be further investigated as it poses a real risk in the population which on 29th of June 2022 had 551,008,863 [23], confirmed cases since the start of the COVID-19 pandemic. We’ve yet to understand the whole clinical picture of long COVID and in view of that the impact it has on psychological health and self-imposed risk should not be omitted.

SUICIDE IDEATION AND ATTEMPTS IN CHILDREN AND ADOLESCENTS DURING COVID-19

Suicide is the second leading cause of death among children and adolescents from age 10 to 17 and that rates have been increasing in the age group over the past years [24].

The outbreak of the SARS-CoV-2 (or COVID-19) has affected all countries around the world and influenced the mental well-being of all the people [25].

In recent world history, major infectious outbreaks were associated with severe mental health sequelae, including suicide. Nevertheless, the impact of COVID-19 on children and adolescents' mental health has not been widely studied.

The COVID-19 pandemic itself can cause fears of infection, uncertainty, and potential economic problems but also family life and relationships can be influenced by remote work lifestyles of parents [26].

What is more, social isolation and loneliness are believed to be associated with increased risk for depression, anxiety, self-harm, and suicidal ideation [27]. Given that the COVID-19 crisis may affect children and adolescents at multiple levels, including at the individual-, school-, and family-level, risk factors for suicide can both deteriorate or lessen [26].

One study held in Japan suggest, that the pandemic lockdown has not affected suicide rates among children and adolescents. The most possible explanation to that finding is the fact that changes in children's lives due to the pandemic crisis, including school closures, may have both positive and negative influences on mental health and suicidality [26].

Surely, the COVID-19 crisis can cause distress, anxiety and potentially even depression among children and adolescents because of the fears, family economic troubles and limited social contacts but on the other hand, some children may notice positive effects of that situation. Some families managed to develop stronger connections; parents started to support their children better by spending more time together. What is more, staying home may relieve stress and pressure from academic or peer problems experienced at school [28].

Researchers from Paris, France found a 50% decrease in the incidence of suicide behavior in children and adolescents during the COVID-19 lockdown. This association might result from a combination of several factors – reduced help-seeking, development of coping mechanisms, changes in familial and lifestyle dynamics [29].

In contrast, studies held in United States show that suicide ideation I children significantly increased during pandemic crisis. Similarly, screen results positive for suicide

attempts were higher. What is important, the number of Emergency Departments visits was substantially reduced during the COVID-19 and that is why direct comparison of rates across years should be made with caution. There appears to have been an early increase in suicide-related behaviors during the onset of the pandemic, possibly because of initial stay-at-home orders and social distancing efforts [24]. Family relationships developed during COVID-19 crisis may help children reduce their anxiety and distress in a long-time perspective [26].

During pandemic adolescents were less concerned about matters at school, including relationships with peers and teachers and bullying. Further studies should evaluate the influence of copying factors in children and adolescents, and the mechanisms underlying the effects of globalised health threat and pandemic lockdown on suicidal behaviour [29].

COVID AFFECTED SOCIETY AND HEALTH

The Corona Virus affected social relations within our communities, due to the set protective measures that the governments have set forth. The measures of social distancing and isolation imposed many challenges on day-to-day interactions between individuals. Human connection is a basic need for our existence. Individuals were challenged to learn how to adapt to their new lives behind closed doors when their face-to-face connections were impermissible. The sudden change, on one hand, can lead to the uprising of mental disorder cases within our community. Individuals can start to feel lonely, depressed, or anxious.

On the other hand, restrictions can bring family members closer to each other. With long term quarantine measures, families were able to spend so much time together and that can be beneficial in reducing the mental disorders of vulnerable individuals like children. With the chance that parents work from home, and schools are dismissed, parents and children were able to build stronger connections away from the stress of school or work. Children may be able to develop a long-term cure against anxiety and stress that they bear from school work. At the same time, parents are not obligated to stay away from their home for the long hours they spend at work.

COVID AFFECTED ECONOMY AND HOW IT CAN LEAD TO SUICIDE.

Furthermore, Covid did not just have its toll on individuals within the society, but it extended its arms around the economy. When individuals were behind doors, the cash flow

towards supermarkets, restaurants, pubs and entertainment facilities was paused. This has definitely dropped the functionality of the economic system as a whole. Many businesses were closed because of the shortage of income. Business owners may have been devastated to see their business shut down and suicide might be an option when they express forms of depression and sadness. However, effects of covid on the economy and how that ties into suicide needs major research efforts in the future.

The COVID-19 pandemic has hit the global population on health, economic and social grounds. In this, the impact on the mental health of individuals and suicide statistics is not without significance. Anxiety, loss of employment, self-isolation and social distancing. Also, the stigma in relation to infected people and their families - these and other factors have an impact on the mental state of the individual. People who are already burdened may experience an exacerbation of the disease, new people may be affected by disorders such as anxiety, depression, and PTSD. Fortunately, people today are more open about depression or anxiety disorders than they were in the past. The topic of death is also discussed more widely now than in the past. In addition to social openness to the above-mentioned topics, the awareness of their essence also influenced the access of people in need to help - which is widely recognized as truly saving lives [30].

Particular attention was paid to the issue of the impact of the pandemic on children and adolescents, which was disproportionately greater than on the adult population. The initial decrease in suicide related to some kind of "honeymoon period" then turned into an increase linked to depression, loneliness, domestic violence, substance abuse or neglect [31].

Apart from infected people, another group of increased risk are people fighting the pandemic on the front lines - healthcare workers. On the basis of the findings, it can be concluded that in this group the most common cause of suicide was infection with the COVID-19 virus, followed by work-related stress, fear of infection, fear of transmitting the virus to others and being overwhelmed by the effects of infection in the form of deaths and mental suffering. It should be remembered that the pandemic exerted enormous pressure on the working physicians, both in terms of the expectations related to the effective fight against the pandemic, as well as creating conditions that were not optimal in terms of safety (such as, for example, poor-quality personal protective equipment). People working in the health care system are also affected by the suicide of their colleagues [32].

This would indicate slightly different reasons than in the general population, which was dominated right after the fear related to the possibility of infection, a difficult economic

situation, loneliness, longing for family, social ostracism, lack of access to alcohol and stress related to work [32]. The aforementioned economic issues undoubtedly turned out to be a high risk factor, which had been observed before. After the 2008 economic crisis, they increased in as many as two-thirds of the 54 countries surveyed, especially men [31].

One of the potential advantages of the pandemic state is an attempt to respond to the need for psychological support - interventions at a distance (e.g. by phone or via video calls), which, despite their limitations, should expand their coverage by engaging a wider group of trained employees, prepared to provide remote consultations in crisis [33].

The effects of a pandemic will not go away long after the pandemic ends, so it is particularly important now to conduct social campaigns to promote mental health, and research is needed on how to mitigate the consequences of the pandemic on the mental health of the population [19].

The authors of the work Suicide prevention and COVID-19 present key recommendations on what we should pay attention to as a society in the context of this and future crisis situations such as the COVID-19 pandemic:

1. “It is essential to have strategic systematic suicide prevention planning for future pandemics as part of disaster response plans taking a universal holistic approach to care.
2. Investing in active labour market programmes will result in a decreased suicide rate during times of high unemployment.
3. People in low paid and casual jobs require specific support because they are most financially vulnerable during a pandemic related crisis.
4. Women require specific support during a pandemic because of the type of employment they have and because they often carry a greater proportion of the domestic burden and are at increased risk of domestic violence during lockdown and crisis.
5. Mental health and substance misuse services need to be appropriately funded and prioritized during and post pandemic, due to the associated increase in substance misuse during a pandemic causing worsening mental health and increased risk of suicide.
6. National Suicide Prevention Strategies should be developed by all countries and should anticipate response to a range of disasters, including a pandemic.
7. Suicide prevention is everybody's business and National Suicide Prevention Strategies should adopt a whole-systems approach including mental health services, primary care, social care, NGO's and other community stakeholders.

8. Suicide is preventable. It is essential to prioritize suicide prevention strategies in the COVID and post-COVID period to ensure that lives are saved" [34].

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Keeping safe - knowledge and opinions of women regarding protective face masks, restrictions and functioning of healthcare facilities during the COVID-19 pandemic

Józefa Dąbek[1], Kacper Staszkiewicz[2], Karolina Biernat[2], Agnieszka Mazanek[3], Zbigniew Gąsior[1]

1. Department of Cardiology, Faculty of Health Sciences in Katowice, Medical University of Silesia, Katowice.
2. Student Scientific Association at the Department of Cardiology, Faculty of Health Sciences in Katowice, Medical University of Silesia, Katowice.
3. University Clinical Center prof. K. Gibiński of the Medical University of Silesia in Katowice

INTRODUCTION

2020 will certainly go down in history as the beginning of one of the most severe pandemics the world has had to face. In March of that year, the World Health Organization (WHO) issued a statement officially assigning the status of a pandemic to the rapidly spreading disease COVID-19 (Coronavirus disease) caused by the SARS-CoV-2 virus [1]. Despite the fact that a large proportion of infections among immunocompetent individuals were asymptomatic, the virus was capable of inducing severe acute respiratory syndrome, which could be fatal in elderly and immunocompromised people [2]. According to official data presented on the WHO website, by July 2022, over 570 000 000 cases and as many as 6 300 000 deaths have been confirmed worldwide [3].

Despite these alarming statistics, it is possible that the total number of deaths caused by the disease could be much higher. That is, because not only the infection itself was hazardous - the unprecedented strain put by it on health care systems worldwide could have indirectly resulted in many, seemingly, COVID-unrelated deaths. Those being caused by much lower standard of care available, and in some cases, a complete breakdown of health care due to overcrowding of hospitals and lacking personnel [4,5].

This is shown, inter alia, by the so-called "excess deaths" - this is the term used to describe the difference between the average number of deaths determined on the basis of historical data and the number actually recorded. In many countries, the number of excess deaths cannot be fully explained just by the number of confirmed deaths from SARS-CoV-2 infection. Some people in the scientific community raise arguments that harder access to medical services related to the limited functioning of health facilities may have contributed to this [6]. Outpatient clinics, hospitals and specialist offices, due to their nature, i.e. facilities helping the sick, became a place of an increased epidemic risk during the pandemic. Patients seeking help in connection with ailments not related to COVID-19 could have become infected, in the absence of an appropriate sanitary regime [7]. For this reason, steps have been taken to ensure patient care without exposition to the SARS-CoV-2 virus [8]. Unfortunately, some of these actions resulted in a significant reduction in contact with the doctor and other health care professionals. This could translate into an inadequate level of medical care and thus deterioration of patient's health, underdiagnosis or even, in the long term, death. With the spread of COVID-19, governments and international organizations have taken action to slow down the transmission of SARS-CoV-2 and reduce the number of daily new cases which, in many places, have been rising almost non-stop since the very first recorded infections. Attempts to control the pandemic have largely taken the form of restrictions imposed on society, intended to isolate infected people, and in the case of exposure to a sick person - to minimize the risk of disease transmission. Social distancing, protective masks, isolation of the sick and quarantine against those exposed to the sick accompanied people for the majority of the pandemic. Despite the scientifically proven effectiveness of these efforts, part of the society strongly opposed them, and even refused to follow the guidelines [9,10,11]. The challenges that society has to face, in some aspects of life, have fallen disproportionately to women. The burden of motherhood and, often, of maintaining a home have increased significantly in the pandemic-reality. Thus, during the pandemic, women constituted an at-risk group, more susceptible to unfavorable social and epidemiological turmoil [12,13].

OBJECTIVE

The goal of the study was to assess the level of knowledge, opinion and women's experiences about the restrictions and functioning of health care facilities during the SARS-CoV-2 pandemic.

MATERIALS AND METHODS

386 women, aged 15 to 80 years, were examined (the arithmetic mean age of the participants was 31,32 years, while the standard deviation was 12,35 years). The inclusion criteria for the study were gender and willingness to participate. An original questionnaire was used to conduct it, the completion of which was completely anonymous and voluntary. The included questions concerned general information (age, place of residence, employment), as well as opinions and experiences on the restrictions and functioning of health care facilities during the pandemic. Statistical significance was assessed using the chi-square test with the assumed level of $p = 0.05$.

RESULTS

General characteristics of the studied group

The general characteristics of the studied group, taking into account; sex, age, place of residence and education level, are presented in Table 1.

Table. 1. The general characteristics of the studied group, taking into account; sex, age, place of residence and education level

Variable		Data	
		n	%
Age	**≤24**	120	31
	25-39	182	47,2
	40-64	77	19,9
	≥65	7	1,8
Place of residence	**City**	247	64
	Village	139	36
Education level	**None**	2	0,52
	Elementary	46	11,9
	Vocational	12	3,1
	Secondary education	138	35,8
	Higher education	188	48,7

Explanation of abbreviations: n – number of respondents

The majority of the study group were women with higher education. The surveyed women mostly lived in urban areas. People with higher and secondary education accounted for over 80% of all respondents.

PROTECTIVE FACE MASKS

The characteristics of the studied group, including the knowledge about protective face masks, are presented in Table 2.

Table 2. The characteristics of the studied group, including the knowledge about protective masks

Statements regarding protective face masks	I agree		I don't agree	
	n	%	n	%
Usage of face masks helps to reduce SARS-CoV-2 transmission	200	51,81%	186	48,19%
Face masks are safe to use	113	29,27%	273	70,73%
Using face masks is bad for your health	88	22,80%	298	77,2%
Face masks provide a level of protection from infection to the person wearing them	81	20,98%	305	79,02%

Explanation of abbreviations: n – number of respondents

Only about half of the respondents believed that the use of face masks helped to reduce the transmission of SARS-CoV-2 virus (200; 51,81%).

The characteristics of the studied group, taking into account the opinions of the respondents about protective face masks, are presented in Table 3.

Table 3. The characteristics of the studied group, taking into account the opinions of the respondents about protective face masks

Statements regarding protective face masks	I agree		I don't agree	
	n	%	n	%
Wearing face masks outside is pointless	247	63,99%	139	36,01%
I often feel shortness of breath while wearing a face mask	188	48,7%	192	51,3%
I change/wash my face mask daily	120	31,09%	266	68,91%
I often wear my face mask under my nose	106	27,46%	280	72,54%
I pay attention to the type of face mask I wear	103	26,68%	283	73,32%

Explanation of abbreviations: n - number of respondents

Only 1/3 of the respondents admitted that they changed or washed their face mask every day (120; 31,09%).

Figure 1 shows the analysis of responses to the subject of protective masks in relation to the education of the respondents.

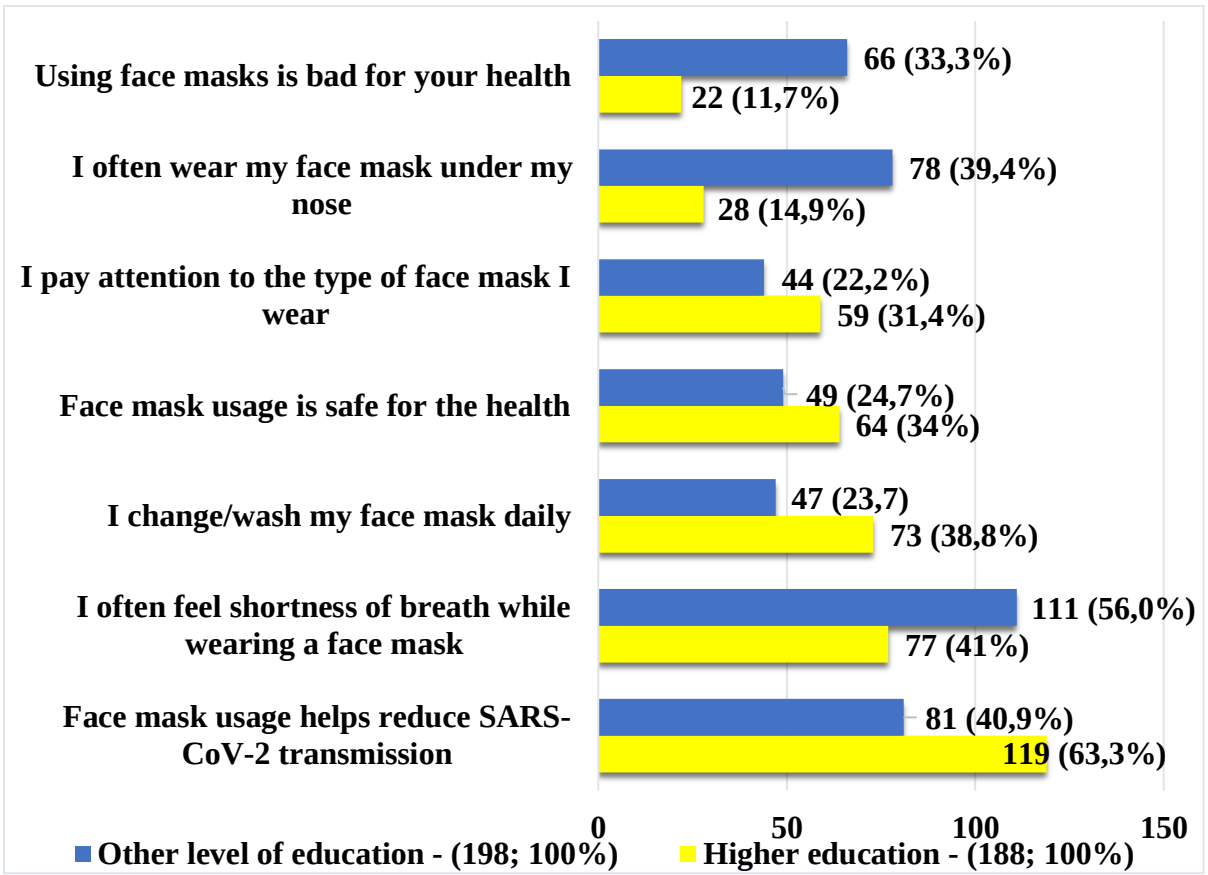

Figure. 1. Analysis of responses to the subject of protective masks in relation to the education of the respondents

Respondents with higher education level were more likely to find that using face masks helps to reduce the spread of SARS-CoV-2 virus (119; 63,3%), while people with a different level of education more often stated that wearing masks may be harmful to health (66; 33,3%).

RESTRICTIONS

Figure 2 shows the characteristics of the studied group, taking into account opinions on the restrictions and the level of knowledge.

About 40% of the respondents believe that the restrictions during the pandemic were too stark (156; 40,41%).

Figure 3 shows the characteristics of the studied group, taking into account the education of the respondents as well as the knowledge and opinions on the restrictions.

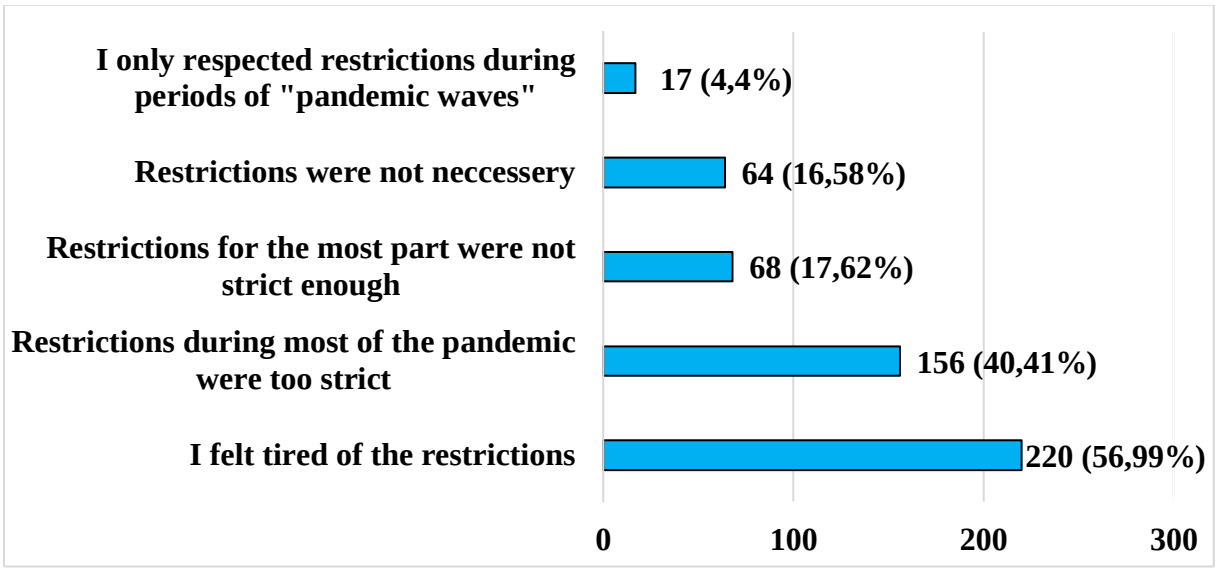

Figure 2. The characteristics of the studied group with regard to opinions on the restrictions and the level of knowledge

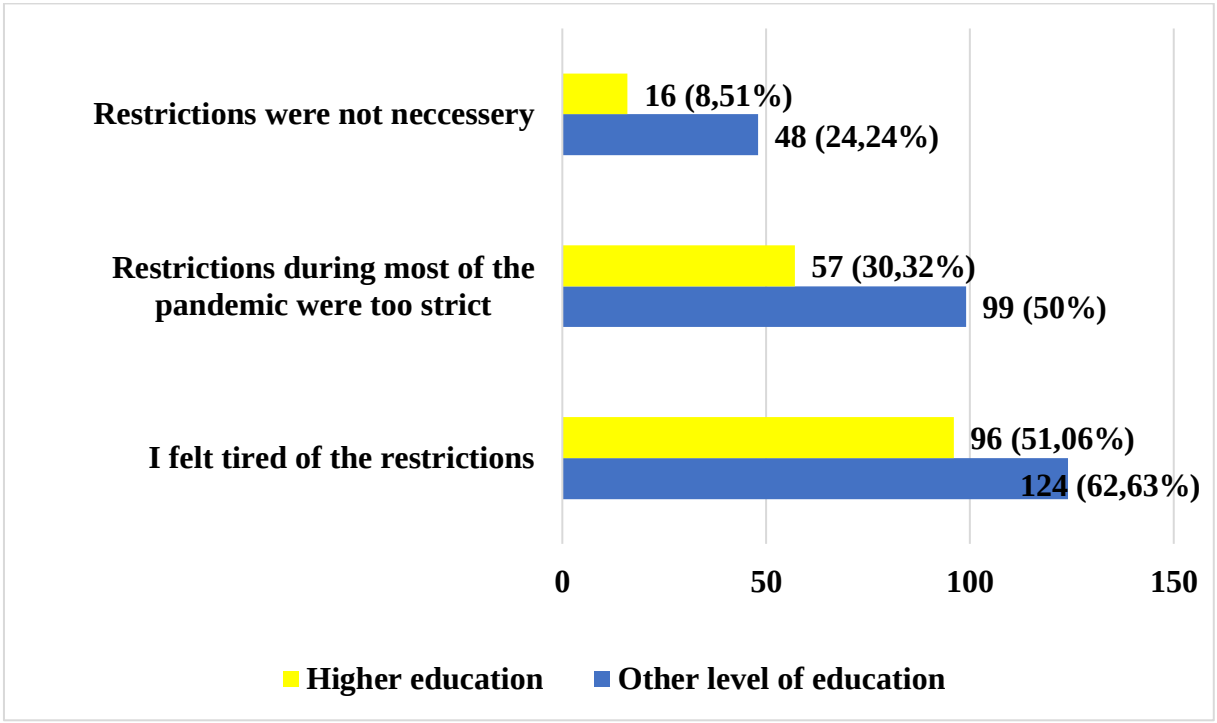

Figure. 3. The characteristics of the studied group, taking into account the education of the respondents as well as the knowledge and opinions on the restrictions

Respondents with non-university education more often claimed that the restrictions were too severe for most of the pandemic (99; 50%).

PANDEMIC REALITY

The characteristics of the studied group, taking into account the opinions of respondents about the claims concerning the SARS-CoV-2 pandemic, are presented in Table 4.

Table 4. The characteristics of the studied group, with regard to the opinions of respondents about the claims concerning the SARS-CoV-2 pandemic

Statements regarding COVID-19 pandemic	I agree	
	n	%
Poland was not ready for SARS-CoV-2 pandemic	262	67,88%
SARS-CoV-2 vaccines can potentially end the pandemic	207	53,63%
SARS-CoV-2 virus could've been made in a laboratory	138	35,75%
Pandemic could've been planned	122	31,61%
Return to the prepandemic social relationships will not be possible	101	26,17%
Doctors have made a lot of money because of SARS-CoV-2	92	23,83%
SARS-CoV-2 vaccines are dangerous to health	75	19,43%

Explanation of abbreviations: n - number of respondents

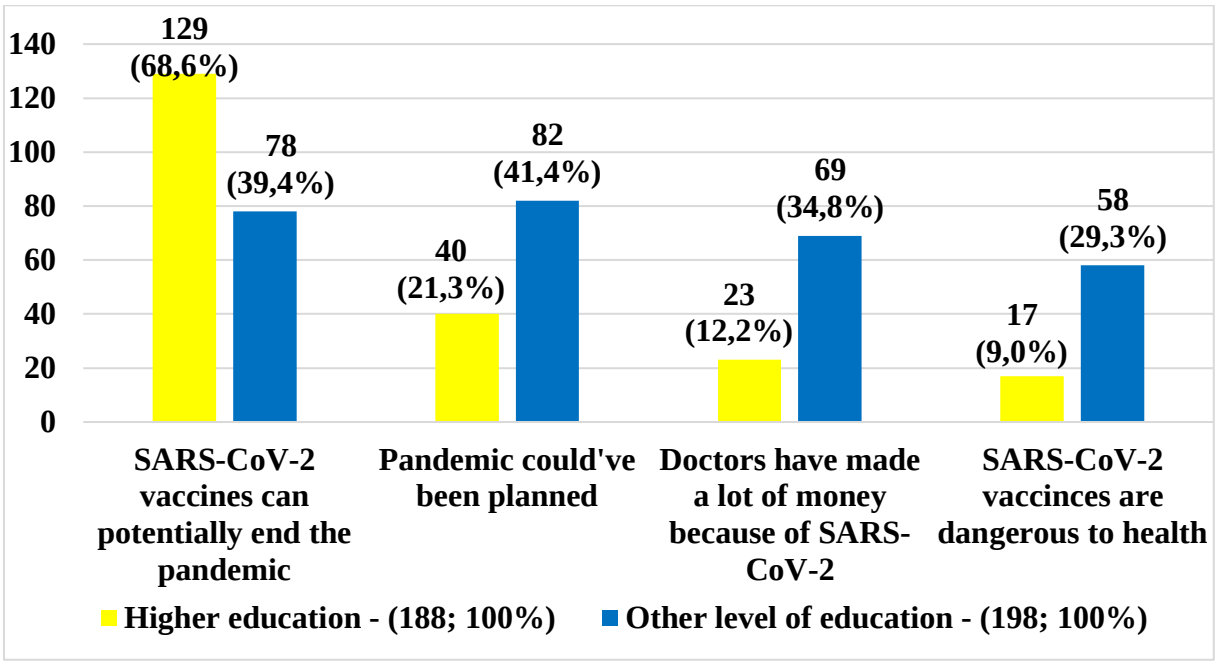

Figure 4. The characteristics of the studied group, taking into account the opinions on the statements regarding the SARS-CoV-2 pandemic and education

Over 30% of respondents believed that the SARS-CoV-2 coronavirus could have been designed in a laboratory (138; 35,75%), and that the pandemic could have been planned "in advance" (122; 31,61%).

HEALTH CARE FACILITIES AND CONTACT WITH A PHYSICIAN

Figure 5 shows the characteristics of the studied group, taking into account the opinions on the functioning of health care facilities during the pandemic SARS-CoV-2 virus.

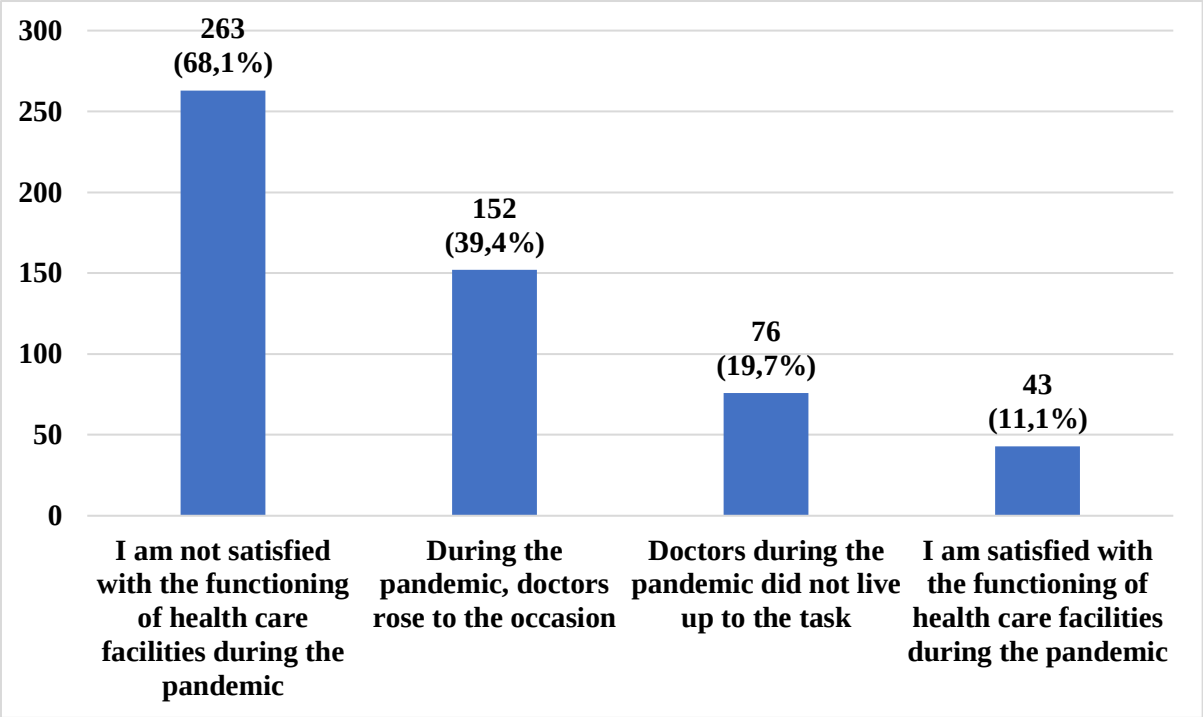

Figure 5. The characteristics of the studied group, taking into account the opinions on the functioning of health care facilities during the pandemic SARS-CoV-2 virus

Almost 70% of the respondents were not satisfied with the functioning of health care facilities during the pandemic (263; 68,1%).

Figure 6 shows the characteristics of the studied group in terms of experiences with access to the resources of the health care system.

Almost every second respondent had difficulty contacting her family doctor or clinic (180; 47%).

Figure 7 shows the characteristics of the studied group in terms of opinions on „telemedicine” and personal visits to private offices during the pandemic.

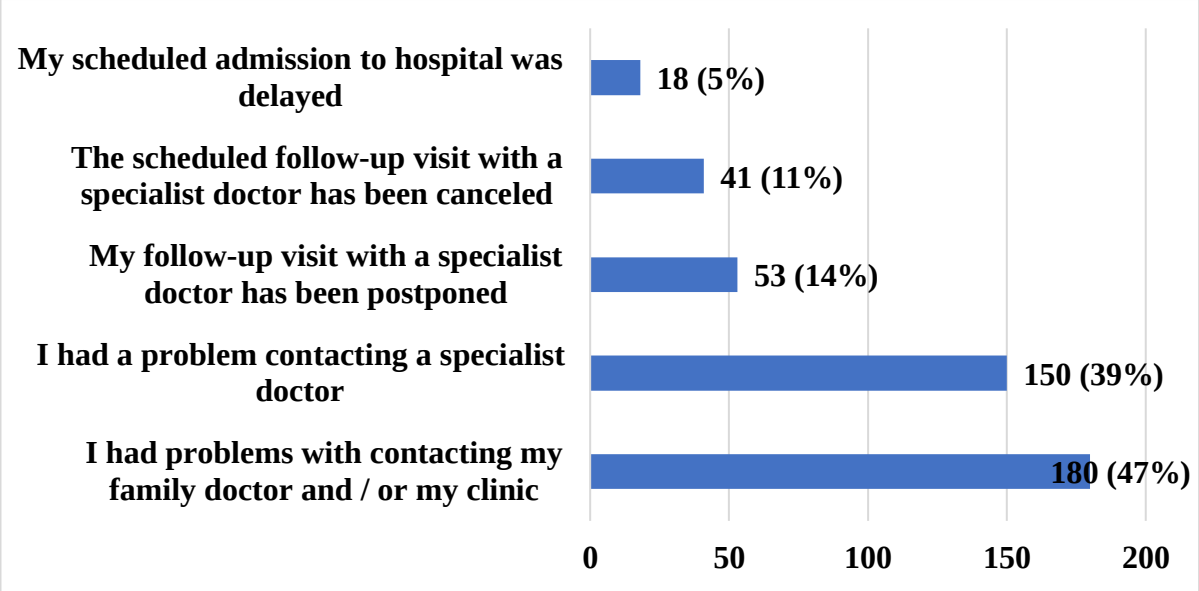

Figure 6. The characteristics of the studied group in terms of experiences with access to the resources of the health care system

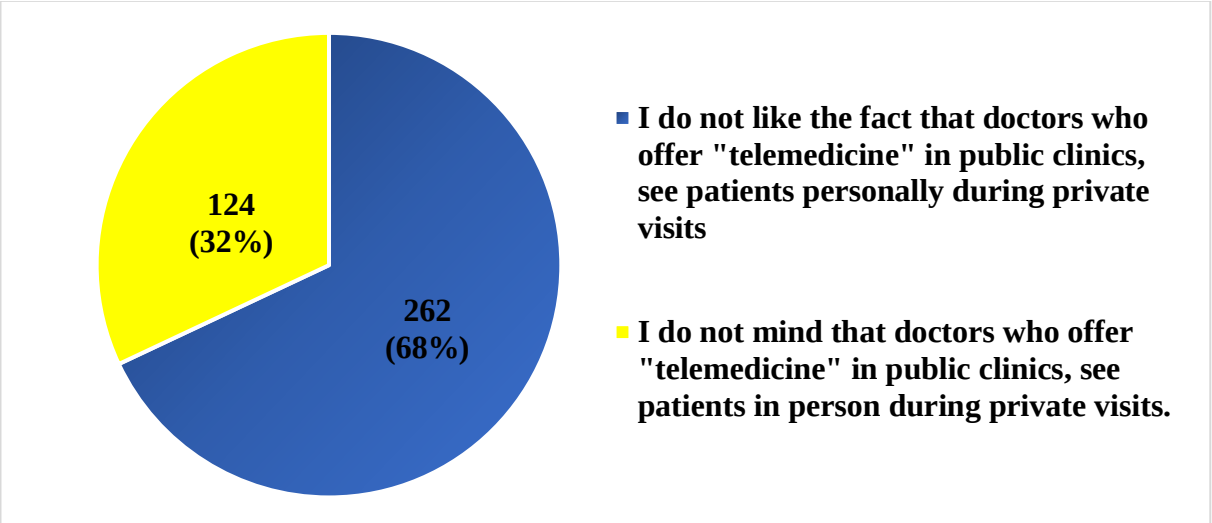

Figure 7. The characteristics of the studied group in terms of opinions on „telemedicine" and personal visits to private offices during the pandemic

Most of the respondents did not like the practice of admitting patients in person only for private visits (262; 68%).

Figure 8 shows the characteristics of the studied group, taking into account the perceived changes in the health condition of the respondents due to the difficult access to medical facilities.

Every fourth respondent felt improperly treated by the employees of her clinic (98; 25,39%).

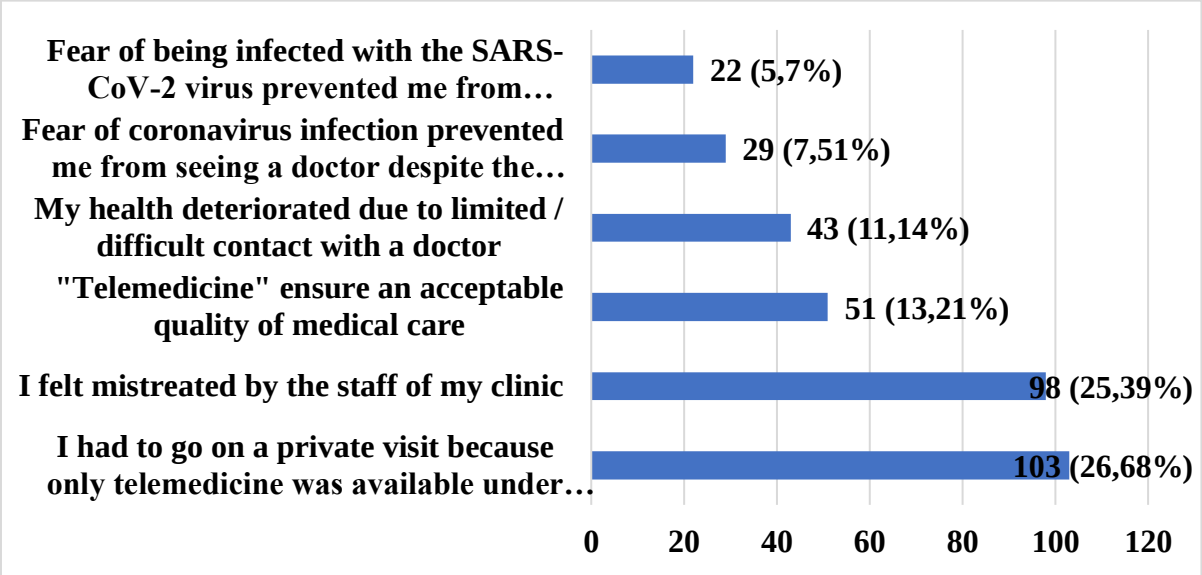

Figure 8. The characteristics of the studied group, taking into account the perceived changes in the health condition of the respondents due to the difficult access to medical facilities

DISCUSSION

The restrictions related to the SARS-CoV-2 virus pandemic led to the creation of a new, unprecedented reality in which people were forced to find themselves. For some people it wasn't easy, as the changes affected almost every sphere of life; however, they particularly strongly affected the area the health care system and its accessibility. Incapacity of the health care systems all around the world was sudden and unexpected. Many people experienced problems with access to medical benefits, and given all that, the full impact of the pandemic on overall mortality and morbidity remains to be seen.

Protective face masks are one of the basic elements of SARS-CoV-2 infection prevention and transmission reduction methods. According to current medical knowledge, wearing face masks is a highly effective and a cheap way of reducing the risk of infection [14, 15]. With respect to the available literature, to be effective, masks do not have to be specialized - even the ones made out of fabric fulfill their function in some regard [16]. Undoubtedly, masks are an effective tool in limiting the spread of COVID-19, so it is disturbing that only 50% of respondents said that their use helps to limit the spread of the disease (200; 51.81%). Education in this regard is desperately needed to help people better understand COVID-19 and in turn, better protect themselves.

Despite the fact that, while maintaining the appropriate standards of use, protective masks are generally safe for health, one must keep those standards in mind - for this reason, it

is unsatisfactory that in our research only 30% of respondents admitted that they change or wash their mask every day (120; 31,09%). It is important to keep in mind, that unwashed and unchanged mask can serve as a breeding ground for microbes, some of which can be a cause of a disease [17,18]. Therefore, it is vital to wear masks with accordance to guidelines and regulations.

One of the well documented side effects of wearing face masks for a prolonged period of time are changes in blood gas concentrations. It is not surprising that almost every second respondent reported a feeling of breathlessness while wearing a face mask (188; 48,7%). Literature on this topic is somewhat conflicting, with some studies suggesting that the risk of developing a full-scale hypoxia is close to zero (even with moderate exercise), while some point to unsettling carbon dioxide retention coupled with lower oxygen concentration within the air inside of the mask [19,20]. Thus, feeling out of breath is a common side effect of face mask usage and is to be expected in certain scenarios. Nevertheless, just because it appears frequently, shortness of breath should not be ignored, and mask wearers should be advised about ways of handling it. In the study by Yaser AAN. et al. 35% of respondents indicated a feeling of discomfort while wearing the mask - these results correspond to those obtained in the own study, where almost every third respondent admitted that she often wears the mask only covering her mouth (106; 27.46%). That may be caused by aforementioned changes in blood gases, caused by the proper positioning of the mask [21].

The fact that respondents with a higher level of education less often presented the opinion about the harmfulness of masks (22; 11,7%) than respondents who did not graduate from higher education (66; 33%) indicates the constant need for social education on personal protective equipment and methods of prevention spreading the infection.

The restrictions imposed on the society in the form of a lockdown were one of the most severe methods of preventing the spread of SARS-CoV-2 infection. Despite the scientifically proven effectiveness of lockdown, its introduction contributed to the development of many social problems [22,23]. For this reason, it is not surprising that more than half of the respondents reported fatigue with the restrictions during the pandemic (220; 56,99%), and part of the study group believed that the restrictions were too radical (156; 40,41%). More research is needed to determine whether better understanding causes of restrictions and their overall purpose helps in accepting them, but it’s worth considering.

During the COVID-19 pandemic, myths and rumors spread even faster than the disease itself. In the study group, almost every third respondent stated that the pandemic could have

been planned (101; 26,17%) and that the SARS-CoV-2 virus could have been manmade in the laboratory (138; 35,75%). These highly disturbing results show clear gaps in public awareness of the disease and general knowledge of scientific facts. Given that COVID-19 has long been ubiquitous in the sphere of public and media life it is highly surprising that people can hold such outlandish opinions [24]. However, women with higher education less frequently indicated that a pandemic could have been planned - this corresponds to the results obtained by Baig M. et al., in which education was described as a factor highly correlated with the avoidance of false information and rumors about the pandemic [25]. Given that misinformation is one of the main driving factors contributing to lower restrictions adherence rates it is vital to take measures aimed at tackling that problem.

The period of the COVID-19 pandemic has posed enormous challenges to health care systems around the world. The rapidly growing number of infections, and thus hospitalizations, reduced the efficiency of hospitals and other medical centers [26,27]. Due to the significant use of the resources of the health care system, it is not surprising that almost 70% of the respondents were not satisfied with the functioning of health facilities during the pandemic (263; 68,1%) and that almost every second woman surveyed experienced problems in contact with GP during the pandemic (180; 47%). These are definitely areas of pandemic reality that the scientific community should pay special attention to in the event of a possible future pandemic.

In the era of the SARS-CoV-2 virus, „telemedicine" has become one of the methods of providing medical care to sick or quarantined patients. Unfortunately, the authors' own research shows that the social attitude towards "telemedicine" is unfavorable. Only about 10% of the respondents believed that it ensures an acceptable quality of medical care (51; 13.21%). These results are supported by a study by Naik N. et al., who showed that almost half of the people interviewed did not feel comfortable with „telemedicine" (47.5%) [28]. Given that "telemedicine" is a very useful tool in many areas of health care steps should be taken in order to better accustom people with this new method of delivering physician's consultations to those in need.

CONCLUSIONS

1. Knowledge of women about protective masks and restrictions was insufficient, and their opinions were often unsupported by the current state of scientific knowledge.
2. The experiences of women in contact with health care institutions and employees during the pandemic were largely unsatisfactory, and contact was difficult.

3. There is a constant need to educate the society in the field of infectious disease prevention methods, their etiology and potential effects, as well as to conduct activities increasing the quality of medical services.

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Consequences of COVID-19 – what an ophthalmologist should be aware of?

Maciej Dyda[1], Lidia Jurczenko[1], Julia Górczyńska[1], Katarzyna Powierża[1], Michał Gebuza[1], Alina Semaniuk[1], Katarzyna Zontek[1], Dominika Musialska[1], Hanna Zając- Pytrus[1,2]

1. Wroclaw Medical University, Wrocław, Poland
2. Department of Opthalmology, Wroclaw Medical University, Wrocław, Poland

List of abbreviations

- PIMS- Paediatric Inflammatory Multisystem Syndrome
- CD- Cluster of Differentiation
- RT-PCR- Real Time Polimerase Chain Reaction
- ACE2- angiotensin converting enzyme 2
- HSPGs- heparan sulfate proteoglycan
- RVOs- retinal vein occlusions
- RAOs retinal artery occlusions
- BRVO- Branch retinal vein occlusion
- CRVO- central retinal vein occlusion
- CRAO- central retinal artery occlusion
- CRP- C- reactive protein
- MHV-A29- mouse hepatitis virus A29
- MRI- Magnetic resonance imaging
- FLAIR- Fluid-attenuated inversion recovery
- CVA- cerebrovascular accident

COVID-19 CORRELATION WITH EYES

Alongside the beginning of Covid-19 pandemic rumours about the consequences of getting infected appeared. Coronavirus exhibits especially great affinity for lung, heart, kidney tissue and the nervous system. For some people, permanent side effects may include breathing

difficulties, dyspnea, coughing, chest pain, impaired kidney function, stroke, brain fog, depression and Guillain-Barre syndrome (related to temporary paralysis). Children often develop PIMS after being through the infection. Chronic fatigue syndrome, joint and muscle pain, lower effort tolerance – are other problems that convalescents are facing [1].

Covid-19 affinity for eyesight is not unlikely, either. Eye doctors noticed the time relationship between infection and changes in the eye. Let us take a closer look at a few occurrences, people struggle with when infected, right after recovering and a few weeks after [2].

- **Conjunctivitis:** or watering eyes might be the first symptom of virus infection. It is caused by inflammation of the clear mucosa which surrounds the eye. Symptoms of conjunctivitis are pink or red color, occurring when the blood vessels in the conjunctiva undergo an inflammatory process, which makes them more visible. The other symptoms comprise eyes redness, pain, itching, watering and eyelids oedema. They occur more often when patients suffer from serious systemic symptoms of Covid-19 [2,3].
- **Episcleritis**: it is inflammation which affects epidural tissue located between the conjunctiva and sclera or the white part of the eye. Patients with episcleritis complain of diffused or concentrated eye redness (one-sided). Some of them do not complain of any other symptoms while others complain of discomfort, photophobia or sensitivity. Strong pain and discharge from the eye may point to episcleritis. The relationship between COVID-19 and episcleritis may involve vascular and immune factors and clotting disorder [3,4].
- **Retinitis:** microvascular changes of the retina were noticed when picturing an eye of people infected with COVID-19. Those symptoms were also noticed when observing asymptomatic patients with normal life parameters. Different fundoscopic results of the retina include microbleeding of the retina, tortuosity and occlusion of retinal vessels, and hyperreflective plaques in the ganglion cell-inner plexiform layer. Retina infections often manifest as worse eyesight or blindness [3,5].
- **Optic neuritis:** people with COVID-19 were diagnosed with different eye-nerves symptoms. Hypotheses explaining the cooccurrence focus on: direct invasion of virus particles on neural networks, endothelial cell dysfunction leading to ischemia both with coagulopathy and common cytokine storm initiated by a virus. Optic neuropathy leads to sudden loss of eyesight, relative afferent pupil dysfunction, pain related to eyeball movements and the vision is blurred [3,6].

- **Mucormycosis:** severe fungal infection, characterized by swelling or redness of the eye, double vision, sight loss, eye pain and falling eyelid. Mainly only people with impaired immune systems, that is with a lower level of lymphocyte CD4+ and CD8+, are susceptible as well as people suffering from different diseases (such as diabetes or respiratory failure) and people that are on immunosuppressive therapy[3,7].

CONJUCTIVITIS

COVID-19 is an infection manifested by several symptoms. The SARS COV-2 virus spreads mainly via droplets and aerosols, so it is worth considering the aspect of direct eye infection by virus-containing droplets and aerosols. Coronaviruses can be present in tears during infection. Coronaviruses such as SARS-CoV, HCoV-NL63 and SARS-CoV-2 were detected by RT-PCR in tears during previous coronavirus outbreaks [8-12]. Although eye diseases are not common in cases of SARS-CoV-2 infection, there is a significant association between COVID-19 infection and the occurrence of conjunctivitis [13]. Moreover, mild conjunctivitis, which manifests itself as conjunctivitis, is common and is one of the leading ocular symptoms in SARS-CoV-2 infected patients, even if the disease is milder [14]. However, ocular symptoms occur most often in patients with a very severe systemic form of the disease accompanied by abnormal blood parameters and inflammation [15].

Overall, the incidence of ocular symptoms in COVID-19 patients ranges from 2% to 32% [2,16-20].

In a study by Sindhuja et al. as many as 8.66% of respondents experienced conjunctivitis accompanied by the reddening of one or both eyes. Moreover, conjunctival hyperaemia clearly correlated with respiratory symptoms[14]. Additionally, as a result of a cross-sectional study, Chen et al. showed a correlation between hand-eye contact and the occurrence of conjunctival hyperaemia[21]. The team also noted that the most common manifestation of eye symptoms was around the thirteenth day of COVID-19 disease. Interestingly, a smear taken from the conjunctiva gave a positive result for the presence of the SARS-CoV-2 virus for five days [21].

Nayak et al. showed that despite the negative result of a nasopharyngeal swab for SARS-CoV-2 virus, the virus might still be present in the conjunctiva [21].

COVID-19 can also present as keratoconjunctivitis without significant respiratory symptoms. The inflammation may be accompanied by photophobia, redness and discharge as observed by Cheem et al. This clearly shows how important it is to consider conjunctivitis as one of the symptoms of SARS-CoV-2 infection [22]. The literature also reports the case of

a patient in the intensive care unit with flu-like symptoms associated with SARS-CoV-2. During daily analysis of bronchial secretions, the genetic material of the virus was identified by a polymerase chain reaction (PCR). Initially there were no eye problems. On the seventeenth day hyperaemia of the conjunctiva with pure secretion was detected and the patient was found to have viral conjunctivitis. The material taken from the conjunctiva did not show any bacteria on microscopic examination and cultivation. On the nineteenth day the symptoms worsened. Yellowish-white, transparent pseudomembranous lesions were identified on the conjunctiva of the lower eyelids. No abnormalities were detected during the examination in posterior segment. Only between the 21st and 26th day of the illness did the eye symptoms improve [23].

This case illustrates the importance of carefully monitoring the patient's symptoms in order to avoid late-onset eye complications in SARS-CoV-2 infected individuals. Unfortunately, conjunctival smears can be wrongly negative, which makes the diagnosis enormously difficult [23].

The mechanism of SARS-CoV-2 invasion into the human body through the eye is not yet fully understood. Most likely, the fluid from the eye is absorbed and then discharged into the nasal cavity through the nasolacrimal canal, from where it then enters the respiratory track through the trachea. As a result the microorganisms in the tears can be transported to the lungs [24].

In addition, we can find the intraocular angiotensin system (RAS) in the human eye. Moreover, ACE2 serves as an entry receptor for viruses such as HCoV-NL63, SARS-CoV, and SARS-CoV-2. This receptor was found in the aqueous humor [25] and in the conjunctival epithelial cells on the surface of the eye [26]. Of course the effectiveness and intensity of a viral infection depends, among other things, on the infection rate and the presence of viral receptors on the host cells. HSPG receptors are responsible for the formation of the first viral junctions near the epithelium, which is made up of cells with a small number of ACE2 receptors. ACE2 receptors greatly facilitate virus entry into these cells, but HSPGs provide a suitable virus enrichment environment close to the host cells through low affinity interactions [27].
Many studies suggest that infection of human cells with SARS-CoV is mediated by more non-ACE2 receptors on the host cell membrane [28].

EPISCLERITIS

Episcleritis is a relatively common, benign, and self-limiting inflammatory disease. It is often recurrent and young adults are mainly affected. The cause of episcleritis is difficult to

identify; most cases are idiopathic. In less than one-third of patients it is associated with systemic diseases such as atopy, systemic vascular disease, and autoimmune disease. Episcleritis has also been described as an ocular manifestation of viral diseases such as Ebola, herpes zoster, and hepatitis C [29,30].

After reviewing the relationship between SARS-Cov-2 and episcleritis in the available literature it can be concluded that the incidence of episcleritis in the course of SARS-Cov-2 is low. A few studies report the following statistics and conclusions.

- Bostanci et al [30,31] identified episcleritis in 2 out of 93 patients with COVID-19 Additionally, this study found that epidural inflammation was associated with higher levels of D-dimers ($p = 0.017$), PCT ($p = 0.045$), and CRP ($p = 0.020$).
- Méndez et al [30,32] describe episcleritis in a 31-year-old woman who presented to the ophthalmology clinic with red eye, foreign-body sensation, epiphora, and photophobia without impaired visual acuity. Ocular symptoms appeared 7 days after systemic symptoms of SARS-CoV-2 infection had been confirmed by RT-PCR test. The patient was diagnosed with nodular episcleritis. Treated with artificial tears on demand and fluorometholone, symptoms resolved on the sixth day after the episcleritis onset.
- Otaif et al [30,33] reported a case of episcleritis in a 29-year-old man who was diagnosed 3 days before the onset of full-blown COVID-19. The patient presented with symptoms of redness and foreign body sensation in his left eye, which started two days before his consultation. He had no history of decreased vision, pain or photophobia; he also had no prior history of similar conditions, ocular surgery or trauma. He had no symptoms in his right eye or any systemic symptoms. The diagnosis of episcleritis was made based on the phenylephrine blanching test. Three days later, the patient reported headache, shortness of breath, cough, and fever. He was found to be infected with SARS-Co-2 by the RT-PCR test.
- Lu et al [33] recount the case of Dr Guangfa Wang who, while working with COVID-19 patients, complained of red eyes 3 days before the onset of COVID-19 symptoms.
- Amirhossein Roshanshad et al [34] reported a case of episcleritis in Spain. A woman presented with cough, myalgia, anosmia and ageusia. Her RT-PCR test was positive. Once the symptoms subsided, the patient consulted the ophthalmology clinic with red eyes, foreign-body sensation, epiphora, and photophobia, and nodular episcleritis was diagnosed.

- A study from Turkey [31,34] revealed a 2.2% prevalence of episcleritis in COVID-19 patients. It was also shown that episcleritis was associated with a higher D-dimer level
- Additionally, ocular complaints were observed after SARS-CoV-2 vaccination. In the study by Francesco Pichi et al [35] 9 patients presented with ocular complaints and one patient was diagnosed with episcleritis.

Currently, in episcleritis, it is recommended to use artificial tears and local non-steroid anti-inflammatory eye drops. Usually, the symptoms completely disappear after two weeks [36].

RETINAL MANIFESTATIONS OF COVID-19

COVID-19 can affect the retina in various ways. On the basis of prevalence we can distinguish 3 main types of retinal manifestations: retinal microvascular impairments, retinal vein occlusions (RVOs) and retinal artery occlusions (RAOs) [37,38].

Retinal microvascular impairments

During COVID-19 we can notice the disturbance of the coagulation mechanisms [39] and function of endothelial cells [40]. This leads to ischemic microvasculopathy and diminishing vascular density in sublingual vessels [41] and vascular sequelae in many other organs. The ocular representation of this anomaly is a decrease in density of capillary plexus vessels in foveal regions [42].

Recent meta-analysis including 401 participants clearly shows that COVID-19 induces the decrease in the vessel density in the foveal deep capillary plexus and decreased subfoveal choroidal thickness [43], which can be linked to decreased perfusion density in these vessels [44] .

These findings were evaluated with optical coherence tomography angiography or with fundus autofluorescence [45] which is widely available and can be used to evaluate patients after COVID-19.

The other way to evaluate microvascular changes is fundoscopic examination. The main manifestations of microvascular anomalies in COVID-19 patients are cotton wool spots and hemorrhages [44,46]. There can also be spotted dilated veins and tortuous vessels. These presentations did not affect visual acuity. In addition, they were more often seen in patients with obesity and diabetes, making it difficult to disentangle the individual impact of the factors [46,47]. The COVID-19 pathophysiological mechanism and its impact on the microvascular system of the retina, still have not been commonly established.

Retinal vein occlusions (RVOs)

There are two types of retinal vein occlusion (RVO): Branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). Patients with BRVO are most likely to maintain proper vision after recovery, so we will mainly focus on CRVO [48].

CRVO is divided into two categories: ischemic and non-ischemic. Non-ischemic CRVO is associated with mild visual field changes and does not strongly affect visual acuity, whereas ischemic CRVO is associated with a worse course of the process. The primary risk factors for CRVO are diabetes, age, hypertension and obesity [40,49].

Retinal vessels in COVID-19 infection may be altered by thrombus, hypoxia and endothelial damage leading to CRVO, vitreous hemorrhage and neovascular glaucoma [39, 49,50]. Endothelial cell dysfunction can also lead to disruption of the blood-retinal barrier, release of vascular endothelial growth factor (VEGF) and thus to increased capillary permeability and subsequent development of macular edema.

In CRVO it can lead to significant loss of vision. Macular edema was the most prominent effect of vision loss in patients with RVO [44].

In available research papers, it has been shown that the age of patients with CRVO due to COVID-19 was lower than the typical age of the onset associated with traditional risk factors such as diabetes, hypertension and obesity . The time to the appearance of symptoms after the first onset of fever ranged from 5 days to 6 weeks [51].

The further evolution of lesions was promising, as the patients improved after the treatment with anti-VEGF injections, steroids and anticoagulants [51,52], which may lead to the conclusion that early induction of proper treatment results in complete resolution of the disease [44].

Retinal artery occlusions (RAOs)

RAO is usually associated with the sudden loss of vision. The main artery blockage, called central retinal artery occlusion (CRAO), leads to painless and extensive visual field loss. The blockage of a smaller arteries is called branch retinal artery occlusion (BRAO), which results mostly in partial loss of vision. The loss of the vision can be unnoticeable until perimetry has been performed.

The most harmful CRAO is the rapid blockage of the central retinal artery, resulting in retinal hypoperfusion with progressive, rapid cellular damage, and vision loss. The survival of the retina depends on the duration of ischemia and degree of collateralization there [2]. RAO can rarely provoke or coexist with ocular inflammation.

The patients with severe COVID-19, who had middle artery occlusion, had also elevated inflammatory markers such as: CRP, D-dimer, ferritin, fibrinogen and IL-6. Thus all these markers could be used to estimate the risk of RAOs. Further research is needed to create the guidelines [2].

Neuro-Ophthalmic manifestations

Neurological symptoms in patients infected with the Sars-Cov-2 virus have well been documented. Neurologic and ophthalmic manifestations may also in the course of polyneuritis, meningitis or encephalitis. Ocular involvement has been observed particularly in patients with demyelinating disorders.

To date, the exact pathogenesis of neuro-ophthalmic events remains unknown. However, there are some hypotheses suggesting direct invasion into the central nervous system, an extensive inflammatory response, also referred to as a cytokine storm, and endothelial cell dysfunction as potential causes of neuro-ocular complications [53].

Koldeki et al. examined retinal and corneal neurodegenerative changes and retinal neurovascular status in 35 patients and compared them with an age-matched control group [54]. The results suggested that even mild or asymptomatic coronavirus infection could cause neurodegenerative changes, which manifested as significantly lower nerve branch. However, the microvascular mechanism of neuro-ophthalmic complications after coronavirus infection were not observed in the study conducted by Kaldeki. To date, symptoms such as optic neuritis, cranial neuropathies, diplopia, Miller Fisher syndrome, various visual disturbances and subacute vision loss have been documented. There are also reports of optic nerve disc oedema, afferent pupillary defects and painful eye movements [54].

OPTIC NEURITIS

To date, optic neuritis has been documented in only a few case reports. Three of them involved patients with serum antibodies to myelin glycoprotein of oligodendrocytes [55]. One recent case was reported by Witoon Mitarnun et al. [56] a 60-year-old man presented with acute visual field loss with impaired eye movements and disc oedema with a relative defect of the centripetal pupil in the right eye. A diagnosis of optic neuritis was made. This event occurred 6 weeks after the onset of SARS-CoV-2 infection. After corticosteroid treatment the patient fully recovered.

Alax Jossy et al. presented three case reports of optic neuritis after mild Covid virus infection. Two patients developed symptoms of optic nerve invasion within 6 weeks and one within 6 months after recovery from coronavirus infection. One was a case of a 35-year-old man who developed sudden loss of vision in his left eye and painful eye movements for 1 week. Six weeks before the onset of ophthalmic symptoms, he had been tested for Sars-CoV-2. On ophthalmic examination the patient was found to have a BCVA of 20/600 in LE with grade I RAPD, choroidal and periocular oedema. In all cases described patients responded well to glucocorticoids with complete visual improvement. In addition, Giaruzzo et al. described a unique case of optic neuritis as the sole manifestation of coronavirus infection. The patient developed unilateral visual loss [57]. The exact pathogenesis of how Sars-CoV2 affects the optic nerves remains unknown. However, some animal models have shown signs of optic neuritis due to coronavirus infection. In 200 8 Shindler et al. documented this phenomenon using MHV-A29, a murine Sars CoV Virus [58].

NEUROPATHY

To date, several case studies revealed neuropathies as an ophthalmic manifestation of coronavirus infection. In the most reports the 6th nerve palsies were documented. In a few of them, palsy had a form of limited Miller Fisher Syndrome.

Guiterrez-Ortiz et al. presented a case of cranial polyneuritis following Covid virus infection [59]. A 39-year-old man presented with bilateral optic nerve palsy and areflexia and cytologic albumin dissociation during admission to the emergency room in Madrid. Three days earlier, he had reported general malaise, lower-grade fever, and diarrhea. He did not present with any respiratory distress syndromes. He was not diagnosed with classic Miller Fisher syndrome but with cranial polyneuropathy. The patient was discharged home and treated with acetaminophen. Two weeks later the patient was completely neurologically healthy. L. Borrego-Sanz described the case of a 66-year-old woman with an unblemished medical history [60]. She reported a painless loss of vision in her left eye. On ophthalmic examination of the right eye visual acuity was 0.9, and a centripetal pupillary defect was present. In the left eye retinal arteriolar stenosis, marked pallor of the optic nerve head and large cupping were found.

Optical coherence tomography showed a significant thickness of the retinal nerve fiber layer in the perifoveal region, which was consistent with the orbital MRI findings of reduced signal enhancement in the left optic nerve. These signs suggested neuropathy, in which progressive vascular phenomenon could be considered as the main cause of optic nerve damage.

MILLER FISHER SYNDROME

Miller Fisher syndrome, considered a limited form of Guillain-Barré syndrome, is characterized by an acute onset of ophthalmoplegia, ataxia and absence of tendon reflexes. Guiterrez-Ortiz et al [57] described a case of a 50-year-old man with right-sided intranuclear ophthalmoplegia and right-sided fascicular oculomotor palsy. On neurological examination all deep tendon reflexes were absent, which could be considered symptoms of Miller Fisher syndrome. Five days earlier the patient reported cough, fever, lower back pain and headache. The patient was treated with a 0.4 g/kg immunoglobin infusion for 5 consecutive days. The total hospital stay was 2 weeks. He showed no neuro-ophthalmic symptoms at discharge.

WERNICKE SYNDROME

Wernicke syndrome is a neurodegenerative disorder caused by vitamin B12 or thiamine deficiency. Wernicke syndrome is common in patients who have undergone bariatric surgery. Decreased vitamin B12 levels may affect patients hospitalized in the intensive care unit. Shepherd et al. described a unique case of bilateral visual loss secondary to Covid's disease. A 36-year-old man with unremarkable history was repeatedly hospitalized for recurrent episodes of diarrhea and odynophagia and severe nausea. Due to these symptoms his body weight decreased significantly. In addition he presented with general malaise, diffuse myalgia, persistent cough, ageusia and anosmia. Six weeks after the onset of infection he developed subacute visual loss .No abnormalities were found on pupillary and fundoscopic examination, suggesting a possible cortical mechanism of bilateral blindness. However, magnetic resonance imaging showed FLAIR hyperintensities in the medial thalami, mammillary bodies, and periventricular grey matter, indicating classic WS lesions. The patient was treated with thiamine infusion and fully recovered after 7 days of therapy. This case indicates that poor nutrition and vomiting secondary to Covid virus infection can lead to severe ophthalmic manifestations of Wernicke's syndrome [60].

VISION LOSS

A study by Cyr et al. described cases of acute bilateral visual loss following coronavirus infection. The first patient was a 61-year-old male diabetic patient. He developed symptoms of infection such as cough, body aches, and fever 7 days before admission to the emergency room.

Five days after the onset of Covid-like symptoms he presented with acute bilateral painless visual loss. On physical examination, light perception was absent. X-ray examination revealed typical lung lesions after Covid virus infection. In addition, dilated fundus examination revealed several diffuse haemorrhages in the macula of both eyes. Magnetic resonance imaging showed bilateral occipital oedema and ischemic infarction. The patient died 3 days after admission to the hospital.

The second patient was a 34-year-old woman who presented to the emergency department with confirmed Sars-CoV-2 pneumonia, with a history of systemic lupus erythematosus, end-stage renal disease treated with hemodialysis, hypertension and chronic obstructive pulmonary disease, and peripheral visual field damage due to CVA in 2016. She developed sudden bilateral visual loss 10 days after admission. Visual acuity in both eyes was clear. In addition, dilatation examination revealed trace pallor in both optic nerve discs. Two days after the onset of visual impairment, MRI revealed an acute ischemic infarct in the right frontal lobe.

These two cases highlighted the higher risk of thromboembolic occlusion in patients with a history of endothelial dysfunction.

Neuro-ophthalmic symptoms are rare but should be considered a potential manifestation of coronavirus disease. Although the true mechanism of this form of the disease remains unknown, as time passes and more data are collected, the relationship between coronavirus and neuro-ophthalmic symptoms will become better described.

Furthermore, this brief review has emphasized that ophthalmologists must be more willing to screen for concurrent coronavirus infection, even in patients with little or no respiratory symptoms [61].

CONCLUSION

The mechanism of COVID-19 induced neurologic manifestations remains still poorly understood. But it has become abundantly clear that, physicians especially frontline ones, should be aware that there are possible associations between SARS-COV-2 and neuro-ophthalmic disease.

As indicated by the literature, the following ophthalmic presentations in the course of Covid infection have been reported new vision loss, new-onset optic neuritis, cranial nerve palsies, Miller Fisher and Wernicke syndrome, episcleritis, retinal microvascular impairments, retinal vein occlusions and retinal artery occlusion.

This is why it is essential, in addition to asking new patients whether they have experienced shortness' of breath, cough, fever', that clinicians should also ask about symptoms such as decreased vision, pain with eye movements, and double vision. If patients complain any of above the mentioned clinical setting, COVID-19 testing should be considered.

During the physical examination, the clinician should pay attention to and look for pupillary and visual acuity abnormalities, extraocular motility deficits, ptosis and optic disc swelling. Checking cranial nerves by neuroimaging is also crucial to rule out cranial neuropathy.

This area of study is still developing as we are learning new facts about COVID-19 each day. It is not unlikely that other new neuro- ophthalmic diagnoses are involved, too. Further research is needed to understand the pathogenesis of Covid changes and their relation to evoked signs and symptoms.

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Neurological manifestations associated with COVID-19

Julia Mężyk[1], Joanna Gołda[1], Aleksandra Snopkowska[1], Marta Nowakowska-Kotas[2]

1. Student Science Association of Neurology, Wroclaw Medical University, Wrocław, Poland
2. Department of Neurology, Wroclaw Medical University, Wrocław, Poland

List of abbreviations

CNS - Central Nervous System

SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2

WHO – World Health Organization

COVID-19 - Coronavirus Disease 19

PNS - Peripheral Nervous System

TNF-α – Tumor Necrosis Factor-alpha

IL – Interleukin

ACE – Angiotensin-converting Enzyme-2

BBB – Blood-brain Barrier

CRP – C Reactive Protein

CK – Creatine Kinase

IFN γ – Interferon gamma

MRI – Magnetic Resonance Imaging

CT – Computerized Tomography

EEG – Electroencephalogram

PET – Positron Emission Tomography

PCR-Ct – Polymerase Chain Reaction – Cycle Threshold

GBS – Guillain-Barré syndrome

IVIG- Intravenous Immunoglobulins

LMWH - Low Molecular Weight Heparin

DWI – Diffusion-Weighted Image

FLAIR- Fluid attenuated inversion image

ADC- Apparent diffusion coefficient

CSF- Cerebrospinal Fluid

NCS- Nerve Conduction Study

EMG - Electromyography

INTRODUCTION

Viral neurotropism

Neurotropic viruses can cause devastating central nervous system (CNS) infections in all age groups. Viral CNS infections are almost as common as bacterial infections, with an incidence of 20–30/100.000 per year [1]. Many of them, including Coronaviruses, H1N1 influenza virus, Herpesviruses, Orthomyxoviruses, and Parvoviruses, represents similar neurological symptoms that causes problems with proper diagnosis and adjustment treatment [2,3,4]. Despite the diversity of viruses that invade the CNS, many infections induce common pathogenic cascades such as the breakdown of CNS barriers and the release of detrimental mediators that can cause neurotoxicity [5]. It is essential to understand interrelated inflammatory mechanisms and identify universal mediators promoting CNS inflammation to develop new diagnostic and treatment strategies [1].

CNS symptoms in viral infections

Previous coronavirus epidemics have reported 10-15% of cases with similar symptomatology [4]. Headache and dizziness have been largely present in most studies conducted across the globe and often occur as a symptom of other viral meningitis, encephalitis or infectious encephalopathy or could be a temporal association with a systemic viral infection [4,6,7]. More than a third of patients experience impaired consciousness or delirium during the acute course of the disease [8]. Signs of impaired corticospinal tract involvement could also be induced by other factors like metabolic imbalances, acute toxic or hypoxic encephalopathies, strokes or seizures with postictal confusion [4].

SARS-CoV-2 INFECTION

In December 2019, a new respiratory virus, later named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first detected in the Chinese city of Wuhan

[2, 9]. WHO declared a coronavirus disease 19 (COVID-19) pandemic in March 2020, caused by SARS-CoV-2 infection [10]. SARS-CoV-2 primarily causes upper and lower respiratory tract infections, manifested by cough and fever. Extrapulmonary symptoms are also common, such as gastrointestinal and neurological symptoms [11]. The condition can lead to severe pneumonia, respiratory failure, sepsis, and multiple organ failure [10]. The clinical course of the disease can vary from asymptomatic cases to those requiring intensive therapy [11]. A higher infection rate is observed in neonates, the elderly and people with comorbidities [9]. Approximately one-third of patients infected with the SARS-COV-2 develop neurological symptoms [2,9].

The neuro-invasive nature of the SARS-COV-2 has been suggested in histopathological studies. The virus is capable of directly infecting central (CNS) and peripheral nervous system (PNS) cells [10]. However, it should not be assumed that all neurological symptoms are due to direct infection of the cells of the central nervous system of the CNS [12]. Hypoxemia, hypoperfusion, dehydration, glucose dysregulation and sedation may also influence the development of neurological symptoms [10].

Transmission of SARS-CoV-2

According to the available literature, SARS-CoV-2 can spread between people differently [13,14,15].

Current evidence suggests that SARS-CoV-2 is primarily transmitted between people directly via respiratory droplets. The virus spreads mainly when people are in close contact with an infected person with respiratory symptoms such as coughing or sneezing. However, infectious particles' droplets can also be released while speaking or even quiet breathing. Inhalation of air carrying contaminated droplets may spread infection [16,17].

The virus can also easily spread in crowded indoor settings, crowded spaces with poor ventilation, or prolonged contact with an infected person. It happens because aerosol particles can remain suspended in the air for minutes to hours [16,17].

Besides that, some data confirm that SARS-CoV-2 can be transmitted into the human body indirectly via contact with surfaces contaminated by the virus [15]. People become infected when they first touch contaminated objects or surfaces, and then their hands come into direct contact with mucous membranes such as the eyes, nose or mouth [16,17].

Recent studies also suggest that transmission of SARS-CoV-2 can be affected by environmental factors such as temperature, humidity, precipitation, air currents, pH and radiation [18].

ROUTES OF ENTERING THE NERVOUS SYSTEM BY SARS-CoV-2

It is supposed that SARS-CoV-2 can attack the nervous system in several different ways and through various mechanisms. First, the virus can directly enter and damage nerve cells. Second, the virus can enter the central nervous system through blood circulation. Third, the virus can transmit through neural pathways, infecting sensory or motor nerve endings.

Hematogenous route

SARS-CoV-2 may infect the endothelial cells of the blood-brain barrier and cause an increase in the permeability of the vascular endothelium. This will allow the virus to penetrate the blood-brain barrier and lead to the induction of local inflammation by increasing the production of chemokines and cytokines. At the same time, the migration of inflammatory cells to the brain parenchyma will be facilitated [14,19,20].

Neuronal route

SARS-CoV-2 can also enter the nervous system by infecting peripheral nerves and then entering the CNS retrograde via active axonal transport. The transport via olfactory pathways can be a great example of that. The unique anatomic [19] construction of the olfactory nerves and olfactory bulb in the nasal cavity and forebrain makes it work as a transport channel between the nasal epithelium and the brain. It is believed that SARS-Cov-2 can reach from the nasal cavity the entire brain and cerebrospinal fluid within days. Further neurodegeneration can be caused by misdirected host immune responses against SARS-CoV-2 or direct damage to neuronal cells by replicating viral particles [14,19,20].

PATHOPHYSIOLOGY

Neurological symptoms of SARS-CoV-2 infection not only can be caused by the direct viral attack on structures such as neurons, glial cells, cerebral vessels and the blood-brain barrier but also secondary due to immune response against the virus. The virus can have an impact both on the central and peripheral nervous systems. There are a few possible mechanisms of neurovirulence of SARS-CoV-2, which are further described below.

Hypoxia

A lot of patients with a severe COVID-19 infection suffer from hypoxia due to shortness of breath and dyspnea. Impaired breathing mechanisms can lead to a build-up of acids in the

brain which contributes to cerebral oedema. As a result the intracranial pressure increases, which can cause drowsiness and sometimes even coma [14].

Infection induced cytokine storm

It is observed that the SARS-CoV-2 may also trigger a systemic inflammatory response syndrome that can contribute to the blood-brain barrier dysfunction. Hyperactivation of the immune system results in activation of glial cells, and afterwards excessive increase of levels of inflammatory factors, such as cytokines, chemokines, and other signals of inflammation. The production of interleukins (ILs) such as IL-6, IL-12, IL-15 and Tumor Necrosis Factor-alpha (TNF-α) is most often observed. Recent studies report that there is a positive correlation between IL-6 and the severity of COVID-19 symptoms. The production of pro-inflammatory cytokines then may lead to significant damage to the blood-brain barrier, which can induce and magnify the neuroinflammatory process [14,19,20].

Angiotensin-converting enzyme-2 (ACE-2) binding related neurovirulence

The angiotensin-converting enzyme-2 is said to be one of the most important targets of SARS-CoV-2. This enzyme has a huge impact on blood pressure regulation and anti-atherosclerosis mechanisms. A lot of receptors for ACE-2 are present in the glial cells and neurons, particularly in the brainstem and also in the regions, which are responsible for the regulation of cardiovascular function. They are also expressed by endothelium. The endothelium also prevents thrombosis and is responsible for hemostasis, therefore endothelial cell dysfunction, induced by COVID-19 infection, can be an important driver of coagulopathy and increased thrombotic burden. To the prothrombotic state contributes factors such as disruption of the antithrombotic endothelial surface caused by endothelial cell activation by infection, excess thrombin generation and early termination of fibrinolysis. It is reported that SARS-CoV-2 in the endothelium is accompanied by inflammatory cells and evidence of endothelial cell death, which suggests an endothelitis and can explain microcirculatory injury and failure or injury of organs. For instance, there has been case report of severely ill patient with COVID19, ARDS, acute renal failure, and altered mental status in whom von Willebrand factor, a marker of endothelial stimulation and damage, was massively elevated at 500% of normal. -It has been also noticed that the most frequent comorbidities of COVID-19 patients are hypertension, diabetes, and cardiovascular disease, which share endothelial dysfunction as a common feature. That is why it is suggested that the vascular endothelium may be a key organ in COVID-19 infection [20,21].

SARS-CoV-2 uses spike proteins present on its surface to bind with ACE-2. This can badly affect the blood pressure regulating mechanism and predispose infected patients to cerebrovascular events. Especially older people or those with treatment-resistant conditions are concerned [19,20].

Demyelination of nerves

There is also some evidence of SARS-CoV-2 involvement in demyelination. Current studies show that COVID-19 infection can be a risk factor for demyelination both in the peripheral and central nervous systems. The demolition of the myelin sheath is mostly provoked by a complex autoimmune reaction [14,22].

EPIDEMIOLOGY OF NEUROLOGICAL AND PSYCHIATRIC MANIFESTATIONS OF SARS-CoV-2

In retrospective studies, it is emphasized that respiratory and gastrointestinal symptoms are the most commonly observed symptoms among patients diagnosed with COVID-19, but the central nervous system may also be affected after the damage of the blood-brain barrier through the blood vessel-rich meninges [23]. Many researchers inform about 36.4% of patients who had neurological involvement more in the CNS than in the peripheral nervous system [4,6] . In the retrospective study from Wuhan, patients developed acute cerebrovascular events during COVID-19 infection. Several other studies have shown neurologic involvement as the presenting feature of SARS-CoV-2 infection or have reported post-infectious neurologic complications [4].

Central nervous system (CNS) manifestations of SARS-CoV-2

Although mostly considered a rather non-specific symptoms of any viral infection, headache has been largely present in most studies conducted across the globe, ranging from 3% to as high as 13% in some studies [25]. Peripheral nervous system (PNS) manifestations of SARS-CoV-2

The SARS-CoV-2 infection may affect cranial nerves (i.e. olfactory and gustatory dysfunction, oculomotor nerve palsy), peripheral nerves (polyradiculopathy, neuropathy, Guillain Barre Syndrome), neuromuscular junction (causing myasthenic crisis in patients with history of myasthenia gravis) and muscles (myopathies) [7].

Table 1. The most common symptoms and disease reported as the manifestation of SARS-CoV-2 infection in central nervous system (based on [7,23,24]) are listed in table below

SYMPTOMES	DISEASES
- Headaches **- Anosmia, Hypogeusia** **- Spasms** **- Confusion** **- Dizziness** **- Conscience problems** **- Nausea, Vomiting** **- Ataxia** **- Seizures**	- Encephalitis , Meningoencephalitis - Encephalopathy - Atypical postpartum reversible encephalopathy syndrome - Stroke - Cerebral hemorrhage - Cerebral venous thrombosis

Epidemiology and symptoms of psychiatric incidents

The estimated cumulative incidence of psychiatric sequelae concurrent with SARS-CoV-2 is about 59% [26]. In this group decreased levels of consciousness and encephalopathy were reported in about 31% of the patients [7]. Possible mechanisms are complex and should include many different issues, caused by infections, immunological response, parenchymal damages, electrolyte imbalance, hypoxic, toxic and metabolic encephalopathy or medical interventions [3,7].

In various studies, a large group of patients was affected by both neurological and psychiatric diagnoses and was identified with altered mental status - defined as an acute alteration in personality, behavior, cognition, or consciousness and peripheral neurology [2,7, 23,24,27]. Other psychiatric findings were dementia-like syndrome, chronic fatigue syndrome, depression, catatonia, mania or anxiety [2]. Moreover, in SARS-CoV-2, after recovery from the infection, sleep disorder, emotional lability, impaired concentration or memory were reported in more than 15% of patients at a follow-up period ranging between 6 weeks and 39 months [3]. Both neurological symptoms (especially cerebrovascular events) and psychiatric impairment such as altered mental status, were identified across all age groups. Moreover, acute alterations in mental status were disproportionately overrepresented in younger patients [2]. The suspected reason for these symptoms is systemic hyperinflammation provoked by innate immunity that may impair neurovascular endothelial function, disrupt BBB and induce para-infectious autoimmunity, potentially contributing to the CNS complications associated with SARS-CoV-2 infection [26]. Many of the cytokines known to be induced in COVID-19 patients, including IL-1β, IL-6 and TNF-α, have been associated with major depression and anxiety disorders [28].

Post-Covid neurological syndrome

The number of case reports of patients having protracted neurologic manifestation after the acute phase of COVID-19 is growing [28]. The relationship between the appearance of complications in mental health is seen in the first 45–60 days after infection (occurs even in young people without specific risk factors) [6]. It constitutes symptoms such as chronic fatigue, dyspnea, or tiredness. It also represents a high-risk period where there is silent target organ damage [6,28]. Stress was identified as the most common mental health consequence (48.1%) of the COVID-19 pandemic, along with depression (26.9%) and anxiety (21.8%) [23]. It is still unknown whether there is greater activation of immune complexes and neurological inflammatory activity after infection or the persistence of symptoms long after the onset of the first sign [6]. In large research, it was found that more than half of the infected patients experienced new or deteriorating behavioural disturbances, including aggression, apathy and depression. Moreover, the researchers determined that COVID-19 indirectly affects the clinical conditions of patients with dementia and other cognitive disturbances [28].

METHODS OF EXAMINATION OF NEUROLOGICAL SYMPTOMS

Blood examination

Specific and non-specific markers should be assessed in suspicion of COVID-19 positive patients, including CBC with differential inflammation markers: CRP, CK, D-dimer, lactate dehydrogenase, transaminase, and azotemia (uremia), creatinine, IL-6 and IL-7. Peripheral cytokines involved in antiviral responses may elicit neuropsychiatric symptoms and neuroinflammatory responses. Increased secretion of proinflammatory cytokines and chemokines such as IL-6, IFNγ are found in the blood of COVID-19 patients [7,29].

Cerebrospinal Fluid (CSF)

An increased level of inflammatory precursors in CSF was described in patients whose either CNS was affected during Sars-CoV-2 infection or in those without neurological manifestations. Infection induces a high level of GM-CSF that stimulates cells to produce granulocytes (neutrophils, eosinophils, and basophils) and monocytes. Because of that peripheral cell, monocyte, and neutrophil counts were significantly higher in patients with COVID-CNS infection than in patients with COVID-respiratory infection and healthy controls. Furthermore, it was observed that such inflammatory chemokines: IL-6, IL-8, and MCP-1 were significantly accumulated in the CSF of patients with neurological symptoms [6].

Neuroimaging

Magnetic resonance imaging (MRI) especially with use of Diffusion weighted image (DWI), Fluid attenuated inversion image (FLAIR) and Apparent diffusion coefficient (ADC) [7] reveals reversible lesions or multiple white matter lesions of the brain and spinal cord, with frequent involvement of the subcortical grey matter structures [26]. Cerebrovascular symptoms (manifested as ischemic stroke or haemorrhagic stroke) were much more common in patients with severe SARS-CoV-2 infection [24,30]. The risk of stroke was directly associated with advanced age and comorbidities. Moreover, ischemic stroke happens not only in the early stages of convalescence, but it can also appear later [23].

In one publication, which describes a brain CT scan in infected patients, it is mentioned evidence of irregular hypodensities in the periventricular deep white matter, bilateral basal ganglia, thalami, pons, cerebellum, and cerebellar pedicles and corpus callosum. MRI revealed multiple areas of signal abnormality in the periventricular deep white matter, subcortical area, corpus callosum, pons, mesencephalon, cerebellum, and upper cervical cord [6].

Although nonspecific symptoms of encephalopathy are common in COVID-19 patients, cerebral neuroimaging evaluation is performed in less than 15% of the patients [30]. This raises a probable selection of underreporting cases with presumable neuroimaging findings but mild clinical symptoms, where a brain MRI or CT was considered unnecessary. Furthermore, neuroimaging findings are also found in many other constellations such as sepsis-associated encephalopathy. Carefully planned and more systematic studies are needed to clarify if observed imaging patterns are attributed to direct COVID-19 pathophysiology [7].

Other examinations

Electroencephalography of infected patients in 21% cases was indicative of encephalopathy and the ratio increased to 74% in critical ill patients. The most common abnormality was the diffuse slowing of wave frequency, especially in the frontal region [28].

Nerve Conduction Study (NCS) and Electromyography (EMG) tests defined dysfunction in the peripheral nervous system. Myopathy is assessed on the basis of NCS or EMG findings. In Covid- positive patients the EMG findings of short motor unit action potentials, with decreased amplitude and duration, along with normal sensory and motor NCS were seen. However, in some of the patients, low compound muscle action potentials are also noted. In addition, these methods are used as well as to define GBS and its variants or other peripheral nervous system abnormalities [22].

In some patients, the brain PET scan highlighted hypometabolism of the left orbitofrontal cortex, which is involved (together with the limbic system) in the chemosensory process [31] as well as hypermetabolism in the cerebellar vermis [32].

Subsequent psychological testing reveals a significant episodic memory decrement both in symptomatic and asymptomatic patients who do not report long-COVID symptoms [33]. COVID-19 survivors are significantly impaired in their ability to sustain attention and motivation on a demanding task up to nine months after COVID-19 infection, along with significantly worse episodic memory [33].

PROPOSED TREATMENT AND THERAPEUTIC OPTIONS

Preventing infections

In preventing infection, it is essential to avoid close contact with infected people, stay at home when symptoms occur, wash your hands frequently, and disinfect regularly used items. Reducing the risk of COVID-19 transmission can be achieved by wearing masks in public, not only by symptomatic people or healthcare workers [34]. Vaccination has been reported to reduce the number of symptomatic cases of COVID-19. As measured by the PCR-Ct value, a reduction in viral load was observed among vaccinated infected [35]. Lower viral load is associated with decreased further transmission, suggesting that vaccination may reduce transmission [35].

General management

The primary clinical treatment includes symptomatic management and oxygen therapy with mechanical ventilation in patients with respiratory failure [36]. The nonspecific neurological symptoms of COVID-19 often resolve with treatment of respiratory symptoms. There is no specific treatment for neurological symptoms in patients with COVID-19 [10]. Decreased platelet levels or increased ferritin levels in patients with severe COVID-19 may signify cytokine storm syndrome. Existing approved therapies for the treatment of hyperinflammation should be used to reduce increasing mortality [36]. Steroids may be considered for post-infectious / para-infective complications in all phases of the disease. The exception is GBS, which should be treated according to protocols using intravenous immunoglobin therapy (IVIG). However, there is a risk that these immune interventions may interfere with the host's protective immune response against SARS-CoV-2 [10].

Delirium

The pathophysiology of delirium in COVID-19 patients is not completely clear, so treatment decisions should be made based on presenting symptoms and comorbidities. Potential drug interaction should also be considered. The first line of treatment for delirium is behavioral modification. If this is not sufficient and the patient is a danger to himself or the medical staff, pharmacological agents are necessary [11]. In the treatment of delirium, there is a growing interest in the use of melatonin and melatonin receptor agonists due to their sleep-regulating, immunomodulatory, and neuroprotective factors. It is recommended that the addition of melatonin be considered in all patients with COVID-19 [11]. Alpha-2 agonists are effective in preventing delirium and treating agitation associated with delirium. Dexmedetomidine may improve delirium and shorten recovery time and should be considered in ICU patients. Clonidine is effective in delirium, alcohol and opioid withdrawal and may also be an appropriate first-line drug for COVID-19 delirium. Antipsychotics are an option for the treatment of behavioral dysregulation or perceptual disturbances [11]. To minimize the risk of extrapyramidal side effects and catatonia, starting treatment with low-potency antipsychotics is recommended. Psychiatrists should be cautious in treating elderly patients with antipsychotic drugs because of the increased risk of death and stroke in patients with dementia. Patients with chronic obstructive pulmonary disease should be closely monitored because they are at increased risk of respiratory failure. The use of valproic acid should be considered if additional medications are required or if antipsychotics are relatively contraindicated. Valproic acid therapy is associated with a reduction in agitation, delirium, and the concomitant use of neuroleptics. It is useful in the treatment of behavioral dysregulation in delirium patients. Trazodone may be effective for daytime impulsivity and restlessness in elderly patients who cannot tolerate antipsychotics. Amantadine and methylphenidate, may be used in patients with akinetic mutism or catatonia. All dopamine agonists can increase delirium and impaired perception [11].

Stroke

Among the critical situations faced by neurologists in the COVID-19 pandemic is the management of acute stroke. The ability to provide prompt and effective care should be considered in the risk of exposure to infection. This becomes particularly important in patients with acute stroke. It should be noted that specifically timed reperfusion therapies, such as thrombolysis and mechanical thrombectomy affect recovery and long-term outcomes in patients with COVID-19 [4]. In addition to stroke evaluation, the attending health care

professional should pay attention to other comorbidities, damage to other organs and general condition that may worsen the prognosis in such patients. Post-stroke care must be then modified according to the patient's condition [4]. The management of ischemic stroke associated with COVID-19 is the early therapeutic anticoagulation of Low Molecular Weight Heparin (LMWH), which may also be beneficial in reducing thromboembolism in these patients. However, the risk of intracranial haemorrhage, including the haemorrhagic transformation of acute myocardial infarction with anticoagulant LMWH therapy, should be considered [37]. Mechanical thrombectomy, which is an invasive procedure, is more challenging. If the patient meets all inclusion criteria, thrombectomy should always be considered a therapeutic option, as it can be performed with appropriate safety precautions, assuming the patient is a COVID-19 case [4]. Ischemic stroke patients with COVID-19 perform worse outcomes after acute revascularization treatments than contemporaneous non-COVID-19 treated patients [38].

Cerebral venous thrombosis

Cerebral venous thrombosis is a rare complication of COVID-19. Patients without risk factors for cerebral venous thrombosis may develop such neurological sequelae due to prothrombotic state induced by COVID-19 [22]. The risk of thrombosis in COVID-19 patients has increased significantly compared to the risk of thrombosis in the general population before the pandemic [38]. Initial symptoms may include signs of increased intracranial pressure such as progressive headache, visual disturbances, optic disc edema, focal neurological deficits, impaired consciousness and seizures. Venous sinus thrombosis is diagnosed based on clinical and radiological criteria. Anticoagulation therapy with heparin is preferred, using therapeutic doses of low molecular weight heparin or unfractionated heparin. Low molecular weight heparin therapy appears to be more effective than unfractionated heparin and is, therefore, a first-line treatment [22].

Post-COVID

Patients require multidisciplinary care, including long-term monitoring of persistent symptoms, to identify the need for physical rehabilitation, mental health, and support for social services. Appropriate rehabilitation is recommended to prevent muscle weakness, deconditioning, myopathies and neuropathies begin in the intensive care unit as soon as sedation and clinical stability permit. Non-hospitalized patients with long-COVID may also require physical rehabilitation [39].

In addition to physical pathologies, the COVID-19 pandemic has placed a strain on the mental health of the world's population. Appropriate mental health support should be provided for patients who require it. Patients found to require additional support were referred to specialist management. Due to persistent symptoms, a significant number of long-COVID patients are unable to return to work and may require financial support from the government. Some patients are unable to cope with daily life, especially if they suffer from social isolation or stigmatization. These groups of patients would benefit from the support of social services [39].

CONCLUSIONS

Many advances in our understanding of neurotropic viruses have been made thus far, but more research is required to improve our ability to diagnose and then treat CNS infections rapidly. Viral diseases of the CNS represent a significant burden to the global community, especially during the COVID-19 pandemic [1].

The virus constantly evolves and spreads through asymptomatic carriers, suggesting a high international health threat [34].

The complexity of COVID-19's pathology and the impact on the brain requires appropriate screening that has to go beyond the psychosocial impact, taking into account how stress and neuroinflammation affect the brain [12].

A thorough understanding of the complex and interrelated inflammatory mechanisms and identifying universal mediators promoting CNS inflammation is essential for developing new diagnostic and treatment strategies [5].

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Review of selected immunological aspects of COVID-19 complications

Sven Solisch[1], Anna Susłow[1], Adam Szwed[1], Krzysztof Gomułka[2]

1. Student Science Association of Adult Allergology, Wroclaw Medical University, Wrocław, Poland
2. Department of Internal Medicine, Pneumology and Allergology, Wroclaw Medical University, Wrocław, Poland

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes coronavirus disease 2019 (COVID-19), has afflicted hundreds of millions of people in a worldwide pandemic [1]. Aside from the symptoms and complications patients experience during the disease period, there is an accumulating body of evidence regarding the late-onset COVID-19 complications, many of which involve SARS-CoV-2 affecting and destabilizing the immunological system [1,2]. As studies continue to unveil the pathophysiology behind those disorders, understanding these mechanisms is vital for employing appropriate diagnostic and therapeutic procedures. In this article selected immunological aspects of COVID-19 complications are reviewed, focusing on the post-COVID-19 syndrome, pediatric inflammatory multisystem syndrome (PIMS), and the role of neutrophils in severe COVID-19.

POST–COVID-19 SYNDROME

Many patients suffering from COVID-19 and presenting different levels of its severity, have reported prolonged symptoms and complications, often affecting patients' quality of life, that continue to occur beyond four weeks after recovering from the infection. The residual effects of SARS-CoV-2 infection may concern various organs and systems leading to manifestations such as i.a., fatigue, dyspnea, chest pain, cognitive dysfunction, diarrhea, and arthralgia [3]. These observations led to the recognition of post-COVID-19 syndrome, also referred to as post-COVID-

19 conditions, post-acute sequelae of SARS-CoV-2 infections or long COVID-19 [4]. There is limited literature concerning post-COVID-19 syndrome, its epidemiology and exact pathophysiological mechanisms behind the disorder.

Although initially there were no uniformly accepted diagnostic criteria, most researchers agreed upon defining post-COVID-19 syndrome as symptoms that persist or develop ≥4 weeks after recovering from initial SARS-CoV-2 infection and cannot be explained by other causes [5,6,7,8,9].

Later in October 2021, World Health Organization (WHO) developed a clinical case definition for post COVID-19 condition based on Delphi consensus that reads as follows: "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time" [10].

The incidence of symptoms that may be attributable to post-COVID-19 syndrome is estimated to be about 20% for COVID-19 survivors aged 18–64 years, 25% for those aged ≥65 years and up to 85% for hospitalized patients [11]. The most frequently observed symptoms are breathing difficulties and/or breathlessness, fatigue and or malaise, chest and/or throat pain, headaches, gastrointestinal symptoms, myalgia, arthralgia, cognitive abnormalities (sometimes referred to as 'brain fog'), anxiety and/or depression [12]. Patients aged 65 or above are observed to be at an elevated risk of neurological and mental health complications [13].

Possible explanations of the mechanisms involved in post-COVID-19 include virus-specific pathophysiological variations, inflammatory injury, oxidative stress and abnormal immune response. SARS-CoV-2 is observed to cause cellular damage through inflammatory cytokines, ACE2 pathway maladaptation and procoagulant activity [7]. Reportedly, similar patterns of symptoms were observed in SARS-CoV patients in 2003 and MERS patients in 2012 [3]. Oxidative stress observed in post-COVID-19 syndrome is thought to be a consequence of mitochondrial damage that follows SARS-CoV-2 infecting type II pneumocytes. Moreover, excessive ROS production is also a known consequence of oxygen treatment that is administered in COVID-19 patients suffering from ARDS during the acute disease phase. Mitochondrial-targeted antioxidants

are proposed as a potential approach in treatment, however, this solution requires further research. The presence of SARS-CoV-2 in alveolar epithelial and endothelial cells causes a cascade of neutrophils, monocytes, and T-cells resulting in diffuse alveolar injury. Patients with severe pneumonia or ARDS in acute COVID-19 are observed to present decreased lymphocyte counts and elevated levels of cytokines, in particular, tumor necrosis factor and pro-inflammatory interleukins, e.g. IL-6 [7].

There are ongoing clinical trials investigating possible therapies for the post-COVID-19 syndrome, including i.a., hyperbaric oxygen therapy, nebulized platelet lysate, and C1-esterase inhibitor recombinant. However, as of May 2022, the only generally accepted and recommended treatment was through rehabilitation exercises that rely on gradual increases in intensity. Breathing exercises aiming to strengthen the respiratory muscles accompanied by a light regimen of aerobic training is proposed as a treatment for patients presenting impairment in physical performance. Cognitive behavioral support combined with psychological support and therapy is also indicated [9,14].

More research is needed to deepen the understanding of mechanisms behind post-COVID-19 syndrome and to form appropriate strategies for dealing with this condition, which came to be recognized as one of the most prominent COVID-19 complications.

PIMS

One of the complications of SARS-CoV-2 infection in children is pediatric inflammatory multisystem syndrome associated with coronavirus disease - PIMS. This is a new disease because the first descriptions appeared in the second quarter of 2020 [15,16]. The prevalence is estimated at about 1: 1000 children infected with SARS-CoV-2, and the mortality rate is around 2% [17]. The pathogenesis of PIMS is associated with a pathological reaction of the immune system, which results from infection with COVID-19 2-4 weeks earlier - often the SARS-CoV-2 infection itself could be mildly symptomatic or even without any clinical symptoms [18].

The main causes of the pathomechanism of PIMS are seen in the increased activity of the NF-κB pathway and the action of IL-6. Increased activity of the NF-κB pathway implies the formation of large amounts of pro-inflammatory cytokines, in particular TNF-α, which in turn causes a significant increase in the concentration of chemokines such as CCL2, CCL3, CCL20,

CXCL10, and CX3CL, whose task is to increase the migration of immunocompetent cells to the sites of inflammation. IL-6 is a pro-inflammatory cytokine whose activity increases mainly due to the activation of Toll-like-4 receptors (TLR4). The mechanism of action of IL-6 is based on the phosphorylation of the STAT3 factor, which directly influences the expression of genes encoding a number of key proteins in maintaining inflammation, including: IL-17, IL-23, IFN-γ, TNF-α, CRP or VEGF. All the above-mentioned occurrences are responsible for the control of the immune response, the initiation of angiogenesis and the activation of fibroblasts [19,20].

The clinical criteria for the diagnosis of PIMS are (1) age below 18 years with a median of 9 years, (2) fever above 38.5°C for at least 3 days, (3) increase in inflammatory markers such as: CRP, procalcitonin, fibrinogen, D-dimers or ferritin, (4) clinical picture indicating the involvement of at least two systems - e.g. severe abdominal pain or vomiting indicating gastrointestinal involvement or features of myocarditis or arrhythmias as a manifestation of cardiovascular system, (5) exclusion of other possible causes - including systemic connective tissue diseases, acute appendicitis and other toxic or infectious agents, (6) connection with COVID-19 - e.g. with a documented infection in the past or positive results of RT-PCR or antigen tests. Criteria 1-5 should always be met, while criterion 6 is not necessary for the diagnosis [21]. Laboratory tests reveal characteristic deviations from the reference ranges: very high CRP, elevated BNP or troponin I levels, and lowered levels of lymphocytes, hemoglobin, albumin and serum sodium levels [17,18].

PIMS should be differentiated from another disease entity seen in children - Kawasaki disease. Although both disorders are associated with autoimmune vasculitis, there are several differences, including PIMS most often affects older children while Kawasaki disease younger, the level of thrombocytes in the blood serum in PIMS is often lowered, in Kawasaki disease it is elevated. Complaints on the part of the digestive system are relatively common in the course of PIMS, while in Kawasaki disease they appear sporadically. Finally, the features of dysfunction of myocardial contractility or acute left ventricular failure often appear in PIMS and rarely in Kawasaki disease [22].

Treatment of PIMS is multidirectional and includes symptomatic (general) and essential (specific) treatment. Symptomatic treatment consists in supporting vital functions and monitoring the patient's haemodynamic status - blood pressure, pulse and saturation. The basic treatment has three levels and its essence is to reduce the activity of the immune system. Intravenous

immunoglobulin infusion (IVIG) is recommended as the first-line treatment. The second-line treatment is the administration of intravenous glucocorticosteroids (GCS) - most often methylprednisolone, and the third-line treatment is biological treatment in the form of preparations containing infliximab or tocilizumab [23,24]. Antiviral treatment should be reserved only for patients with positive RT-PCR results and saturation below 95% [25]. Empirical antibiotic therapy is not recommended in PIMS - it should be implemented only in severely ill patients with symptoms of sepsis or bacterial superinfections. Whereas, antiplatelet therapy in patients with PIMS should be continued until no coronary artery lesions are confirmed in the ECHO study [21,23].

Vaccination against COVID-19 should be recommended to all children over the age of five, because the disease, and above all complications in the form of PIMS, pose a real threat to the health and life of children.

ROLE OF NEUTROPHILS IN COVID-19 COMPLICATIONS

SARS-CoV-2 infection can cause mild or sometimes subclinical symptoms, but it can also lead to serious complications, presenting as severe pneumonia and ARDS. ARDS is an uncontrolled systematic inflammatory reaction associated with a tremendous amount of pro-inflammatory cytokines being released into the bloodstream and tissues, called cytokine storm. Cytokine storm drives severe and poorly understood host response, but little do we know about what actually triggers the whole cascade of hyper-inflammation in COVID-19 patients. Recent studies showed significant role of neutrophils in aggravated host response in patients with severe COVID-19. Neutrophils are first line fighters in battle against microorganisms, especially bacteria and fungi. They use many mechanisms that allow them to kill pathogens attacking our organism such as oxidative burst and phagocytosis [26]. One particular method called NETs is especially interesting considering SARS-CoV-2 infection.

Neutrophil extracellular traps (NETs) are comprised of DNA, histones and granule proteins - lactoferrin, cathepsins, neutrophil elastase (NE) and myeloperoxidase (MPO), as well as cytoplasmic and cytoskeletal proteins [27]. In general NETs entrap pathogens by its web-like structure. This mechanism is not considered as a critical immune function, but apart from its benefits, excessive NET formation can be responsible for inflammatory reactions that destroy surrounding tissues, facilitates microthrombosis, and results in permanent organ damage [26].

Unrestrained NET release has been already associated with numerous diseases, such as small-vessel vasculitis [28] and systematic lupus erythematosus [29].

Veras et al. in their cohort studies found that viable SARS-CoV-2 can directly induce the release of NETs by healthy neutrophils [30]. SARS-CoV-2 binds to ACE2 and enters epithelial cells. As a result, ACE2 expression decreases and neutrophil recruitment is stimulated. NETs produced by neutrophils, induce necrosis in epithelial cell. This leads to the release of associated molecular patterns and sets up a self-perpetuating loop of inflammation-causing exacerbating severity during COVID-19 [31]. What is more, intravascular NETs have been shown to play a vital role in initiating and congregating thrombosis in arteries and veins, what may explain hyperactive coagulation in severe COVID-19 [32]. NETs activate the contact pathway of coagulation by interacting with platelet phospholipids. In conclusion, high blood levels of circulating NETs can trigger the occlusion of small vessels, leading to damage to the lungs, heart and kidneys [26].

Analyzing the role of neutrophils in severe cases of COVID-19, another clinical consequence must be taken under consideration. The severe cases of COVID-19 were likely to present higher neutrophil count but lower lymphocyte count compared with non-severe patients [33]. As a result neutrophil-to-lymphocyte ratio (NLR) is also increased and it is found to be an independent risk factor of the in-hospital mortality for COVID-19 patients, in particular male. NLR can be quickly calculated based on a routine blood test taken on admission, allowing early identification of high-risk individuals. NLR is a valuable predictor of overall inflammatory status, up to now it was used in other than COVID-19 infectious disease, in malignancy, acute coronary syndrome, intracerebral haemorrhage, polymyositis and dermatomyositis [34].

Crucial, although not yet clarified, neutrophil role in COVID-19 pathogenesis, may imply potential treatment strategies. Thus far, systemic glucocorticoids and heparin are well-established medications used in COVID-19 patients. Heparin neutralizes histones forming NETs and accelerate DNAse I, an enzyme that degrades NETs mediated clots. Glucocorticoids, including dexamethasone, have been reported to reduce NET formation most likely by suppressing the expression of inflammatory mediators that activates neutrophils [27]. In contrast to universal immunosuppression, the specific inflammatory pathways can be targeted. Inhibitors of NETs synthesis or promotors of NETs fragmentation, as well as inhibitors of neutrophil recruitment, are suggested as future therapeutics [31,34,35,36].

CONCLUSIONS

The disease caused by SARS-CoV-2 should definitely be seen through the prism of events at the level of immune mechanisms. This applies to both the infection itself and its complications, such as PIMS. Due to the high mortality rate, not only of COVID-19, but also the above-mentioned complications resulting directly from the primary infection, we are convinced that preventive vaccination can save not only health but also life on several occasions.

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Seasonality of COVID-19

Sven Solisch[1], Anna Susłow[1], Adam Szwed[1], Krzysztof Gomułka[2]

1. Student Science Association of Adult Allergology, Wroclaw Medical University, Wrocław, Poland
2. Department of Internal Medicine, Pneumology and Allergology, Wroclaw Medical University, Wrocław, Poland

INTRODUCTION

As SARS-CoV-2, the novel coronavirus that causes coronavirus disease 2019 (COVID-19), continues to circulate around the world, patterns indicating an influence of environmental factors on its transmission have been observed.

Since there is a number of other determinants of current development of the pandemic (including social distancing, lockdowns, and vaccination campaigns), it is challenging to analyze the seasonal components having to separate their impact from that of remaining circumstances [1]. Modelling seasonal variation of COVID-19 transmission, leading to more accurate predictions, is a valuable tool in managing the pandemic [2].

SEASONALITY OF INFECTIOUS DISEASES

The role of the seasonality of infectious diseases is one of the key elements in understanding the impact of particular infections on the biological variability of the human population. Undoubtedly, the cyclical nature of infectious diseases is associated with many environmental factors, which include: weather changes, such as heavy rainfall or fluctuations in atmospheric air temperature, development cycles of vectors or pathogens themselves, fluctuations in social behavior of people (e.g., intensive contacts of children in kindergarten), but also changes in human immunity status in given populations. Many infectious diseases are characterized by a well-known seasonality [3,4].

The best-described vector-borne diseases associated with cyclical incidence are malaria, West Nile fever, and Dengue fever. All of the above-mentioned disease entities share the fact that they have the highest incidence in hot and relatively humid conditions. The most common infections occur in summer and early fall, when many people travel to tropical countries. Heavy rains of zenith along with the accompanying high temperature are responsible for the increase in the number of vectors and enable the development of microorganisms in the body of vectors [3,5,6,7].

Studies on bloodstream infections caused by Gram-negative bacilli infections have shown that they occur much more frequently in the warmer months. It was found that high temperature positively influences the colonization of the human body by *Acinetobacter spp.*, *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella spp.*, and *Pseudomonas aeruginosa* - the latter microorganism tolerates the increased level of humidity equally well [8,9].

The well-documented seasonality of the disease also applies to infectious diarrhea [3]. A bacterial disease with intense and watery diarrhea is cholera caused by *Vibrio cholerae* (most often strains O1 and O139) [4,10]. It has been proven that rains combined with a moderate ambient temperature help in the spread and survival of microorganisms. Therefore, the most frequent increase in cholera cases occurs in spring and autumn [11]. In turn, *Rotavirus* infection is one of the most common viral diseases characterized by the seasonality of infections linked with diarrhea [4]. The peak of incidence occurs in the autumn and winter period and is associated mainly with intensive contact between children in school and kindergarten, and a natural decrease in immunity during the cold months [3,12].

The most common infectious diseases concern the upper and lower respiratory tract. Diseases affecting the respiratory system are characterized by various etiologies - viral or bacterial [13]. It is the influenza virus, RSV and *Streptococcus pneumoniae* that are responsible for a significant number of respiratory ailments in adults and children. The greatest number of cases is usually recorded in winter when the effectiveness of the immune system to fight pathogens decreases and due to persistent low temperatures, we use less leisure time outdoors, crowding inside buildings. It is conducive to the transmission of infections [14,15,16]. Measles, on the other hand, was characterized by a cyclical increase in infections, on average, every 2.5 years, most often in spring or autumn. The increased incidence in these periods corresponds to the children's return to school, and hence - to increased contact between the children, which has helped spread the disease.

Fortunately, the introduction of vaccination against measles has significantly reduced the incidence of this disease [4,17]. In the last three years, we have also observed the seasonality of a new disease entity – COVID-19 [18].

The above examples show that infectious diseases constitute a heterogeneous group in terms of the seasonality of their occurrence.

COVID-19 SEASONALITY BEFORE VACCINES (2020)

"Will COVID-19 become a seasonal disease?" is one of the most important questions nowadays, considering the economical, political and social aspects of the pandemic. Predictions about seasonal outbreaks will help to prepare sufficient amount of vaccines and healthcare system resources.

Considering seasonality, we must take a memory lane and acknowledge what we already know about other human coronaviruses. Four known seasonal coronaviruses (sCoVs) circulate in human populations, including two alpha-coronaviruses (NL63 and 229E) and two beta-coronaviruses (OC43 and HKU1). In temperate climate sCoVs occurred mainly in winter months. In China and tropical climate less seasonality was observed. Winter outbreaks were similar for all species of sCoVs in the temperate climate, which suggests that SARS-CoV-2 may follow the example [19]. Furthermore, interactions between SARS-CoV-2 and sCoVs can cause cross-reactive T-cell recognition that may modulate our immune response and impact the dynamics of the COVID-19 epidemiology [20]. Tedijanto and Kissler predict that if duration of immunity to SARS-CoV-2 mimics that to other related coronaviruses, recurrent outbreaks are likely to occur [21].

Understanding what drives the seasonality of disease is essential to control it. Before launch of COVID-19 vaccines, three types of factors were mainly associated with the disease seasonality: environmental factors, viral characteristic and host features. Bukhari and Jameel claim that the novel COVID-19 pandemic has affected more seriously countries within a temperature range of 3°C to 17°C with absolute humidity between 3 g/m^3 and 9 g/m^3 [22,23], concluding that moderate temperature and dry environment are the most optimal for spreading of SARS-CoV-2 and present higher morbidity [18,24]. Cold weather increase in-door activity of humans and enhance person-to-person contact. In addition, in autumn and winter we are influenced by greater temperature

fluctuations between indoor and outdoor. When temperature in the nose drops by 5ºC, our antiviral defence weakens and we are more prone to infections [18]. Moreover, temperature has larger effects when containment measures are lifted and people mobility is higher [25].

On the contrary, other studies indicate that the most critical feature of seasonality is the day length period. Seasonal conditions with constantly changing day length and UV levels may modulate virus spread and host immune system. Correlation between UV levels and COVID-19 is not fully examined, yet promising and needs further study. UV radiation also correlates with vitamin D levels [26]. Vitamin D has a positive effect on the immune system and stimulates antimicrobial activity [27]. Seasonal changes of vitamin D levels can also influence host sensitivity to COVID-19 infection. What is more, there are also other immune system related factors. Enzyme called Furin, causes conformational changes separating the S1 and S2 domains of SARS-Co-V2 spike glycoprotein allowing viral endocytosis [18]. Dopico et al., detected that Furin transcripts in human leukocytes exhibit seasonal rhythmicity in children, with higher expression in summer and low in winter [18,28].

Another protein related to host response to viral infections including SARS-CoV-2 is ANTX1. Transcriptome analyses of human leukocytes showed that ANTXR2 expression is seasonally dependant [18,28]. These lead to a conclusion that there might be an endogenous seasonal change in immune defence against SARS-CoV-2, although further studies are needed to establish the importance of this finding.

Analysing viral features is as important as other two indicators of possible seasonality of COVID-19. Researches point out that SARS-CoV-2 stability in the air and on surface is influenced by humidity, temperature and sunlight. The virus is stable at low-temperature and low-humidity conditions, on the other hand warmer temperature and higher humidity shorten its half-life [1]. Furthermore, viral ability to spread is measured as a basic reproduction number (R_0). For SARS-CoV-2 R_0 is estimated to be about 3 (3.32 or between 2 and 3 depending on source) [29,30]. For comparison, seasonal influenza virus R_0 is estimated to be 1,27 and for SARS-CoV is between 2 and 3. Basic reproduction number briefly is the number of secondary cases resulting from one infected person and describes the transmissibility of the pathogen within a specific population and setting [30]. R_0 indicates needed mitigation efforts and mitigation reduces the effective transmission rate, also called effective R_0. It is proposed that virus will follow a seasonal pattern if its effective R_0 drops below 1 [29]. In the early pandemic times high R_0, high stability of SARS-

Cov-2 and the fact that global population was immunologically naïve against SARS-CoV-2, it was unlikely to drop R_0 in summer. Nevertheless, studies showed that a 1ºC increase in temperature and a 1% increase in relative humidity can lower the daily effective reproductive number (re) by 0,0383 and 0,0224 [22]. Nowadays, in light of gaining natural immunity and through vaccinations, we shall assume that R_0 might drop and the virus will more likely enter seasonal occurrence [30].

COVID-19 SEASONALITY AFTER VACCINES (2021 – PRESENT)

Overall, vaccines against SARS-CoV-2 are observed to prevent severe infection and COVID-19-related hospitalizations, also reducing the mortality [2,31,32].

According to recent studies by D'Amico et al. (2021), and Coccia (2022) COVID-19 seasonality in countries and regions of temperate climate, being expressed there more sharply [1], in general presented no significant alteration caused by the vaccines [33]. In comparison to the period preceding introduction of the vaccines, daily reported deaths attributed to COVID-19 manifest similar trends, reaching peak values during the winter months and subsequently decreasing throughout late spring and summer months. Likewise, the decrease in mortality observed during the warmer months was comparable across countries that presented varied vaccination rates in population [2].

Interestingly, the beneficial effect of the vaccines on reducing the mortality was observed to be stronger during the colder months. According to models and estimations for certain temperate American states presented by D'Amico et al. one percent increase of fully vaccinated citizens results in a drop of about 27 COVID-19 deaths per million on a yearly basis. When calculating the vaccination effect independently for high temperature months and low temperature months, the mortality reduction is estimated to reach about 22 and 46 deaths less respectively [2].

CONCLUSIONS

SARS-CoV-2 infection can undoubtedly be classified as an infectious disease characterized by a kind of seasonality. It has been proven that environmental factors such as the temperature or the length of the day have an impact on the course of the disorder. However, there have been no significant changes resulting from the introduction of vaccines that specifically address the

seasonality of COVID-19. Further observation of seasonality patterns can be an advantageous tool in predicting future pandemic waves which facilitates adjusting containment as needed [2].

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Impact of COVID-19 pandemic on suicide rate among various demographics

Natalia Nowak, Klaudia Włodarczyk, Weronika Biziorek, Mikołaj Palczewski, Haytham Al Hamaydeh

Faculty of Medicine, Students' Scientific Group at the Department of Psychiatry, Medical University Piastów Śląskich of Wroclaw, Wroclaw, Poland

List of abbreviations

PTSD – ang. post-traumatic stress disorder

PASC – ang. post-acute sequelae of SARS CoV-2 infection

ARDS – ang. acute respiratory distress syndrome

NGO – ang. non-governmental organization

INTRODUCTION

From the very beginning COVID-19 pandemic and its' global consequences caused a tremendous effect on lives and mental wellbeing of millions of people all around the world. The unprecedented scale of socioeconomic changes resulted in deprivation of sense of safety and demanded an abrupt and total modification of the way of living. The impact of the pandemic was particularly devastating for specific groups of people. Lack of social help for elderly resulted in them being deprived of the possibility to safely take care of their essential daily duties like grocery shopping. Shutting down of workplaces of many low-income individuals resulted in lots of people suddenly being unable to earn money needed to fulfill their existential needs. Schoolchildren were unable to have regular social contacts with their peers and were forced to spend most of the time indoors attending online classes. Due to the shutdown of face-to-face classes in most of the universities many college students had to return to their family houses. Medical staff was forced to adapt to the new reality and work under entirely different circumstances with problems they have never dealt with before and risking their own health in order to do their job. Data indicates that contraction of COVID-19 may also lead to severe psychiatric problems. Isolation and physical weakness combined with cognitive and

psychological malfunction may result in long lasting trauma and psychological function impairment.

These circumstances have led to such a significant increase in mental health issues, that some experts call it psychiatric epidemics. The prevalence of psychological problems in general population varied depending on many factors but overall an upward tendency was observed in many different age and social groups all around the world. There are many psychological problems experienced by patients in the COVID era. Some of them are depression, anxiety disorders, panic disorders, anger, impulsivity, somatization disorder, sleep disorder, PTSD, and emotional disturbances. Apart from those, probably the most severe consequence of psychological suffering - suicide [1], which is the most complicated issue related to mental health in this pandemic. Although there is strong evidence on mental health problems rising due to COVID-19, the data concerning suicidal ideations, suicidal behavior and general suicide rate presents conflicting results. Before first statistics appeared, many researchers feared of a huge spike in suicide rate. Surprisingly, the data seems not to support the idea that the general suicide rate increased during the COVID pandemic. There are significant differences in suicidal thoughts and attempts between different age groups, genders and countries of origin [2]. Early predictions projected a sharp increase in suicides in developed countries like Norway. Surprisingly, the statistics seem to suggest that it did not happen. An increase in suicide rate could be observed outside the COVID outbreak, while during the outbreak itself the number of suicides decreased [3]. On the other hand, some studies underline an increase in suicide ideation, suicide attempts and self-harm numbers especially in groups of risk, such as young people, women and individuals from democratic countries when compared to pre-pandemic levels [4]. The conflicting results emphasize the need to conduct more long-term studies. In our work, we try to focus on suicide related health issues in several groups of risk and review available data to learn more about the complex topic of suicidal behavior related to the coronavirus pandemic.

COVID-19 SUICIDE IN MEDICAL STAFF

Although the pandemic affected everyone’s lives, some groups were struck more than others. From the very beginning of it, the COVID-19 outbreak forced medical care workers to adapt to a new reality. Due to the sudden influx of new patients, many of whom were in life-threatening conditions, medics had to quickly learn new skills that were necessary to help them.

Prolonged shifts reduced the amount of time that could be devoted to their friends and families. Perpetual exposure to highly contagious patients triggered a feeling of constant tension. Even before the pandemic, health care professionals were in high risk of committing suicide compared to general population. COVID-19 exacerbated the difficult conditions faced by the medics. One of the studies conducted in Poland among health care professionals including doctors, nurses and paramedics stated that while all of the groups experienced elevated stress levels, nurses were the ones with the highest level of pressure, which lead to psychopathological symptoms, such as insomnia and depression. In the researched group, many coping mechanisms could be observed including adaptive and non-adaptive ones. One of the most frequent non-adaptive coping mechanisms was the use of psychoactive substances that ultimately resulted in deterioration of mental health [5]. Another study was conducted among Australian paramedics. Almost two-third of them reported experiencing professional burnout. When asked about concerns about their job, most frequent answers were concerning risk and safety in the workplace, uncertainty, and upheaval both at work and at home and lack of crisis preparedness. The results confirmed the lack of mental health support and wide range of psychopathological symptoms associated with COVID-19 pandemic [6].

Yet again in terms of suicide rate, the problem is more complicated than in other manifestations of psychological disturbances. Suicide can be regarded as occupational hazard in health industry. The pandemic deteriorated a situation that has already been difficult. The risk factors during COVID-19 era included increased workload, burnout, fatigue, multifaceted challenges and substance abuse [7]. As a recent Brazilian study report the suicide rate of doctors in the pandemic era seemed to be influenced by age, gender and race. Overall, the suicide rate increased in white male physicians and black male physicians but decreased in white female physicians. Among the various health occupations, the suicide rates varied depending on ethnicity. Overall, white males and females had highest suicide rates in most health occupations compared with general population. Black and white male physicians' suicide rate both increased significantly. There is little data to compare suicide among physicians in different countries [8].

The common expectation in the society is that health care professionals would put their patients' interest first before themselves in terms of their physical and mental health needs. The social support for medics struggling with psychiatric issues is insufficient. Various factors lead to burnout and suicidal behavior among physicians at work, including a lack of flexibility, lack of meaning, no sense of community, and scarce resource availability [9]. Analysis of the health

care workers' suicides reported by the press found that the most common reason for committing suicide was being infected with COVID-19, followed by work-related stress, fear concerning a COVID-19 infection, fear of transmitting the virus to others, anxiety caused by witnessing an overwhelming amount of death and mental suffering. The findings differed slightly from those found in the general population, in which the COVID-19 infection was the most common reason, but the second most common reason was economic distress [10]. Another meta-analysis of precursory literature concluded that main risk factors for suicide among physicians were loneliness, not having children and personal history of mental disorders [11].

A study conducted after the first year of the pandemic underscored the importance of moral injury which led many health professionals to suicidal ideations and suicidal behavior. Moral injury is described as a psychological consequence of transgressing moral values and witnessing such transgressions. The difficult choices the medics had to make every day, especially during early months of the pandemic caused some health care workers to have a sense of betraying their moral obligations and neglecting patients' needs. Many of them had to risk their families' health by being exposed to COVID-19 every day, which resulted in many existential dilemmas. Moral injury was described as a sense of betrayal, guilt, shame, moral concerns, loss of trust, loss of meaning, difficulty forgiving, self-condemnation, faith struggle and loss of faith. It is found to be strongly correlated with high risk of significant PTSD symptoms and suicidal behavior [12].

Another suicide risk factor was change of workplace for many physicians that were not experienced in handling of the critically ill patients. Many doctors that were not accustomed to extreme levels of pain and suffering were redeployed to unfamiliar wards due to staff shortages. Depressive symptoms were found to be disproportionately elevated among medics redeployed to intensive care units [13]. Recent study conducted among healthcare workers in United Kingdom reported that 3,4% of them experienced thoughts of suicide or self-harm in the 2 preceding weeks. When asked about the difficulties that they had to struggle with, they reported that the pandemic exacerbated many pre-existing life challenges, such as living with mental illness, working in an unsupportive environment, and experiencing personal difficulties such as relationship violence and illness of family members [14].

One of the recently published case studies blames the culture of medicine for a toxic working environment. The COVID-19 pandemic added pressure to the system that has already been a huge burden for health care workers. The article describes the gradual deterioration of mental health of an emergency medicine doctor that struggled with staff shortages, deteriorating

working conditions which resulted in him eventually committing suicide. His pleas directed to the management for more help or physician coverage were declined. Even when he admitted to his wife about his mental health problems, he insisted on keeping it secret from his colleagues because of fear of being unable to work again. Lack of support from the management, sense of ostracism from workmates ultimately caused the physician to eventually commit suicide, a situation that perhaps could have been avoided if needed support was given earlier [15].

The concerning data about mental health issues faced by health care professionals and high suicide risk demands taking action immediately to reduce psychological damage experienced by millions of medics all around the world. Some of the solutions include periodic mental health assessment, easily accessible professional psychological consultation in the workplace, peer support groups, case consultation groups, where staff could openly discuss challenging cases and increased availability to convalescent leave or mental health treatment in case of decreased functioning over several weeks. Those are some of the proposals that could possibly decrease the prevalence of burnout, depression, suicidal ideations, and suicidal behavior in health care professionals [16].

The virus that causes COVID-19 can have long-lasting symptoms in certain affected individuals. These effects are referred to as post-COVID conditions (PCC) or extended COVID long COVID, long-haul COVID, post-acute COVID-19, post-acute sequelae of SARS CoV-2 infection (PASC), long-term consequences of COVID, and chronic COVID.

Numerous persistent health issues included in post COVID-syndrome can continue for weeks, months, or years and anyone who has been infected with the virus that causes COVID-19, even those who had minor illness or no symptoms from coronavirus, can have post-COVID syndrome but it is more frequently detected in individuals who had severe COVID-19. Also, people who have not been vaccinated may be at higher risk of developing post COVID syndrome than those vaccinated [17]. Common symptoms of long COVID include: fatigue, shortness of breath, problems with memory and concentration ("brain fog"), dizziness, heart palpitations, joint pain, depression and anxiety, chest pain or tightness, insomnia, a high temperature, cough, headaches, sore throat, changes to sense of smell or taste, pins and needles, tinnitus, earaches, rashes, feeling sick, diarrhea, stomach aches, loss of appetite [18].

In the aftermath of COVID-19 infection incresed risk of suicide may have many origins: social (for eg. losing loved ones due to ARDS or other severe complications of the infection), economical (for eg. higher psychological burden caused by decreased earnings due to changes in workforce during and after pandemic) and biological which we aim to discuss here further.

According to studies, the COVID-19 pandemic is linked to worry, anxiety, fear of spreading the disease, depression, and insomnia in both the general public and among medical professionals. In vulnerable populations, such as those with pre-existing psychiatric disorders and people who live in high COVID-19 prevalence areas, social isolation, anxiety, fear of contracting an illness, uncertainty, chronic stress, and financial difficulties may cause the development or exacerbation of depressive, anxiety, substance use, and other psychiatric disorders [19]. Research suggests that in the six months after COVID-19, around 34% of patients who survive receive a diagnosis of a mental illness.

Psychological aspects and neurobiological damage may be linked to COVID-19 survivors' persistent mental problems like sadness, anxiety, post-traumatic symptoms, and cognitive impairment. Anosmia, ageusia, headaches, dizziness and seizures are some neurological symptoms of COVID-19 that may last for a very long time after the acute sickness. Suicidal ideation and behavior are likely to be more prevalent in this patient population as a result of the signs and symptoms of psychiatric, neurological and physical disorders as well as inflammatory brain damage. Additionally, the direct biological effects of the virus, such as its signature pathology - hyperinflammation, may have contributed to the rise in suicide risk during the pandemic's later phases, which may have increased among COVID-19 survivors [20]. There’ve been also reports of COVID-induced psychosis and even Cottard syndrome occurring in patients after acute COVID-19 infection [21].

In other instances that have been reported COVID-19 first appears in otherwise asymptomatic, SARS-CoV-2 positive patients, it causes severely disordered behavior, including homicidal and suicidal thoughts [22].

As psychotic disorders are typically linked to significant premature mortality and morbidity, this case demonstrates how acute psychiatric complications in COVID-19 patients can be a serious concern [21].

Although at this point the data to sufficiently examine the problem of suicide in post-COVID syndrome is not present due to not sufficient amount of case. The problem should be further investigated as it poses a real risk in the population which on 29th of June 2022 had 551,008,863 [23], confirmed cases since the start of the COVID-19 pandemic. We’ve yet to understand the whole clinical picture of long COVID and in view of that the impact it has on psychological health and self-imposed risk should not be omitted.

SUICIDE IDEATION AND ATTEMPTS IN CHILDREN AND ADOLESCENTS DURING COVID-19

Suicide is the second leading cause of death among children and adolescents from age 10 to 17 and that rates have been increasing in the age group over the past years [24].

The outbreak of the SARS-CoV-2 (or COVID-19) has affected all countries around the world and influenced the mental well-being of all the people [25].

In recent world history, major infectious outbreaks were associated with severe mental health sequelae, including suicide. Nevertheless, the impact of COVID-19 on children and adolescents' mental health has not been widely studied.

The COVID-19 pandemic itself can cause fears of infection, uncertainty, and potential economic problems but also family life and relationships can be influenced by remote work lifestyles of parents [26].

What is more, social isolation and loneliness are believed to be associated with increased risk for depression, anxiety, self-harm, and suicidal ideation [27]. Given that the COVID-19 crisis may affect children and adolescents at multiple levels, including at the individual-, school-, and family-level, risk factors for suicide can both deteriorate or lessen [26].

One study held in Japan suggest, that the pandemic lockdown has not affected suicide rates among children and adolescents. The most possible explanation to that finding is the fact that changes in children's lives due to the pandemic crisis, including school closures, may have both positive and negative influences on mental health and suicidality [26].

Surely, the COVID-19 crisis can cause distress, anxiety and potentially even depression among children and adolescents because of the fears, family economic troubles and limited social contacts but on the other hand, some children may notice positive effects of that situation. Some families managed to develop stronger connections; parents started to support their children better by spending more time together. What is more, staying home may relieve stress and pressure from academic or peer problems experienced at school [28].

Researchers from Paris, France found a 50% decrease in the incidence of suicide behavior in children and adolescents during the COVID-19 lockdown. This association might result from a combination of several factors – reduced help-seeking, development of coping mechanisms, changes in familial and lifestyle dynamics [29].

In contrast, studies held in United States show that suicide ideation I children significantly increased during pandemic crisis. Similarly, screen results positive for suicide

attempts were higher. What is important, the number of Emergency Departments visits was substantially reduced during the COVID-19 and that is why direct comparison of rates across years should be made with caution. There appears to have been an early increase in suicide-related behaviors during the onset of the pandemic, possibly because of initial stay-at-home orders and social distancing efforts [24]. Family relationships developed during COVID-19 crisis may help children reduce their anxiety and distress in a long-time perspective [26].

During pandemic adolescents were less concerned about matters at school, including relationships with peers and teachers and bullying. Further studies should evaluate the influence of copying factors in children and adolescents, and the mechanisms underlying the effects of globalised health threat and pandemic lockdown on suicidal behaviour [29].

COVID AFFECTED SOCIETY AND HEALTH

The Corona Virus affected social relations within our communities, due to the set protective measures that the governments have set forth. The measures of social distancing and isolation imposed many challenges on day-to-day interactions between individuals. Human connection is a basic need for our existence. Individuals were challenged to learn how to adapt to their new lives behind closed doors when their face-to-face connections were impermissible. The sudden change, on one hand, can lead to the uprising of mental disorder cases within our community. Individuals can start to feel lonely, depressed, or anxious.

On the other hand, restrictions can bring family members closer to each other. With long term quarantine measures, families were able to spend so much time together and that can be beneficial in reducing the mental disorders of vulnerable individuals like children. With the chance that parents work from home, and schools are dismissed, parents and children were able to build stronger connections away from the stress of school or work. Children may be able to develop a long-term cure against anxiety and stress that they bear from school work. At the same time, parents are not obligated to stay away from their home for the long hours they spend at work.

COVID AFFECTED ECONOMY AND HOW IT CAN LEAD TO SUICIDE.

Furthermore, Covid did not just have its toll on individuals within the society, but it extended its arms around the economy. When individuals were behind doors, the cash flow

towards supermarkets, restaurants, pubs and entertainment facilities was paused. This has definitely dropped the functionality of the economic system as a whole. Many businesses were closed because of the shortage of income. Business owners may have been devastated to see their business shut down and suicide might be an option when they express forms of depression and sadness. However, effects of covid on the economy and how that ties into suicide needs major research efforts in the future.

The COVID-19 pandemic has hit the global population on health, economic and social grounds. In this, the impact on the mental health of individuals and suicide statistics is not without significance. Anxiety, loss of employment, self-isolation and social distancing. Also, the stigma in relation to infected people and their families - these and other factors have an impact on the mental state of the individual. People who are already burdened may experience an exacerbation of the disease, new people may be affected by disorders such as anxiety, depression, and PTSD. Fortunately, people today are more open about depression or anxiety disorders than they were in the past. The topic of death is also discussed more widely now than in the past. In addition to social openness to the above-mentioned topics, the awareness of their essence also influenced the access of people in need to help - which is widely recognized as truly saving lives [30].

Particular attention was paid to the issue of the impact of the pandemic on children and adolescents, which was disproportionately greater than on the adult population. The initial decrease in suicide related to some kind of "honeymoon period" then turned into an increase linked to depression, loneliness, domestic violence, substance abuse or neglect [31].

Apart from infected people, another group of increased risk are people fighting the pandemic on the front lines - healthcare workers. On the basis of the findings, it can be concluded that in this group the most common cause of suicide was infection with the COVID-19 virus, followed by work-related stress, fear of infection, fear of transmitting the virus to others and being overwhelmed by the effects of infection in the form of deaths and mental suffering. It should be remembered that the pandemic exerted enormous pressure on the working physicians, both in terms of the expectations related to the effective fight against the pandemic, as well as creating conditions that were not optimal in terms of safety (such as, for example, poor-quality personal protective equipment). People working in the health care system are also affected by the suicide of their colleagues [32].

This would indicate slightly different reasons than in the general population, which was dominated right after the fear related to the possibility of infection, a difficult economic

situation, loneliness, longing for family, social ostracism, lack of access to alcohol and stress related to work [32]. The aforementioned economic issues undoubtedly turned out to be a high risk factor, which had been observed before. After the 2008 economic crisis, they increased in as many as two-thirds of the 54 countries surveyed, especially men [31].

One of the potential advantages of the pandemic state is an attempt to respond to the need for psychological support - interventions at a distance (e.g. by phone or via video calls), which, despite their limitations, should expand their coverage by engaging a wider group of trained employees, prepared to provide remote consultations in crisis [33].

The effects of a pandemic will not go away long after the pandemic ends, so it is particularly important now to conduct social campaigns to promote mental health, and research is needed on how to mitigate the consequences of the pandemic on the mental health of the population [19].

The authors of the work Suicide prevention and COVID-19 present key recommendations on what we should pay attention to as a society in the context of this and future crisis situations such as the COVID-19 pandemic:

1. “It is essential to have strategic systematic suicide prevention planning for future pandemics as part of disaster response plans taking a universal holistic approach to care.
2. Investing in active labour market programmes will result in a decreased suicide rate during times of high unemployment.
3. People in low paid and casual jobs require specific support because they are most financially vulnerable during a pandemic related crisis.
4. Women require specific support during a pandemic because of the type of employment they have and because they often carry a greater proportion of the domestic burden and are at increased risk of domestic violence during lockdown and crisis.
5. Mental health and substance misuse services need to be appropriately funded and prioritized during and post pandemic, due to the associated increase in substance misuse during a pandemic causing worsening mental health and increased risk of suicide.
6. National Suicide Prevention Strategies should be developed by all countries and should anticipate response to a range of disasters, including a pandemic.
7. Suicide prevention is everybody's business and National Suicide Prevention Strategies should adopt a whole-systems approach including mental health services, primary care, social care, NGO's and other community stakeholders.

8. Suicide is preventable. It is essential to prioritize suicide prevention strategies in the COVID and post-COVID period to ensure that lives are saved" [34].

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Keeping safe - knowledge and opinions of women regarding protective face masks, restrictions and functioning of healthcare facilities during the COVID-19 pandemic

Józefa Dąbek[1], Kacper Staszkiewicz[2], Karolina Biernat[2], Agnieszka Mazanek[3], Zbigniew Gąsior[1]

1. Department of Cardiology, Faculty of Health Sciences in Katowice, Medical University of Silesia, Katowice.
2. Student Scientific Association at the Department of Cardiology, Faculty of Health Sciences in Katowice, Medical University of Silesia, Katowice.
3. University Clinical Center prof. K. Gibiński of the Medical University of Silesia in Katowice

INTRODUCTION

2020 will certainly go down in history as the beginning of one of the most severe pandemics the world has had to face. In March of that year, the World Health Organization (WHO) issued a statement officially assigning the status of a pandemic to the rapidly spreading disease COVID-19 (Coronavirus disease) caused by the SARS-CoV-2 virus [1]. Despite the fact that a large proportion of infections among immunocompetent individuals were asymptomatic, the virus was capable of inducing severe acute respiratory syndrome, which could be fatal in elderly and immunocompromised people [2]. According to official data presented on the WHO website, by July 2022, over 570 000 000 cases and as many as 6 300 000 deaths have been confirmed worldwide [3].

Despite these alarming statistics, it is possible that the total number of deaths caused by the disease could be much higher. That is, because not only the infection itself was hazardous - the unprecedented strain put by it on health care systems worldwide could have indirectly resulted in many, seemingly, COVID-unrelated deaths. Those being caused by much lower standard of care available, and in some cases, a complete breakdown of health care due to overcrowding of hospitals and lacking personnel [4,5].

This is shown, inter alia, by the so-called "excess deaths" - this is the term used to describe the difference between the average number of deaths determined on the basis of historical data and the number actually recorded. In many countries, the number of excess deaths cannot be fully explained just by the number of confirmed deaths from SARS-CoV-2 infection. Some people in the scientific community raise arguments that harder access to medical services related to the limited functioning of health facilities may have contributed to this [6]. Outpatient clinics, hospitals and specialist offices, due to their nature, i.e. facilities helping the sick, became a place of an increased epidemic risk during the pandemic. Patients seeking help in connection with ailments not related to COVID-19 could have become infected, in the absence of an appropriate sanitary regime [7]. For this reason, steps have been taken to ensure patient care without exposition to the SARS-CoV-2 virus [8]. Unfortunately, some of these actions resulted in a significant reduction in contact with the doctor and other health care professionals. This could translate into an inadequate level of medical care and thus deterioration of patient's health, underdiagnosis or even, in the long term, death. With the spread of COVID-19, governments and international organizations have taken action to slow down the transmission of SARS-CoV-2 and reduce the number of daily new cases which, in many places, have been rising almost non-stop since the very first recorded infections. Attempts to control the pandemic have largely taken the form of restrictions imposed on society, intended to isolate infected people, and in the case of exposure to a sick person - to minimize the risk of disease transmission. Social distancing, protective masks, isolation of the sick and quarantine against those exposed to the sick accompanied people for the majority of the pandemic. Despite the scientifically proven effectiveness of these efforts, part of the society strongly opposed them, and even refused to follow the guidelines [9,10,11]. The challenges that society has to face, in some aspects of life, have fallen disproportionately to women. The burden of motherhood and, often, of maintaining a home have increased significantly in the pandemic-reality. Thus, during the pandemic, women constituted an at-risk group, more susceptible to unfavorable social and epidemiological turmoil [12,13].

OBJECTIVE

The goal of the study was to assess the level of knowledge, opinion and women's experiences about the restrictions and functioning of health care facilities during the SARS-CoV-2 pandemic.

MATERIALS AND METHODS

386 women, aged 15 to 80 years, were examined (the arithmetic mean age of the participants was 31,32 years, while the standard deviation was 12,35 years). The inclusion criteria for the study were gender and willingness to participate. An original questionnaire was used to conduct it, the completion of which was completely anonymous and voluntary. The included questions concerned general information (age, place of residence, employment), as well as opinions and experiences on the restrictions and functioning of health care facilities during the pandemic. Statistical significance was assessed using the chi-square test with the assumed level of $p = 0.05$.

RESULTS

General characteristics of the studied group

The general characteristics of the studied group, taking into account; sex, age, place of residence and education level, are presented in Table 1.

Table. 1. The general characteristics of the studied group, taking into account; sex, age, place of residence and education level

Variable		Data	
		n	%
Age	**≤24**	120	31
	25-39	182	47,2
	40-64	77	19,9
	≥65	7	1,8
Place of residence	**City**	247	64
	Village	139	36
Education level	**None**	2	0,52
	Elementary	46	11,9
	Vocational	12	3,1
	Secondary education	138	35,8
	Higher education	188	48,7

Explanation of abbreviations: n – number of respondents

The majority of the study group were women with higher education. The surveyed women mostly lived in urban areas. People with higher and secondary education accounted for over 80% of all respondents.

PROTECTIVE FACE MASKS

The characteristics of the studied group, including the knowledge about protective face masks, are presented in Table 2.

Table 2. The characteristics of the studied group, including the knowledge about protective masks

Statements regarding protective face masks	I agree		I don't agree	
	n	%	n	%
Usage of face masks helps to reduce SARS-CoV-2 transmission	200	51,81%	186	48,19%
Face masks are safe to use	113	29,27%	273	70,73%
Using face masks is bad for your health	88	22,80%	298	77,2%
Face masks provide a level of protection from infection to the person wearing them	81	20,98%	305	79,02%

Explanation of abbreviations: n – number of respondents

Only about half of the respondents believed that the use of face masks helped to reduce the transmission of SARS-CoV-2 virus (200; 51,81%).

The characteristics of the studied group, taking into account the opinions of the respondents about protective face masks, are presented in Table 3.

Table 3. The characteristics of the studied group, taking into account the opinions of the respondents about protective face masks

Statements regarding protective face masks	I agree		I don't agree	
	n	%	n	%
Wearing face masks outside is pointless	247	63,99%	139	36,01%
I often feel shortness of breath while wearing a face mask	188	48,7%	192	51,3%
I change/wash my face mask daily	120	31,09%	266	68,91%
I often wear my face mask under my nose	106	27,46%	280	72,54%
I pay attention to the type of face mask I wear	103	26,68%	283	73,32%

Explanation of abbreviations: n - number of respondents

Only 1/3 of the respondents admitted that they changed or washed their face mask every day (120; 31,09%).

Figure 1 shows the analysis of responses to the subject of protective masks in relation to the education of the respondents.

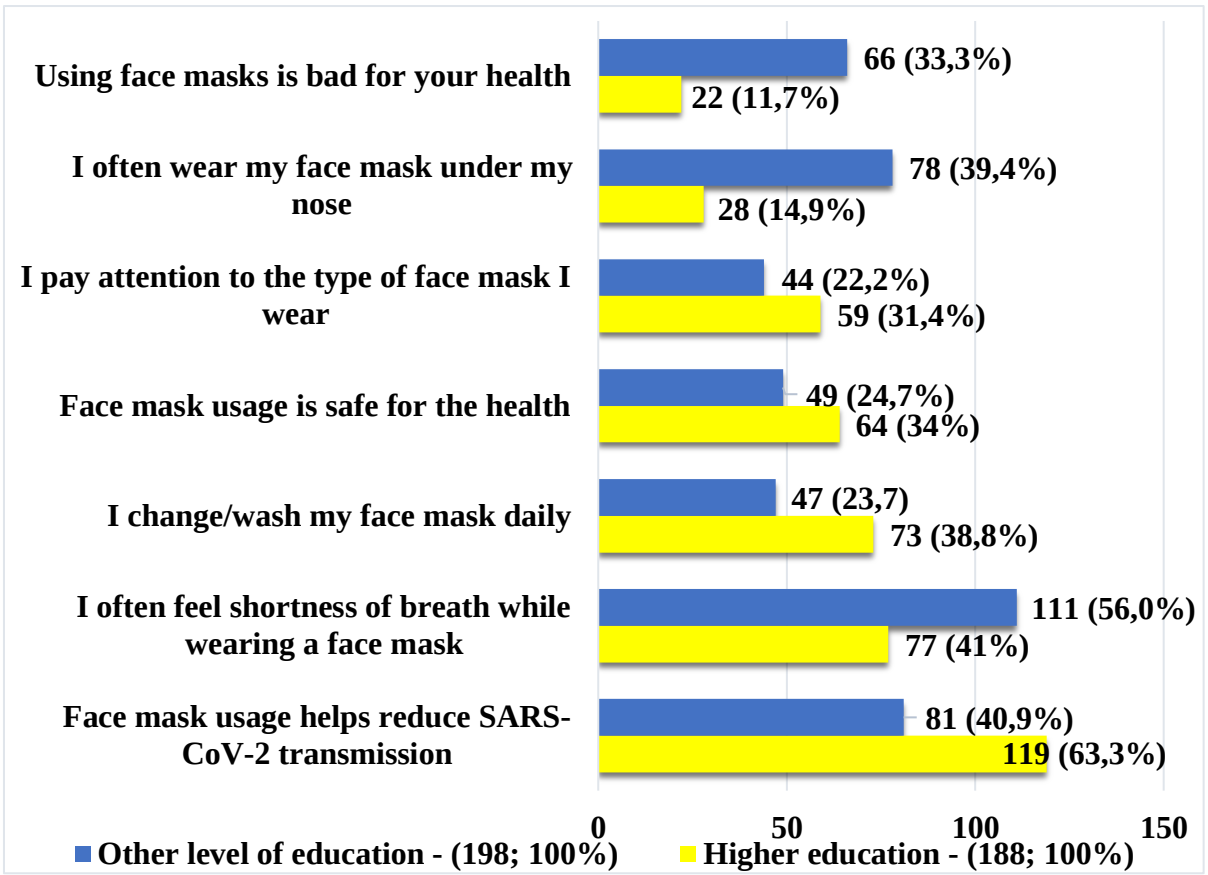

Figure. 1. Analysis of responses to the subject of protective masks in relation to the education of the respondents

Respondents with higher education level were more likely to find that using face masks helps to reduce the spread of SARS-CoV-2 virus (119; 63,3%), while people with a different level of education more often stated that wearing masks may be harmful to health (66; 33,3%).

RESTRICTIONS

Figure 2 shows the characteristics of the studied group, taking into account opinions on the restrictions and the level of knowledge.

About 40% of the respondents believe that the restrictions during the pandemic were too stark (156; 40,41%).

Figure 3 shows the characteristics of the studied group, taking into account the education of the respondents as well as the knowledge and opinions on the restrictions.

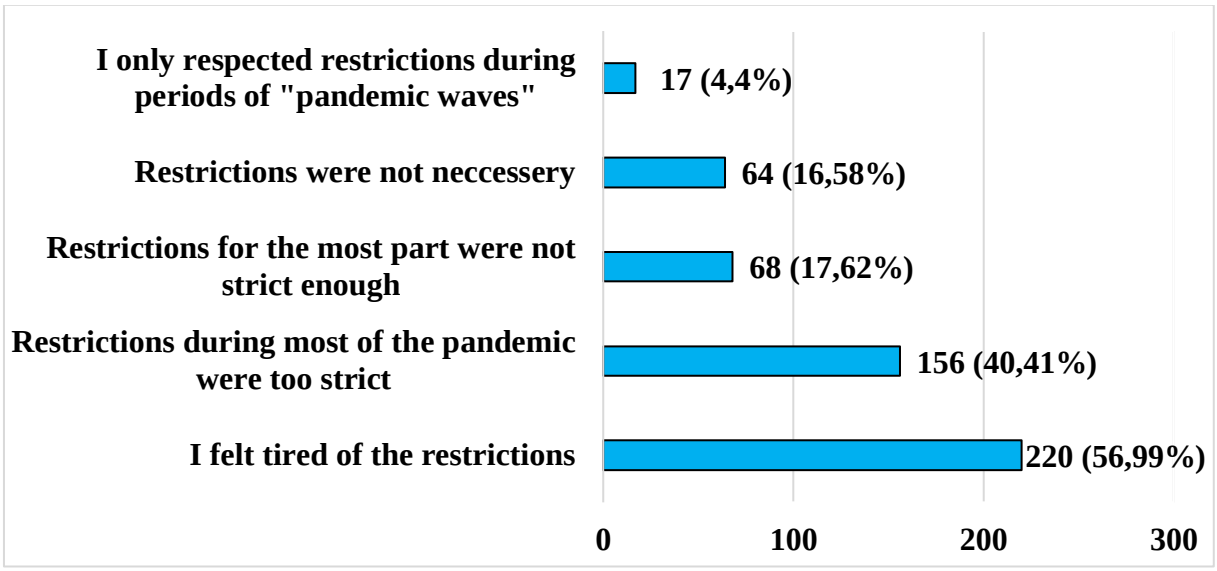

Figure 2. The characteristics of the studied group with regard to opinions on the restrictions and the level of knowledge

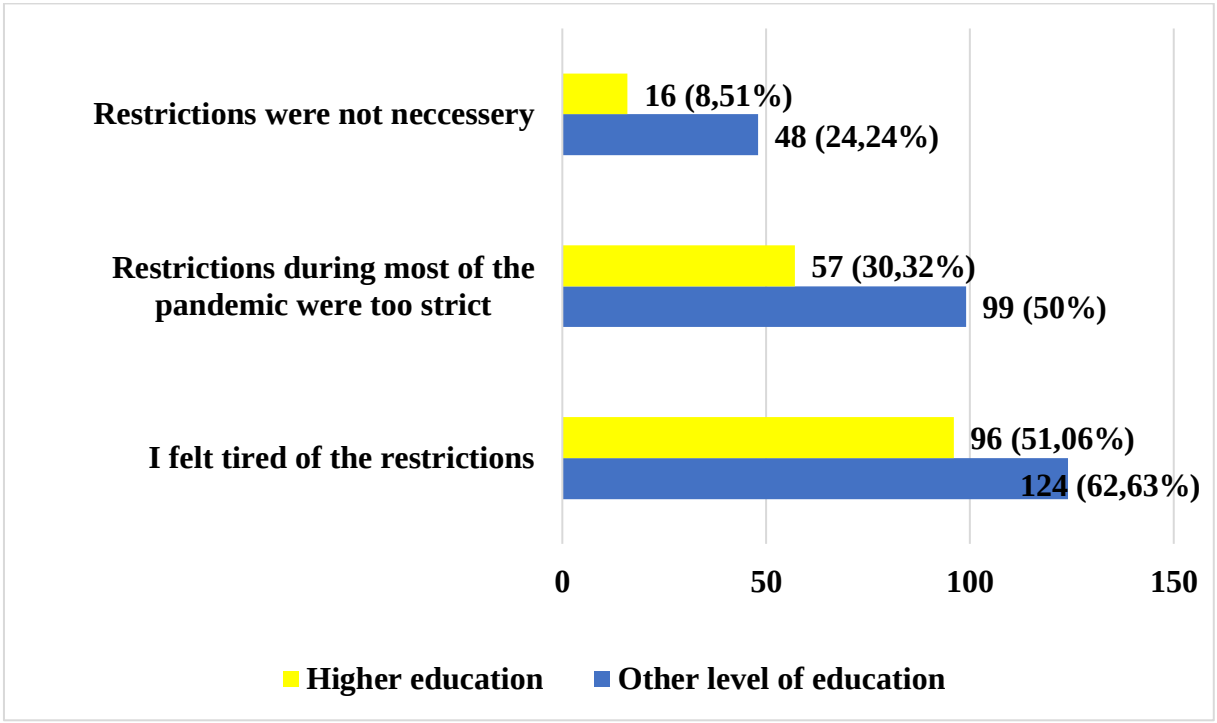

Figure. 3. The characteristics of the studied group, taking into account the education of the respondents as well as the knowledge and opinions on the restrictions

Respondents with non-university education more often claimed that the restrictions were too severe for most of the pandemic (99; 50%).

PANDEMIC REALITY

The characteristics of the studied group, taking into account the opinions of respondents about the claims concerning the SARS-CoV-2 pandemic, are presented in Table 4.

Table 4. The characteristics of the studied group, with regard to the opinions of respondents about the claims concerning the SARS-CoV-2 pandemic

Statements regarding COVID-19 pandemic	I agree	
	n	%
Poland was not ready for SARS-CoV-2 pandemic	262	67,88%
SARS-CoV-2 vaccines can potentially end the pandemic	207	53,63%
SARS-CoV-2 virus could've been made in a laboratory	138	35,75%
Pandemic could've been planned	122	31,61%
Return to the prepandemic social relationships will not be possible	101	26,17%
Doctors have made a lot of money because of SARS-CoV-2	92	23,83%
SARS-CoV-2 vaccines are dangerous to health	75	19,43%

Explanation of abbreviations: n - number of respondents

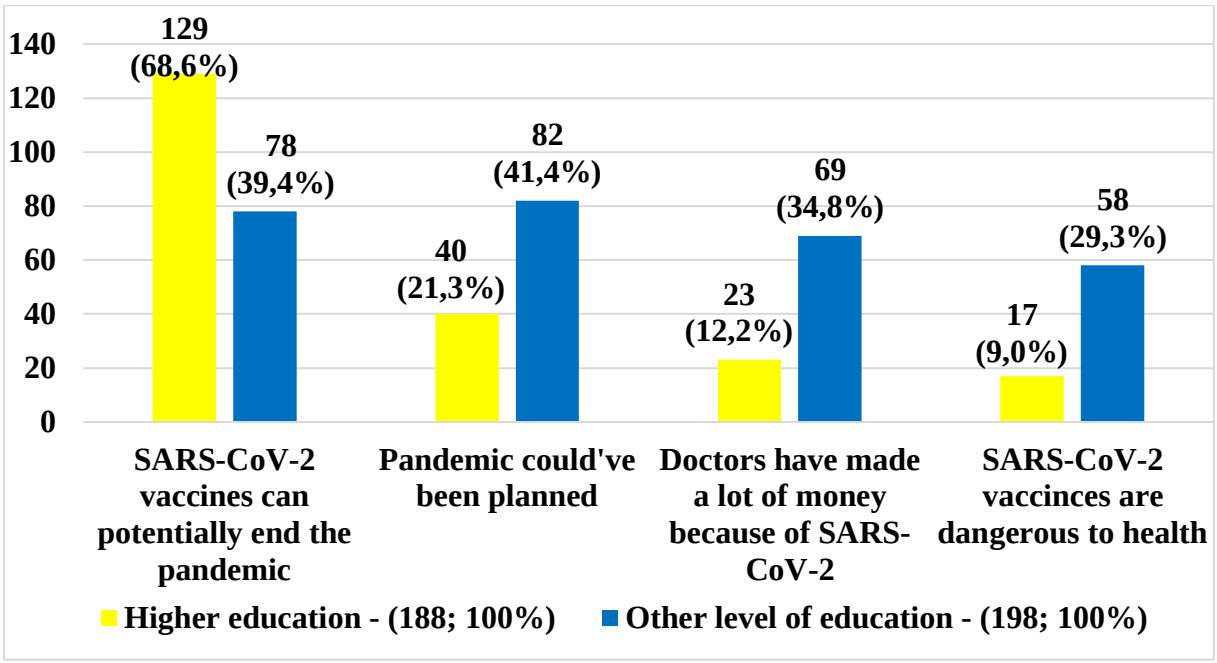

Figure 4. The characteristics of the studied group, taking into account the opinions on the statements regarding the SARS-CoV-2 pandemic and education

Over 30% of respondents believed that the SARS-CoV-2 coronavirus could have been designed in a laboratory (138; 35,75%), and that the pandemic could have been planned "in advance" (122; 31,61%).

HEALTH CARE FACILITIES AND CONTACT WITH A PHYSICIAN

Figure 5 shows the characteristics of the studied group, taking into account the opinions on the functioning of health care facilities during the pandemic SARS-CoV-2 virus.

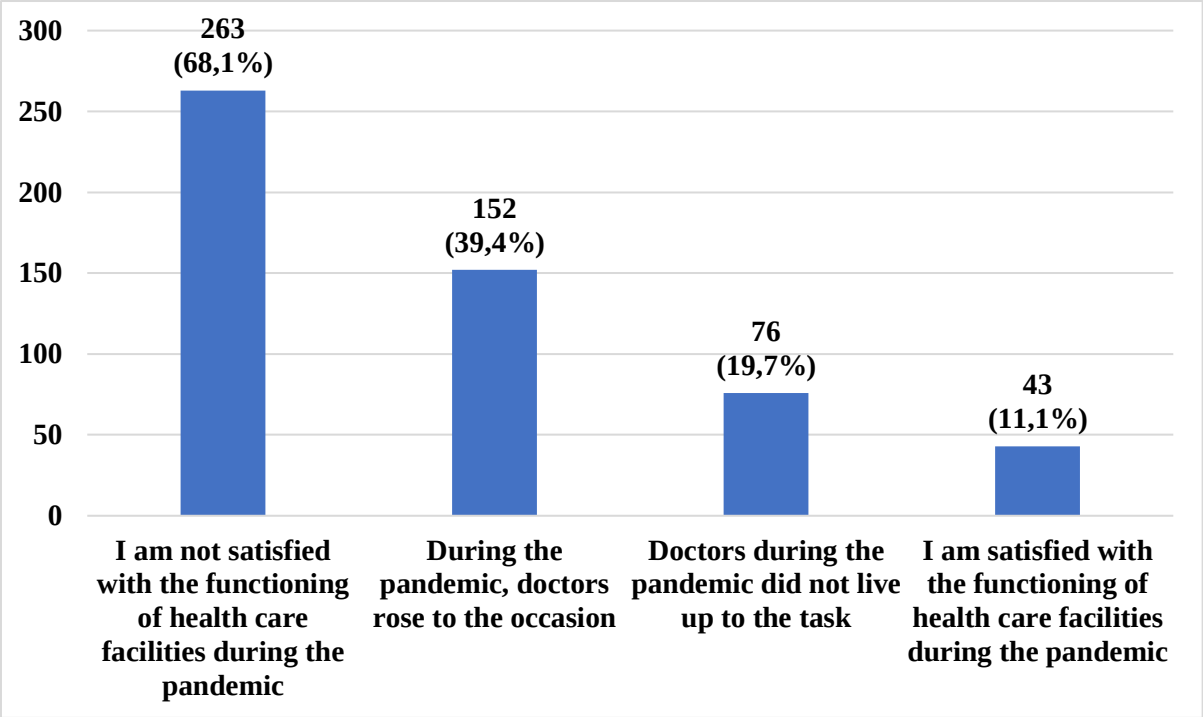

Figure 5. The characteristics of the studied group, taking into account the opinions on the functioning of health care facilities during the pandemic SARS-CoV-2 virus

Almost 70% of the respondents were not satisfied with the functioning of health care facilities during the pandemic (263; 68,1%).

Figure 6 shows the characteristics of the studied group in terms of experiences with access to the resources of the health care system.

Almost every second respondent had difficulty contacting her family doctor or clinic (180; 47%).

Figure 7 shows the characteristics of the studied group in terms of opinions on „telemedicine” and personal visits to private offices during the pandemic.

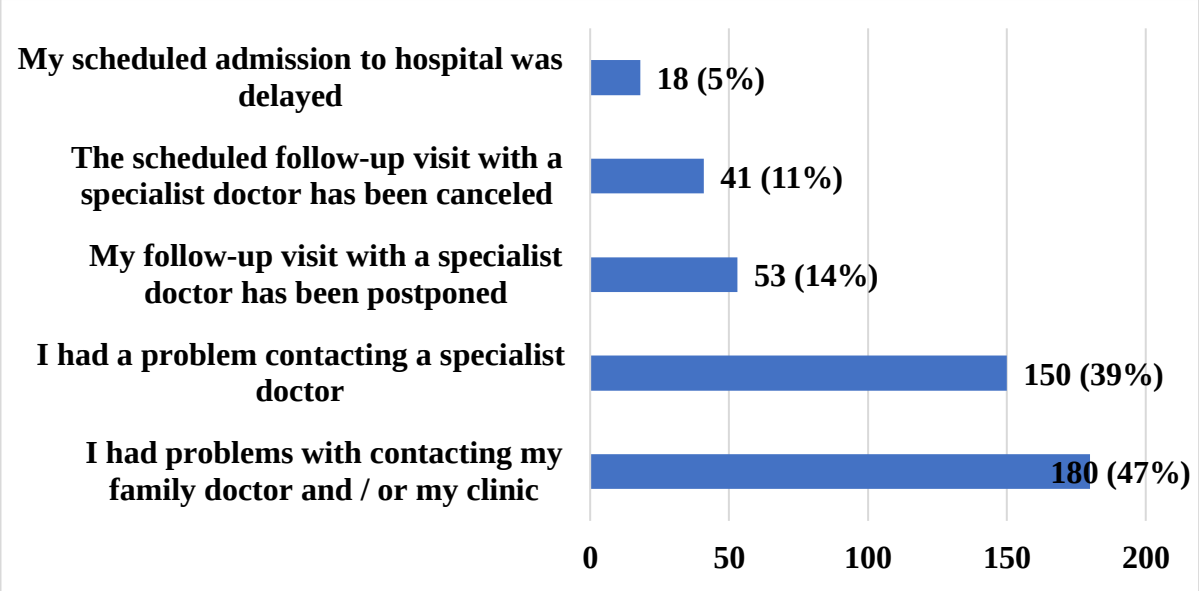

Figure 6. The characteristics of the studied group in terms of experiences with access to the resources of the health care system

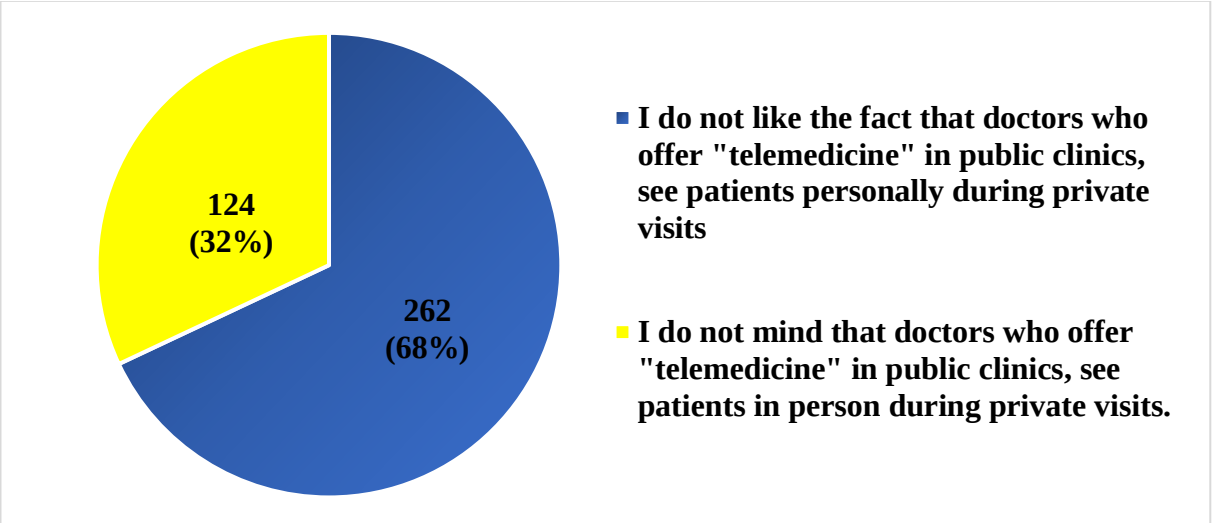

Figure 7. The characteristics of the studied group in terms of opinions on „telemedicine" and personal visits to private offices during the pandemic

Most of the respondents did not like the practice of admitting patients in person only for private visits (262; 68%).

Figure 8 shows the characteristics of the studied group, taking into account the perceived changes in the health condition of the respondents due to the difficult access to medical facilities.

Every fourth respondent felt improperly treated by the employees of her clinic (98; 25,39%).

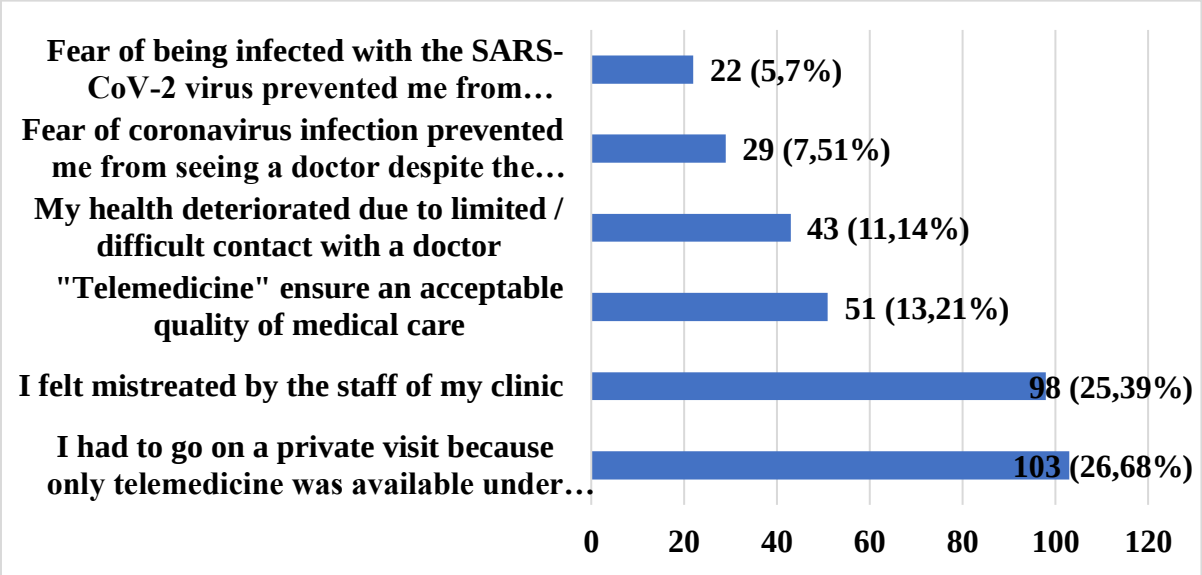

Figure 8. The characteristics of the studied group, taking into account the perceived changes in the health condition of the respondents due to the difficult access to medical facilities

DISCUSSION

The restrictions related to the SARS-CoV-2 virus pandemic led to the creation of a new, unprecedented reality in which people were forced to find themselves. For some people it wasn't easy, as the changes affected almost every sphere of life; however, they particularly strongly affected the area the health care system and its accessibility. Incapacity of the health care systems all around the world was sudden and unexpected. Many people experienced problems with access to medical benefits, and given all that, the full impact of the pandemic on overall mortality and morbidity remains to be seen.

Protective face masks are one of the basic elements of SARS-CoV-2 infection prevention and transmission reduction methods. According to current medical knowledge, wearing face masks is a highly effective and a cheap way of reducing the risk of infection [14, 15]. With respect to the available literature, to be effective, masks do not have to be specialized - even the ones made out of fabric fulfill their function in some regard [16]. Undoubtedly, masks are an effective tool in limiting the spread of COVID-19, so it is disturbing that only 50% of respondents said that their use helps to limit the spread of the disease (200; 51.81%). Education in this regard is desperately needed to help people better understand COVID-19 and in turn, better protect themselves.

Despite the fact that, while maintaining the appropriate standards of use, protective masks are generally safe for health, one must keep those standards in mind - for this reason, it

is unsatisfactory that in our research only 30% of respondents admitted that they change or wash their mask every day (120; 31,09%). It is important to keep in mind, that unwashed and unchanged mask can serve as a breeding ground for microbes, some of which can be a cause of a disease [17,18]. Therefore, it is vital to wear masks with accordance to guidelines and regulations.

One of the well documented side effects of wearing face masks for a prolonged period of time are changes in blood gas concentrations. It is not surprising that almost every second respondent reported a feeling of breathlessness while wearing a face mask (188; 48,7%). Literature on this topic is somewhat conflicting, with some studies suggesting that the risk of developing a full-scale hypoxia is close to zero (even with moderate exercise), while some point to unsettling carbon dioxide retention coupled with lower oxygen concentration within the air inside of the mask [19,20]. Thus, feeling out of breath is a common side effect of face mask usage and is to be expected in certain scenarios. Nevertheless, just because it appears frequently, shortness of breath should not be ignored, and mask wearers should be advised about ways of handling it. In the study by Yaser AAN. et al. 35% of respondents indicated a feeling of discomfort while wearing the mask - these results correspond to those obtained in the own study, where almost every third respondent admitted that she often wears the mask only covering her mouth (106; 27.46%). That may be caused by aforementioned changes in blood gases, caused by the proper positioning of the mask [21].

The fact that respondents with a higher level of education less often presented the opinion about the harmfulness of masks (22; 11,7%) than respondents who did not graduate from higher education (66; 33%) indicates the constant need for social education on personal protective equipment and methods of prevention spreading the infection.

The restrictions imposed on the society in the form of a lockdown were one of the most severe methods of preventing the spread of SARS-CoV-2 infection. Despite the scientifically proven effectiveness of lockdown, its introduction contributed to the development of many social problems [22,23]. For this reason, it is not surprising that more than half of the respondents reported fatigue with the restrictions during the pandemic (220; 56,99%), and part of the study group believed that the restrictions were too radical (156; 40,41%). More research is needed to determine whether better understanding causes of restrictions and their overall purpose helps in accepting them, but it’s worth considering.

During the COVID-19 pandemic, myths and rumors spread even faster than the disease itself. In the study group, almost every third respondent stated that the pandemic could have

been planned (101; 26,17%) and that the SARS-CoV-2 virus could have been manmade in the laboratory (138; 35,75%). These highly disturbing results show clear gaps in public awareness of the disease and general knowledge of scientific facts. Given that COVID-19 has long been ubiquitous in the sphere of public and media life it is highly surprising that people can hold such outlandish opinions [24]. However, women with higher education less frequently indicated that a pandemic could have been planned - this corresponds to the results obtained by Baig M. et al., in which education was described as a factor highly correlated with the avoidance of false information and rumors about the pandemic [25]. Given that misinformation is one of the main driving factors contributing to lower restrictions adherence rates it is vital to take measures aimed at tackling that problem.

The period of the COVID-19 pandemic has posed enormous challenges to health care systems around the world. The rapidly growing number of infections, and thus hospitalizations, reduced the efficiency of hospitals and other medical centers [26,27]. Due to the significant use of the resources of the health care system, it is not surprising that almost 70% of the respondents were not satisfied with the functioning of health facilities during the pandemic (263; 68,1%) and that almost every second woman surveyed experienced problems in contact with GP during the pandemic (180; 47%). These are definitely areas of pandemic reality that the scientific community should pay special attention to in the event of a possible future pandemic.

In the era of the SARS-CoV-2 virus, „telemedicine" has become one of the methods of providing medical care to sick or quarantined patients. Unfortunately, the authors' own research shows that the social attitude towards "telemedicine" is unfavorable. Only about 10% of the respondents believed that it ensures an acceptable quality of medical care (51; 13.21%). These results are supported by a study by Naik N. et al., who showed that almost half of the people interviewed did not feel comfortable with „telemedicine" (47.5%) [28]. Given that "telemedicine" is a very useful tool in many areas of health care steps should be taken in order to better accustom people with this new method of delivering physician's consultations to those in need.

CONCLUSIONS

1. Knowledge of women about protective masks and restrictions was insufficient, and their opinions were often unsupported by the current state of scientific knowledge.
2. The experiences of women in contact with health care institutions and employees during the pandemic were largely unsatisfactory, and contact was difficult.

3. There is a constant need to educate the society in the field of infectious disease prevention methods, their etiology and potential effects, as well as to conduct activities increasing the quality of medical services.

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Consequences of COVID-19 – what an ophthalmologist should be aware of?

Maciej Dyda[1], Lidia Jurczenko[1], Julia Górczyńska[1], Katarzyna Powierża[1], Michał Gebuza[1], Alina Siemaniuk[1], Katarzyna Zontek[1], Dominika Musialska[1], Hanna Zając- Pytrus[1,2]

1. Wroclaw Medical University, Wrocław, Poland
2. Department of Opthalmology, Wroclaw Medical University, Wrocław, Poland

List of abbreviations

- PIMS- Paediatric Inflammatory Multisystem Syndrome
- CD- Cluster of Differentiation
- RT-PCR- Real Time Polimerase Chain Reaction
- ACE2- angiotensin converting enzyme 2
- HSPGs- heparan sulfate proteoglycan
- RVOs- retinal vein occlusions
- RAOs retinal artery occlusions
- BRVO- Branch retinal vein occlusion
- CRVO- central retinal vein occlusion
- CRAO- central retinal artery occlusion
- CRP- C- reactive protein
- MHV-A29- mouse hepatitis virus A29
- MRI- Magnetic resonance imaging
- FLAIR- Fluid-attenuated inversion recovery
- CVA- cerebrovascular accident

COVID-19 CORRELATION WITH EYES

Alongside the beginning of Covid-19 pandemic rumours about the consequences of getting infected appeared. Coronavirus exhibits especially great affinity for lung, heart, kidney tissue and the nervous system. For some people, permanent side effects may include breathing

difficulties, dyspnea, coughing, chest pain, impaired kidney function, stroke, brain fog, depression and Guillain-Barre syndrome (related to temporary paralysis). Children often develop PIMS after being through the infection. Chronic fatigue syndrome, joint and muscle pain, lower effort tolerance – are other problems that convalescents are facing [1].

Covid-19 affinity for eyesight is not unlikely, either. Eye doctors noticed the time relationship between infection and changes in the eye. Let us take a closer look at a few occurrences, people struggle with when infected, right after recovering and a few weeks after [2].

- **Conjunctivitis:** or watering eyes might be the first symptom of virus infection. It is caused by inflammation of the clear mucosa which surrounds the eye. Symptoms of conjunctivitis are pink or red color, occurring when the blood vessels in the conjunctiva undergo an inflammatory process, which makes them more visible. The other symptoms comprise eyes redness, pain, itching, watering and eyelids oedema. They occur more often when patients suffer from serious systemic symptoms of Covid-19 [2,3].
- **Episcleritis**: it is inflammation which affects epidural tissue located between the conjunctiva and sclera or the white part of the eye. Patients with episcleritis complain of diffused or concentrated eye redness (one-sided). Some of them do not complain of any other symptoms while others complain of discomfort, photophobia or sensitivity. Strong pain and discharge from the eye may point to episcleritis. The relationship between COVID-19 and episcleritis may involve vascular and immune factors and clotting disorder [3,4].
- **Retinitis:** microvascular changes of the retina were noticed when picturing an eye of people infected with COVID-19. Those symptoms were also noticed when observing asymptomatic patients with normal life parameters. Different fundoscopic results of the retina include microbleeding of the retina, tortuosity and occlusion of retinal vessels, and hyperreflective plaques in the ganglion cell-inner plexiform layer. Retina infections often manifest as worse eyesight or blindness [3,5].
- **Optic neuritis:** people with COVID-19 were diagnosed with different eye-nerves symptoms. Hypotheses explaining the cooccurrence focus on: direct invasion of virus particles on neural networks, endothelial cell dysfunction leading to ischemia both with coagulopathy and common cytokine storm initiated by a virus. Optic neuropathy leads to sudden loss of eyesight, relative afferent pupil dysfunction, pain related to eyeball movements and the vision is blurred [3,6].

- **Mucormycosis:** severe fungal infection, characterized by swelling or redness of the eye, double vision, sight loss, eye pain and falling eyelid. Mainly only people with impaired immune systems, that is with a lower level of lymphocyte CD4+ and CD8+, are susceptible as well as people suffering from different diseases (such as diabetes or respiratory failure) and people that are on immunosuppressive therapy[3,7].

CONJUCTIVITIS

COVID-19 is an infection manifested by several symptoms. The SARS COV-2 virus spreads mainly via droplets and aerosols, so it is worth considering the aspect of direct eye infection by virus-containing droplets and aerosols. Coronaviruses can be present in tears during infection. Coronaviruses such as SARS-CoV, HCoV-NL63 and SARS-CoV-2 were detected by RT-PCR in tears during previous coronavirus outbreaks [8-12]. Although eye diseases are not common in cases of SARS-CoV-2 infection, there is a significant association between COVID-19 infection and the occurrence of conjunctivitis [13]. Moreover, mild conjunctivitis, which manifests itself as conjunctivitis, is common and is one of the leading ocular symptoms in SARS-CoV-2 infected patients, even if the disease is milder [14]. However, ocular symptoms occur most often in patients with a very severe systemic form of the disease accompanied by abnormal blood parameters and inflammation [15].

Overall, the incidence of ocular symptoms in COVID-19 patients ranges from 2% to 32% [2,16-20].

In a study by Sindhuja et al. as many as 8.66% of respondents experienced conjunctivitis accompanied by the reddening of one or both eyes. Moreover, conjunctival hyperaemia clearly correlated with respiratory symptoms[14]. Additionally, as a result of a cross-sectional study, Chen et al. showed a correlation between hand-eye contact and the occurrence of conjunctival hyperaemia[21]. The team also noted that the most common manifestation of eye symptoms was around the thirteenth day of COVID-19 disease. Interestingly, a smear taken from the conjunctiva gave a positive result for the presence of the SARS-CoV-2 virus for five days [21].

Nayak et al. showed that despite the negative result of a nasopharyngeal swab for SARS-CoV-2 virus, the virus might still be present in the conjunctiva [21].

COVID-19 can also present as keratoconjunctivitis without significant respiratory symptoms. The inflammation may be accompanied by photophobia, redness and discharge as observed by Cheem et al. This clearly shows how important it is to consider conjunctivitis as one of the symptoms of SARS-CoV-2 infection [22]. The literature also reports the case of

a patient in the intensive care unit with flu-like symptoms associated with SARS-CoV-2. During daily analysis of bronchial secretions, the genetic material of the virus was identified by a polymerase chain reaction (PCR). Initially there were no eye problems. On the seventeenth day hyperaemia of the conjunctiva with pure secretion was detected and the patient was found to have viral conjunctivitis. The material taken from the conjunctiva did not show any bacteria on microscopic examination and cultivation. On the nineteenth day the symptoms worsened. Yellowish-white, transparent pseudomembranous lesions were identified on the conjunctiva of the lower eyelids. No abnormalities were detected during the examination in posterior segment. Only between the 21st and 26th day of the illness did the eye symptoms improve [23].

This case illustrates the importance of carefully monitoring the patient's symptoms in order to avoid late-onset eye complications in SARS-CoV-2 infected individuals. Unfortunately, conjunctival smears can be wrongly negative, which makes the diagnosis enormously difficult [23].

The mechanism of SARS-CoV-2 invasion into the human body through the eye is not yet fully understood. Most likely, the fluid from the eye is absorbed and then discharged into the nasal cavity through the nasolacrimal canal, from where it then enters the respiratory track through the trachea. As a result the microorganisms in the tears can be transported to the lungs [24].

In addition, we can find the intraocular angiotensin system (RAS) in the human eye. Moreover, ACE2 serves as an entry receptor for viruses such as HCoV-NL63, SARS-CoV, and SARS-CoV-2. This receptor was found in the aqueous humor [25] and in the conjunctival epithelial cells on the surface of the eye [26]. Of course the effectiveness and intensity of a viral infection depends, among other things, on the infection rate and the presence of viral receptors on the host cells. HSPG receptors are responsible for the formation of the first viral junctions near the epithelium, which is made up of cells with a small number of ACE2 receptors. ACE2 receptors greatly facilitate virus entry into these cells, but HSPGs provide a suitable virus enrichment environment close to the host cells through low affinity interactions [27].
Many studies suggest that infection of human cells with SARS-CoV is mediated by more non-ACE2 receptors on the host cell membrane [28].

EPISCLERITIS

Episcleritis is a relatively common, benign, and self-limiting inflammatory disease. It is often recurrent and young adults are mainly affected. The cause of episcleritis is difficult to

identify; most cases are idiopathic. In less than one-third of patients it is associated with systemic diseases such as atopy, systemic vascular disease, and autoimmune disease. Episcleritis has also been described as an ocular manifestation of viral diseases such as Ebola, herpes zoster, and hepatitis C [29,30].

After reviewing the relationship between SARS-Cov-2 and episcleritis in the available literature it can be concluded that the incidence of episcleritis in the course of SARS-Cov-2 is low. A few studies report the following statistics and conclusions.

- Bostanci et al [30,31] identified episcleritis in 2 out of 93 patients with COVID-19 Additionally, this study found that epidural inflammation was associated with higher levels of D-dimers ($p = 0.017$), PCT ($p = 0.045$), and CRP ($p = 0.020$).
- Méndez et al [30,32] describe episcleritis in a 31-year-old woman who presented to the ophthalmology clinic with red eye, foreign-body sensation, epiphora, and photophobia without impaired visual acuity. Ocular symptoms appeared 7 days after systemic symptoms of SARS-CoV-2 infection had been confirmed by RT-PCR test. The patient was diagnosed with nodular episcleritis. Treated with artificial tears on demand and fluorometholone, symptoms resolved on the sixth day after the episcleritis onset.
- Otaif et al [30,33] reported a case of episcleritis in a 29-year-old man who was diagnosed 3 days before the onset of full-blown COVID-19. The patient presented with symptoms of redness and foreign body sensation in his left eye, which started two days before his consultation. He had no history of decreased vision, pain or photophobia; he also had no prior history of similar conditions, ocular surgery or trauma. He had no symptoms in his right eye or any systemic symptoms. The diagnosis of episcleritis was made based on the phenylephrine blanching test. Three days later, the patient reported headache, shortness of breath, cough, and fever. He was found to be infected with SARS-Co-2 by the RT-PCR test.
- Lu et al [33] recount the case of Dr Guangfa Wang who, while working with COVID-19 patients, complained of red eyes 3 days before the onset of COVID-19 symptoms.
- Amirhossein Roshanshad et al [34] reported a case of episcleritis in Spain. A woman presented with cough, myalgia, anosmia and ageusia. Her RT-PCR test was positive. Once the symptoms subsided, the patient consulted the ophthalmology clinic with red eyes, foreign-body sensation, epiphora, and photophobia, and nodular episcleritis was diagnosed.

- A study from Turkey [31,34] revealed a 2.2% prevalence of episcleritis in COVID-19 patients. It was also shown that episcleritis was associated with a higher D-dimer level
- Additionally, ocular complaints were observed after SARS-CoV-2 vaccination. In the study by Francesco Pichi et al [35] 9 patients presented with ocular complaints and one patient was diagnosed with episcleritis.

Currently, in episcleritis, it is recommended to use artificial tears and local non-steroid anti-inflammatory eye drops. Usually, the symptoms completely disappear after two weeks [36].

RETINAL MANIFESTATIONS OF COVID-19

COVID-19 can affect the retina in various ways. On the basis of prevalence we can distinguish 3 main types of retinal manifestations: retinal microvascular impairments, retinal vein occlusions (RVOs) and retinal artery occlusions (RAOs) [37,38].

Retinal microvascular impairments

During COVID-19 we can notice the disturbance of the coagulation mechanisms [39] and function of endothelial cells [40]. This leads to ischemic microvasculopathy and diminishing vascular density in sublingual vessels [41] and vascular sequelae in many other organs. The ocular representation of this anomaly is a decrease in density of capillary plexus vessels in foveal regions [42].

Recent meta-analysis including 401 participants clearly shows that COVID-19 induces the decrease in the vessel density in the foveal deep capillary plexus and decreased subfoveal choroidal thickness [43], which can be linked to decreased perfusion density in these vessels [44] .

These findings were evaluated with optical coherence tomography angiography or with fundus autofluorescence [45] which is widely available and can be used to evaluate patients after COVID-19.

The other way to evaluate microvascular changes is fundoscopic examination. The main manifestations of microvascular anomalies in COVID-19 patients are cotton wool spots and hemorrhages [44,46]. There can also be spotted dilated veins and tortuous vessels. These presentations did not affect visual acuity. In addition, they were more often seen in patients with obesity and diabetes, making it difficult to disentangle the individual impact of the factors [46,47]. The COVID-19 pathophysiological mechanism and its impact on the microvascular system of the retina, still have not been commonly established.

Retinal vein occlusions (RVOs)

There are two types of retinal vein occlusion (RVO): Branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO). Patients with BRVO are most likely to maintain proper vision after recovery, so we will mainly focus on CRVO [48].

CRVO is divided into two categories: ischemic and non-ischemic. Non-ischemic CRVO is associated with mild visual field changes and does not strongly affect visual acuity, whereas ischemic CRVO is associated with a worse course of the process. The primary risk factors for CRVO are diabetes, age, hypertension and obesity [40,49].

Retinal vessels in COVID-19 infection may be altered by thrombus, hypoxia and endothelial damage leading to CRVO, vitreous hemorrhage and neovascular glaucoma [39, 49,50]. Endothelial cell dysfunction can also lead to disruption of the blood-retinal barrier, release of vascular endothelial growth factor (VEGF) and thus to increased capillary permeability and subsequent development of macular edema.

In CRVO it can lead to significant loss of vision. Macular edema was the most prominent effect of vision loss in patients with RVO [44].

In available research papers, it has been shown that the age of patients with CRVO due to COVID-19 was lower than the typical age of the onset associated with traditional risk factors such as diabetes, hypertension and obesity . The time to the appearance of symptoms after the first onset of fever ranged from 5 days to 6 weeks [51].

The further evolution of lesions was promising, as the patients improved after the treatment with anti-VEGF injections, steroids and anticoagulants [51,52], which may lead to the conclusion that early induction of proper treatment results in complete resolution of the disease [44].

Retinal artery occlusions (RAOs)

RAO is usually associated with the sudden loss of vision. The main artery blockage, called central retinal artery occlusion (CRAO), leads to painless and extensive visual field loss. The blockage of a smaller arteries is called branch retinal artery occlusion (BRAO), which results mostly in partial loss of vision. The loss of the vision can be unnoticeable until perimetry has been performed.

The most harmful CRAO is the rapid blockage of the central retinal artery, resulting in retinal hypoperfusion with progressive, rapid cellular damage, and vision loss. The survival of the retina depends on the duration of ischemia and degree of collateralization there [2]. RAO can rarely provoke or coexist with ocular inflammation.

The patients with severe COVID-19, who had middle artery occlusion, had also elevated inflammatory markers such as: CRP, D-dimer, ferritin, fibrinogen and IL-6. Thus all these markers could be used to estimate the risk of RAOs. Further research is needed to create the guidelines [2].

Neuro-Ophthalmic manifestations

Neurological symptoms in patients infected with the Sars-Cov-2 virus have well been documented. Neurologic and ophthalmic manifestations may also in the course of polyneuritis, meningitis or encephalitis. Ocular involvement has been observed particularly in patients with demyelinating disorders.

To date, the exact pathogenesis of neuro-ophthalmic events remains unknown. However, there are some hypotheses suggesting direct invasion into the central nervous system, an extensive inflammatory response, also referred to as a cytokine storm, and endothelial cell dysfunction as potential causes of neuro-ocular complications [53].

Koldeki et al. examined retinal and corneal neurodegenerative changes and retinal neurovascular status in 35 patients and compared them with an age-matched control group [54]. The results suggested that even mild or asymptomatic coronavirus infection could cause neurodegenerative changes, which manifested as significantly lower nerve branch. However, the microvascular mechanism of neuro-ophthalmic complications after coronavirus infection were not observed in the study conducted by Kaldeki. To date, symptoms such as optic neuritis, cranial neuropathies, diplopia, Miller Fisher syndrome, various visual disturbances and subacute vision loss have been documented. There are also reports of optic nerve disc oedema, afferent pupillary defects and painful eye movements [54].

OPTIC NEURITIS

To date, optic neuritis has been documented in only a few case reports. Three of them involved patients with serum antibodies to myelin glycoprotein of oligodendrocytes [55]. One recent case was reported by Witoon Mitarnun et al. [56] a 60-year-old man presented with acute visual field loss with impaired eye movements and disc oedema with a relative defect of the centripetal pupil in the right eye. A diagnosis of optic neuritis was made. This event occurred 6 weeks after the onset of SARS-CoV-2 infection. After corticosteroid treatment the patient fully recovered.

Alax Jossy et al. presented three case reports of optic neuritis after mild Covid virus infection. Two patients developed symptoms of optic nerve invasion within 6 weeks and one within 6 months after recovery from coronavirus infection. One was a case of a 35-year-old man who developed sudden loss of vision in his left eye and painful eye movements for 1 week. Six weeks before the onset of ophthalmic symptoms, he had been tested for Sars-CoV-2. On ophthalmic examination the patient was found to have a BCVA of 20/600 in LE with grade I RAPD, choroidal and periocular oedema. In all cases described patients responded well to glucocorticoids with complete visual improvement. In addition, Giaruzzo et al. described a unique case of optic neuritis as the sole manifestation of coronavirus infection. The patient developed unilateral visual loss [57]. The exact pathogenesis of how Sars-CoV2 affects the optic nerves remains unknown. However, some animal models have shown signs of optic neuritis due to coronavirus infection. In 200 8 Shindler et al. documented this phenomenon using MHV-A29, a murine Sars CoV Virus [58].

NEUROPATHY

To date, several case studies revealed neuropathies as an ophthalmic manifestation of coronavirus infection. In the most reports the 6th nerve palsies were documented. In a few of them, palsy had a form of limited Miller Fisher Syndrome.

Guiterrez-Ortiz et al. presented a case of cranial polyneuritis following Covid virus infection [59]. A 39-year-old man presented with bilateral optic nerve palsy and areflexia and cytologic albumin dissociation during admission to the emergency room in Madrid. Three days earlier, he had reported general malaise, lower-grade fever, and diarrhea. He did not present with any respiratory distress syndromes. He was not diagnosed with classic Miller Fisher syndrome but with cranial polyneuropathy. The patient was discharged home and treated with acetaminophen. Two weeks later the patient was completely neurologically healthy. L. Borrego-Sanz described the case of a 66-year-old woman with an unblemished medical history [60]. She reported a painless loss of vision in her left eye. On ophthalmic examination of the right eye visual acuity was 0.9, and a centripetal pupillary defect was present. In the left eye retinal arteriolar stenosis, marked pallor of the optic nerve head and large cupping were found.

Optical coherence tomography showed a significant thickness of the retinal nerve fiber layer in the perifoveal region, which was consistent with the orbital MRI findings of reduced signal enhancement in the left optic nerve. These signs suggested neuropathy, in which progressive vascular phenomenon could be considered as the main cause of optic nerve damage.

MILLER FISHER SYNDROME

Miller Fisher syndrome, considered a limited form of Guillain-Barré syndrome, is characterized by an acute onset of ophthalmoplegia, ataxia and absence of tendon reflexes. Guiterrez-Ortiz et al [57] described a case of a 50-year-old man with right-sided intranuclear ophthalmoplegia and right-sided fascicular oculomotor palsy. On neurological examination all deep tendon reflexes were absent, which could be considered symptoms of Miller Fisher syndrome. Five days earlier the patient reported cough, fever, lower back pain and headache. The patient was treated with a 0.4 g/kg immunoglobin infusion for 5 consecutive days. The total hospital stay was 2 weeks. He showed no neuro-ophthalmic symptoms at discharge.

WERNICKE SYNDROME

Wernicke syndrome is a neurodegenerative disorder caused by vitamin B12 or thiamine deficiency. Wernicke syndrome is common in patients who have undergone bariatric surgery. Decreased vitamin B12 levels may affect patients hospitalized in the intensive care unit. Shepherd et al. described a unique case of bilateral visual loss secondary to Covid's disease. A 36-year-old man with unremarkable history was repeatedly hospitalized for recurrent episodes of diarrhea and odynophagia and severe nausea. Due to these symptoms his body weight decreased significantly. In addition he presented with general malaise, diffuse myalgia, persistent cough, ageusia and anosmia. Six weeks after the onset of infection he developed subacute visual loss .No abnormalities were found on pupillary and fundoscopic examination, suggesting a possible cortical mechanism of bilateral blindness. However, magnetic resonance imaging showed FLAIR hyperintensities in the medial thalami, mammillary bodies, and periventricular grey matter, indicating classic WS lesions. The patient was treated with thiamine infusion and fully recovered after 7 days of therapy. This case indicates that poor nutrition and vomiting secondary to Covid virus infection can lead to severe ophthalmic manifestations of Wernicke's syndrome [60].

VISION LOSS

A study by Cyr et al. described cases of acute bilateral visual loss following coronavirus infection. The first patient was a 61-year-old male diabetic patient. He developed symptoms of infection such as cough, body aches, and fever 7 days before admission to the emergency room.

Five days after the onset of Covid-like symptoms he presented with acute bilateral painless visual loss. On physical examination, light perception was absent. X-ray examination revealed typical lung lesions after Covid virus infection. In addition, dilated fundus examination revealed several diffuse haemorrhages in the macula of both eyes. Magnetic resonance imaging showed bilateral occipital oedema and ischemic infarction. The patient died 3 days after admission to the hospital.

The second patient was a 34-year-old woman who presented to the emergency department with confirmed Sars-CoV-2 pneumonia, with a history of systemic lupus erythematosus, end-stage renal disease treated with hemodialysis, hypertension and chronic obstructive pulmonary disease, and peripheral visual field damage due to CVA in 2016. She developed sudden bilateral visual loss 10 days after admission. Visual acuity in both eyes was clear. In addition, dilatation examination revealed trace pallor in both optic nerve discs. Two days after the onset of visual impairment, MRI revealed an acute ischemic infarct in the right frontal lobe.

These two cases highlighted the higher risk of thromboembolic occlusion in patients with a history of endothelial dysfunction.

Neuro-ophthalmic symptoms are rare but should be considered a potential manifestation of coronavirus disease. Although the true mechanism of this form of the disease remains unknown, as time passes and more data are collected, the relationship between coronavirus and neuro-ophthalmic symptoms will become better described.

Furthermore, this brief review has emphasized that ophthalmologists must be more willing to screen for concurrent coronavirus infection, even in patients with little or no respiratory symptoms [61].

CONCLUSION

The mechanism of COVID-19 induced neurologic manifestations remains still poorly understood. But it has become abundantly clear that, physicians especially frontline ones, should be aware that there are possible associations between SARS-COV-2 and neuro-ophthalmic disease.

As indicated by the literature, the following ophthalmic presentations in the course of Covid infection have been reported new vision loss, new-onset optic neuritis, cranial nerve palsies, Miller Fisher and Wernicke syndrome, episcleritis, retinal microvascular impairments, retinal vein occlusions and retinal artery occlusion.

This is why it is essential, in addition to asking new patients whether they have experienced shortness' of breath, cough, fever', that clinicians should also ask about symptoms such as decreased vision, pain with eye movements, and double vision. If patients complain any of above the mentioned clinical setting, COVID-19 testing should be considered.

During the physical examination, the clinician should pay attention to and look for pupillary and visual acuity abnormalities, extraocular motility deficits, ptosis and optic disc swelling. Checking cranial nerves by neuroimaging is also crucial to rule out cranial neuropathy.

This area of study is still developing as we are learning new facts about COVID-19 each day. It is not unlikely that other new neuro- ophthalmic diagnoses are involved, too. Further research is needed to understand the pathogenesis of Covid changes and their relation to evoked signs and symptoms.

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Corneal Burns - Symptoms, Diagnostics, Treatment and Surgical Management

Julia Górczyńska[1,2], Michał Gebuza[1,2], Aleksandra Jany[1,2], Agnieszka Kowal- Lange[3], Magdalena Targońska[3], Joanna Bogusławska[3], Jan Gnus[1,3]

1. Wroclaw Medical University, Wrocław, Poland
2. Students' Research Group of Ophthalmic Surgery, Wroclaw Medical University, Wrocław, Poland
3. Regional Specialist Hospital in Wroclaw, Research and Development Center, Wrocław, Poland

List of aBbreviations

AMT - Amniotic membrane transplantation
AS-OCT - Anterior segment optical coherence tomography (AS-OCT)
DALK - Deep anterior lamellar keratoplasty
EDTA - ethylenediaminetetraacetic acid
IOP - Intraocular pressure
LSCD - Limbal stem cell deficiency
LSCT - Limbal stem cell transplantation
OCT - Optical coherence tomography
OCTA - Optical coherence tomography angiography
PK - Penetrating keratoplasty
UV - Ultraviolet

INTRODUCTION

Burns to the eye mainly affect conjunctiva, cornea, eyelids and sclera. We can divide eye burns according to etiological factors into radiant energy burns (e.g. caused by heat, electricity or ultraviolet [UV]) and chemical burns (e.g. caused by acid or alkali). Chemical damage to the conjunctiva and cornea is an emergency condition requiring immediate medical

intervention. Eye burns can lead to extensive damage to the cornea and anterior segment of the eye, resulting in visual impairment (the most severe cases result in a condition known as corneal blindness) and in some cases even enucleation [1,2].

CHEMICAL BURNS

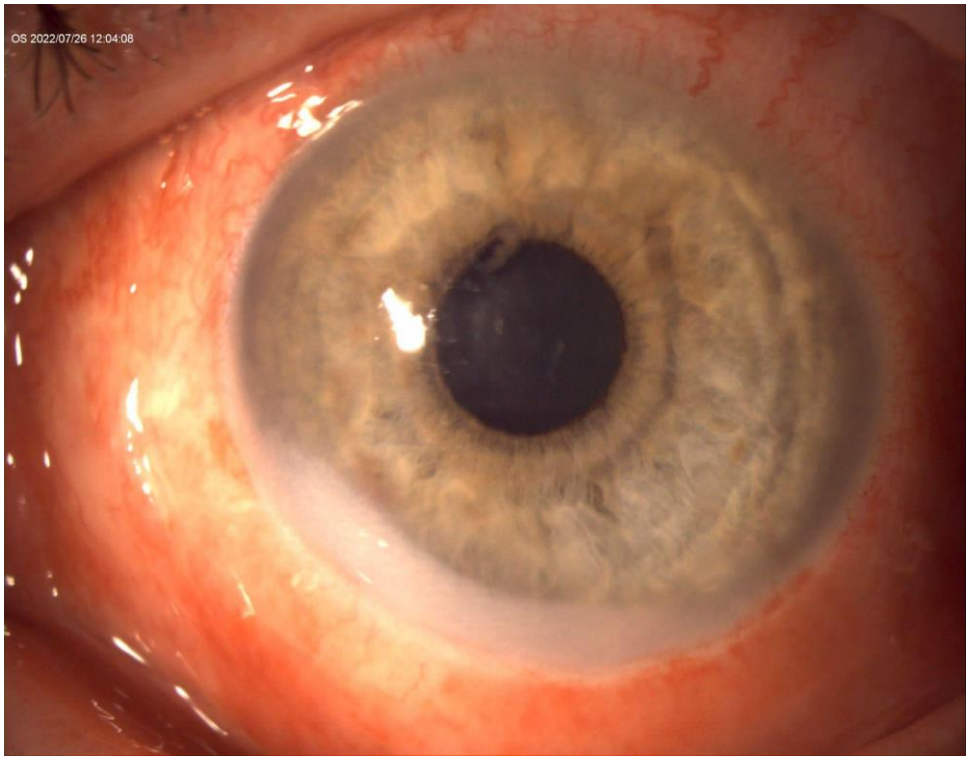
Chemical eye burns vary in severity from mild discontinuance of the corneal epithelium, eyelids injury, those resulting in corneal haze, astigmatism, loss of vision and enucleation. Chemical eye burns occur mainly in industrial facilities and during household chores, mostly with alkalis, and people without proper eye protection [3]. The scale of the chemical burn depends on the energy released in the reaction. This amount of energy is dependent on the concentration and the strength (pH) of the chemical compounds [4].

We should always try to identify the type of substance. Among alkaline substances, the most common are ammonium hydroxide, calcium hydroxide, lyes, magnesium and potassium hydroxide. They are found in supplies such as cleaning products, drain cleaners, fireplace cleaners, plant fertilizers and chemicals used during construction [5].

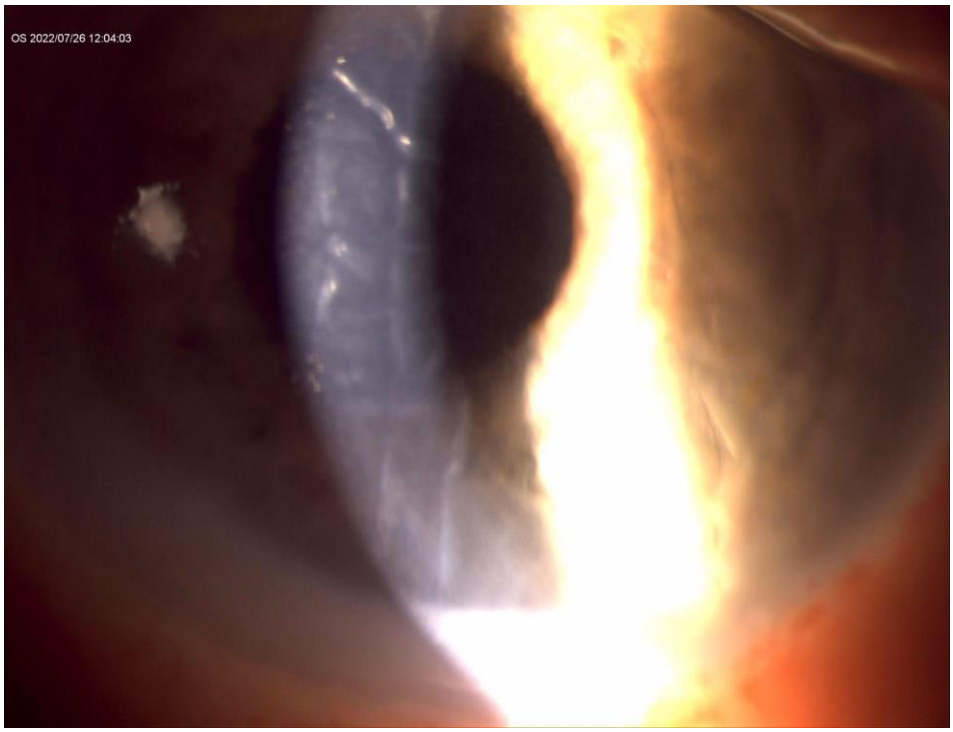
The most common acids are sulfuric acid, sulfurous acid, acetic acid, chromic acid, hydrochloric acid and nitric acid [5]. Those acids can be found in car batteries (sulfuric acid) and can get into the eyes by the battery explosion. Acetic acid is present in vinegar and some nail polish removers. Sulfurous acid is contained in bleach and cooling liquids [6].

Alkali Burns

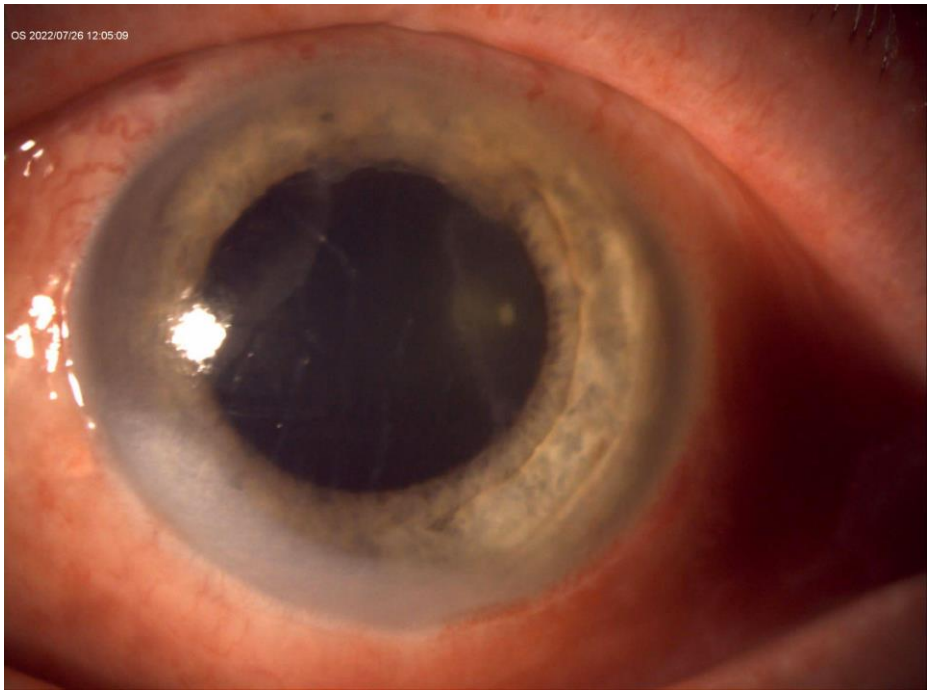
Alkali burns are the most hazardous burns due to the mechanism of action. Alkali develops saponification of fatty acids in cell membranes leading to their disruption, it facilitates further penetration of alkali to deeper layers of the cornea and into the fluid in the anterior chamber of the eye. In experiments, performed on mice and rabbits, the pH in the anterior chamber was elevated from 7,4 to 11,4 in just 40 seconds after alkali burn with 1 or 2 mol/L sodium hydroxide [7,8]. Damaged tissues stimulate an inflammatory reaction, which causes the release of proteolytic enzymes. Those processes result in liquefractive necrosis, which quickly (within 5-15 minutes) involves the deep structures of the eyeball even resulting in inflammation of the eye, increased intraocular pressure (IOP), cataract and secondary glaucoma [4,6]. Prognosis depends on the type and strength of substance and the grade of injury.



Photograph 1: Immediate condition after alkali burn with the complete loss of the corneal epithelium, descemet membrane folding and limbal anemization in the inferior and in nasal quadrant for nearly 4 clock hours with corneal haze in the limbus, *Photograph by lek. Joanna Bogusławska*



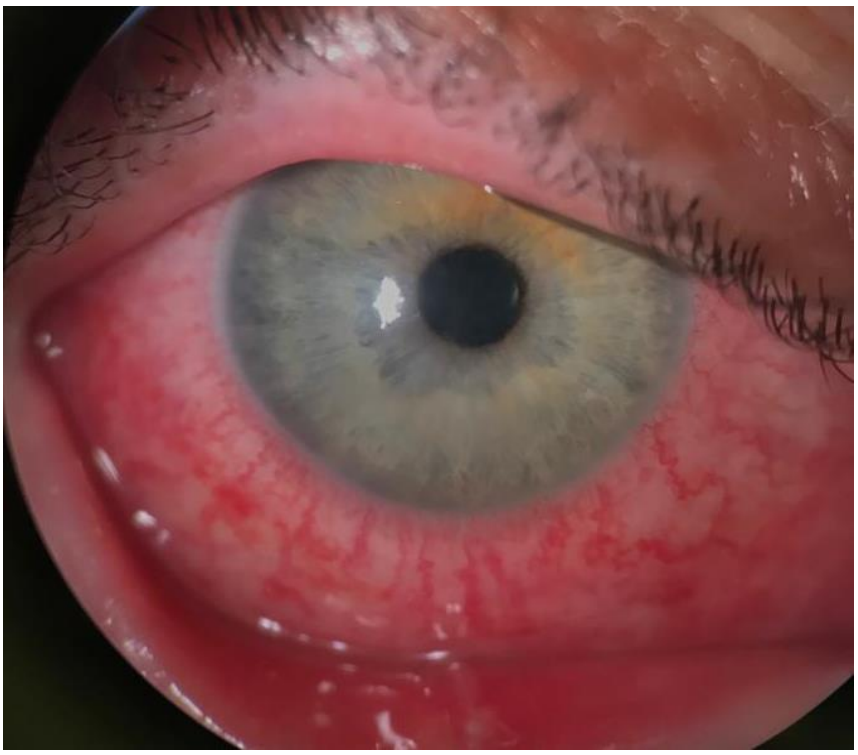
Photograph 2: Descemet's folded membrane - condition after chemical burn of the cornea *Photograph by lek. Joanna Bogusławska*



Photograph 3: Visible corneal epithelialization from the sides, leaving a centrally located triangular abrasion of the cornea, *Photograph by lek. Joanna Bogusławska*

Acid Burns

This type of burns is less extensive. Acids cause protein coagulation or denaturation of corneal epithelium and corneal stroma [9].

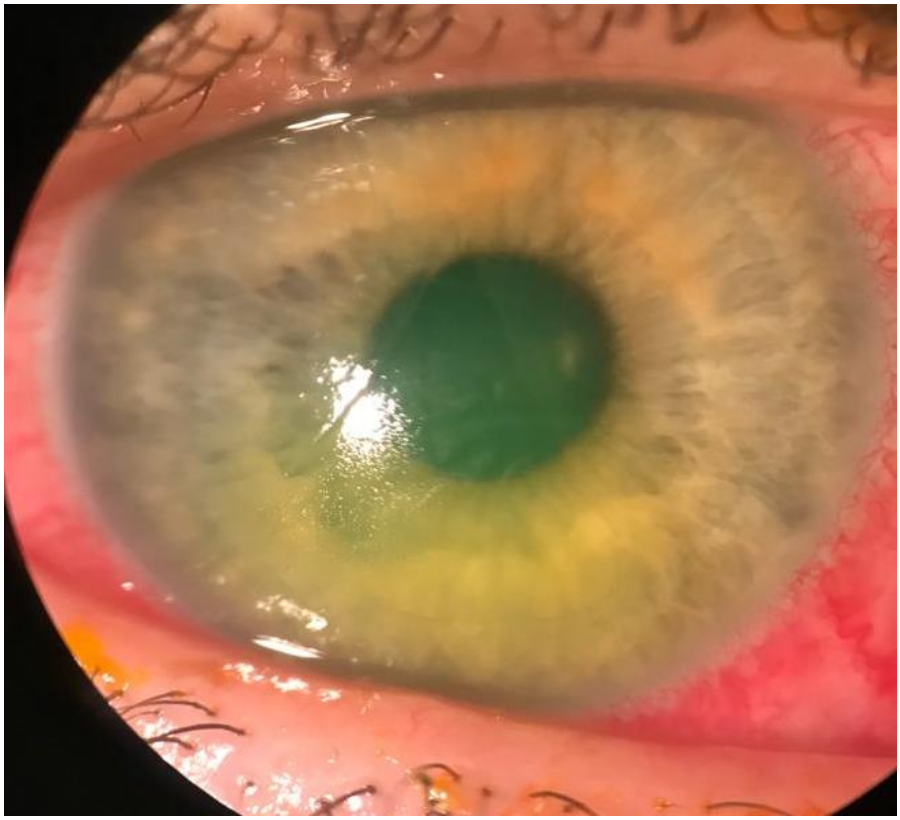


Photograph 4: Corneal burn in an intoxicated patient, *Photograph by lek. Magdalena Targońska*

This creates a physical barrier, which prevents further penetration of acids into the cornea. In addition, the cornea has buffering properties allowing it to neutralize low pH [9].

The process of coagulation creates increased corneal opacity. Exception to low acid penetration is hydrofluoric acid, which is very powerful against cell membranes and is able to develop extensive lesions of the anterior segment of the eye [10].

Unlike alkali, acids do not deplete the proteoglycans in the extracellular matrix in corneal stroma. Alkali can develop inflammation, corneal erosion and fusion of the eyelids. Despite their different effects on eye tissue, both acids and bases can cause extensive tissue damage [11].



Photograph 5: The same patient after staining of the epithelium and Descemet's membrane with fluorescein, *Photograph by lek. Magdalena Targońska*

RADIANT ENERGY BURNS

Thermal burn

Heat is a main cause of inflammation and the expression of proteases in the corneal stroma can lead to collagen breakdown. Defense mechanisms such as rapid eyelid closure and Bell's reflex limit damage to the eyeball caused by a flame (the eyelashes and lids are mainly

affected). Curling iron, cigarettes and hot liquids poured into the eye (mainly during cooking) are the most common causes of corneal burns, occurring at home. They are mostly restricted to the epithelium. They usually require only short-term treatment with topical medications – antibiotics, steroids, artificial tears and mydriatics [12].

Electricity

The severity of an electric current injury is due to different components, such as type of electric current (direct or alternating), the power of current and the duration of exposure [13].

Electric burns to the eye are relatively rare and cataract formation is the most common side effect, reported by patients. Trauma to the eye caused by the electric current can lead to erosion of corneal epithelium. In the case of extensive injury it can develop complete opacification, thinning, necrosis, and perforation of cornea [12,13].

Ionizing radiation

Exposure to ionizing radiation can occur in contact with either UV light, X-rays, gamma radiation, nuclear explosions or radioisotopes [12].

The magnitude of exposure is related to the amount of ionizing radiation energy, the type of radiation emitted, the exposure time and the distance from the radiation source. The consequential trauma can be the result of direct cellular destruction and mutations in DNA [12].

Punctate corneal erosions can be observed in the acute phase. Explosions of radioactive materials can cause perforation of eye tissues (cornea, conjunctiva, sclera) and immediate necrosis. Late complications of ionizing radiation exposure include decreased tear production, loss of corneal sensation and impaired corneal epithelial cell healing [12].

UV radiation

The most common cause of UV-induced eye injury is a lack of eye protection during exposure to arc welding, sunlamps and tanning beds [12,14].

Acute inflammation of the conjunctiva and corneal epithelium caused by exposure to UV, so-called "snow blindness", occurs in skiers and mountain climbers at high altitudes, which is caused by less atmospheric diffraction of UV radiation..Symptoms seen in patients with UV-induced eye injuries include swollen eyelids, conjunctival congestion, diffuse punctate keratitis and even outer retina burns [12,14].

CLASSIFICATION

Treatment, management and prognosis of corneal burns depend on the damage severity. There are two main classification systems to assess grade and development of ocular lesions.

Roper-Hall (modified Hughes classification) [9].

Roper-Hall classification			
Grade	**Cornea**	**Conjunctiva**	**Prognosis**
I	Corneal epithelial damage	No limbal ischemia	Good
II	Corneal haze with visible iris details	<⅓ limbal ischemia	Good
III	Total epithelial loss, stromal haze, with obscured iris details	⅓ to > ½ limbal ischemia	Guarded
IV	Opaque cornea, with obscured iris and pupil	>½ limbal ischemia	Poor

Grades I and II are classified as benign - prognosis is good, usually heal within 10 days. Grades III and IV are classified as serious [15].

Dua classification

The second main classification. It is more accurate and provides better stratification for extensive injuries [16].

The Roper-Hall classification is based on the presence of perilimbal ischemia, while the Dua classification requires the presence of fluorescein staining of the limbal area. Fluorescein staining can reveal complete absence of limbal epithelium, which implicates massive loss of stem cells. It is important to point out that corneal involvement is not included in the Dua classification.

Dua classification is also more accurate in severe cases. Those which can be assigned to grades 4, 5 and 6 in Dua classification, in Roper-Hall scale correspond to one grade with poor prognosis - grade 4.

To properly evaluate the possible damage, beside grading we need to know additional data about the source of the burn: type (Acid, Alkaline, UV, etc.), the energetic level of the source, amount and concentration, period of the exposure, area of affected tissue and other factors (viscosity of solution, the speed and pressure of particles, transmission to the second eye by the patient, etc.) [16].

Dua classification				
Grade	**Prognosis**	**Clinical findings**	**Conjunctival involvement**	**Analogue Scale***
I	Very good	0 clock hours of limbal involvement	0%	0/0%
II	Good	⩽3 clock hours of limbal involvement	⩽30%	0.1–3/1–29.9%
III	Good	> 3–6 clock hours of limbal involvement	>30–50%	3.1–6/31–50%
IV	Good to guarded	> 6–9 clock hours of limbal involvement	>50–75%	6.1–9/51–75%
V	Guarded to poor	> 9–< 12 clock hours of limbal involvement	>75– < 100%	9.1–11.9/75.1–99.9%
VI	Veyr poor	Total limbus (12 clock hours) involved	Total conjunctiva (100%) involved	12/100%

*The analogue scale records accurately the limbal involvement in clock hours of affected limbus/percentage of conjunctival involvement

The clinical course of chemical eye injury, according to McCulley, can be divided into following stages [17]:

- Immediate - the moment when a chemical agent comes in contact with the surface of eye,
- Acute (0 - 7 days) - acute inflammation is developed, undamaged limbal stem cells attempt to restore the epithelium of exposed stroma of the cornea and IOP can vary. It is a crucial period for the protection of the corneal stroma from proteolytic enzymes and enzymes from the immune cells, which may impair healing in later stages [7,10,18].

- Early reparative (8 to 21 days)- Chronic inflammation, stromal repair and scarring, corneal ulceration is possible.
- Late reparative (after 21 days) - termination of healing with good visual prognosis (mainly I and II grade) and complications in those with uncertain visual prognosis (mainly III and IV grade). There may be late complications of chemical burns, e.g. vision deterioration, xerophthalmia, corneal scarring, dry eyes, cataract, symblepharon, glaucoma, uveitis, adenexal abnormalities such as lagophthalmos, entropion, ectropion and trichiasis [17,19].

DIAGNOSIS

The assessment of a patient with corneal injury includes a complete ocular examination, which evaluates anterior segment of the eye in a slit lamp with fluorescein staining, visual acuity, eye movements and IOP. It is important to inspect the entire cornea, including lid eversion and examination of fornices for the presence of a foreign body [20,21]. If there is suspicion of a potential intracorneal debris, the optical coherence tomography (OCT) provides proper visualization of foreign bodies localization.

Recent study shows that anterior segment optical coherence tomography (AS-OCT) and OCT angiography (OCTA) can also be used to show characteristic pathological changes in the eyes. The main lesions visible in AS-OCTA and OCTA are epithelial bullae, epithelial erosions, Descemet's membrane detachment, stromal cysts and neovascularization. The severe corneal opacity and anterior chamber inflammation in the aqueous humor of the eye also can be detected with these techniques [22].

Treatment and Management

The goal of the treatment is to restore the proper function of the eye to the greatest extent possible and prevent potential complications [23]. The initial management of chemical burns at site is immediate and continuous irrigation of the eye, to provide neutralization of pH. The conjunctival sac pH can be evaluated with urine pH test strips [24]. This can require from 2 up to 10 liters of continuous irrigation, during minimum 30 minutes to 4 hours depending on the case [11]. The eye rinsing also provides removal of potential foreign objects, which can be hidden in fornices [25]. Any visible foreign objects should be removed with forceps.

Lactate ringers are preferable for eye rinsing [26]. Other possible solutions are balanced salt solutions, tap water or amphoteric solutions (e.g., Diphoterine®) [27]. Soft drinks which

contain sugar have stable osmolarity and can be also considered to be used when none of the above liquids is available [26]. Nevertheless, early initiation of the eye irrigation is more important than the aqueous solution which is used. Burns with calcium oxide (CaO) must not be removed with water irrigation, they should be removed with oils or swabs soaked with ethylenediaminetetraacetic acid (EDTA) [1].

Treatment of chemical burn injuries

The main treatment during the acute and early reparative phase is initial suppression of inflammation and ocular surface reepithelialization. Mild lesions require antibiotic ointments and artificial tears, which are used among all stages of healing. More severe cases require regular monitoring and additional studies in order to find possible complications (e.g. stromal thinning, elevated IOP, etc.).

The most important goal in treating a corneal burn is to stop the inflammatory response. Strong topical corticosteroids (e.g. prednisolone acetate 1.0% or dexamethasone 0.1%) are the first line of treatment and should be used with high frequency in the treatment of acute corneal burns (one drop every hour) [18,28].

To relieve the pain in the acute phase there are used cycloplegic agents as well as systemic analgesics. It is recommended to use tetracycline (p.o.) 25-50 mg twice a day and supplement 1000 mg of vitamin C (p.o.) for supporting wound healing [11].

Vitamin C can be also used in eyedrops. Topical antibiotics can also be used. It is crucial to avoid aminoglycosides as they are toxic to the corneal epithelium (gentamicin and tobramycin) [11].

Erythromycin, from the macrolide family, is safe to use in prophylaxis of bacterial infection. Damage to the anterior segment of the eye can cause contracture of the sclera or damage to the trabecular meshwork, resulting in an increased IOP [29].

IOP-lowering drugs are given, as elevated IOP worsens the healing of the cornea in the early stages of treatment. In addition, secondary glaucoma is prevented by this treatment. Care should be taken in selecting secondary glaucoma therapy, as some eye drops may be toxic to the epithelium and slow down its regeneration. Alternatively systemic drugs can be used to lower the IOP. IOP should be monitored, while it may vary during treatment due to eye surgery or corticosteroid therapy [30].

More severe burns, in particular alkaline burns, require specialized therapies requiring hospitalization. Local treatment with autologous serum and platelet rich plasma applied on cornea surface is currently used. Bandage contact lenses are considered in corneal epithelial

loss and management of pain, when corneal nerves are exposed. It is important to include concomitant antibiotic prophylaxis against *Pseudomonas aeruginosa*. In the late reparative phase the treatment of inflammation and reconstruction of the eye surface are conducted [11,19]. Amniotic membrane transplantation is a very effective form of treatment for corneal burns, both chemical and thermal [31].

Treatment of radiant energy burns

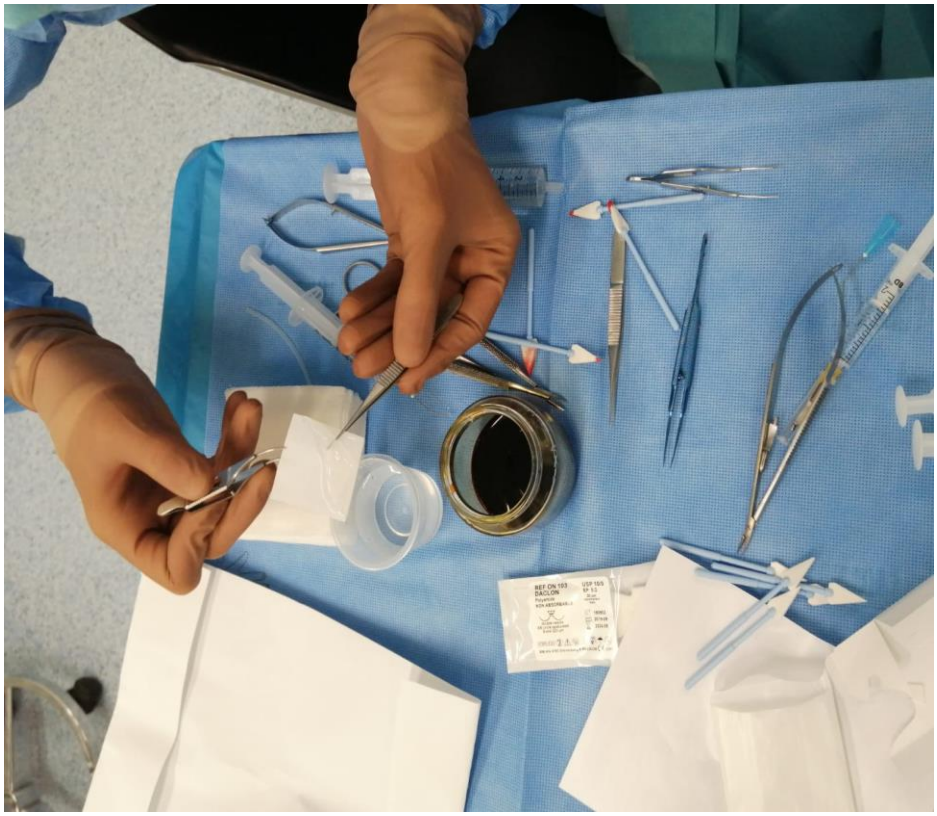
Similar to chemical burn management, it is necessary to remove the harmful agents and apply irrigation. Further treatment requires cooling the surface of the eye (cold saline compresses), applying topical antibiotic therapy, to prevent intraocular inflammation, and applying an occlusive dressing of the eye to create sealed isolation for reepithelialization. Burned eyelashes and eschar may need to be removed [1,11]. Treatment of burns caused by UV radiation includes covering the eye (this minimizes the discomfort associated with eyelid movement), the usage of antibiotic ointment, mild topical steroids, artificial tears and pharmacological pupil paralysis. Occasionally, patients require pain relief medication. Complete healing of the epithelium usually takes about 24-72 hours. The usage of UV-filtered eyeglasses can prevent this kind of injury [12].

SURGICAL MANAGEMENT

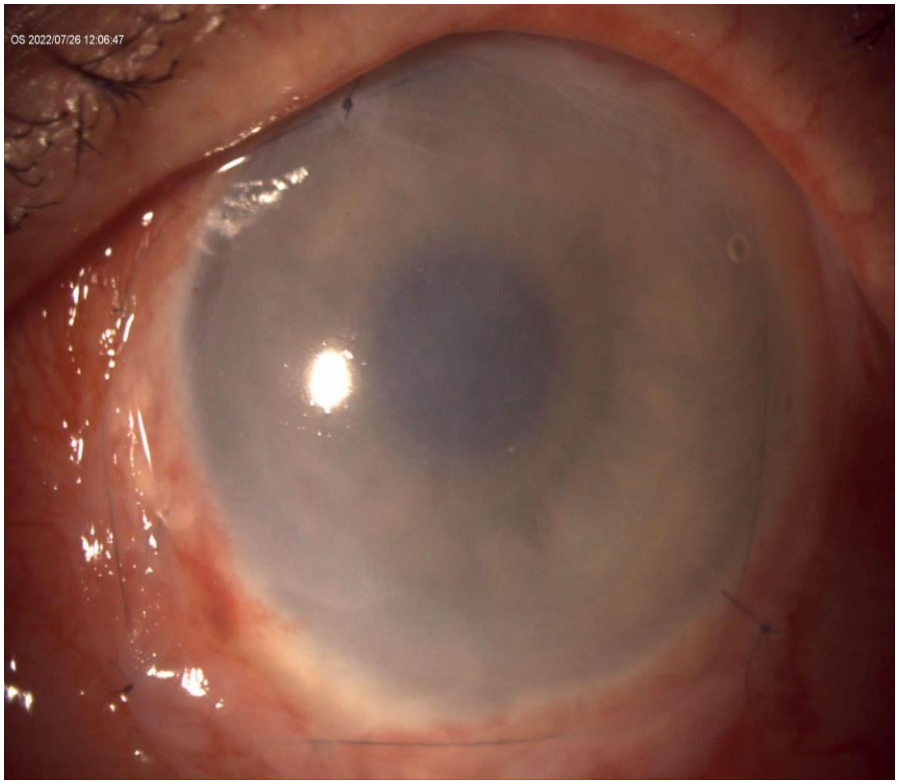
Surgical procedures are mainly used in high grade burns (III - VI in the Dua classification) and they are recommended to accelerate the healing process and reduce the frequency of complications.

Amniotic membrane transplantation (AMT)

Amniotic membrane does not express tissue compatibility antigens, which allows it to be transplanted without complementary immunosuppression and without the risk of graft rejection. Amniotic membrane has strong antibacterial properties, which contributes to the low risk of postoperative complications. If there is a partial deficiency of the corneal stem cell, the amniotic membrane facilitates reepithelialization while reducing inflammation, pathological vascularization and scar formation. If there is a complete deficiency of corneal stem cells, with deep involvement of the parenchymal layer, an additional limbal stem cell transplantation (LSCT) and sometimes a penetrating keratoplasty is required [32,33].



Photograph 6: Amniotic membrane on the substrate, *Photograph by lek. Magdalena Targońska*

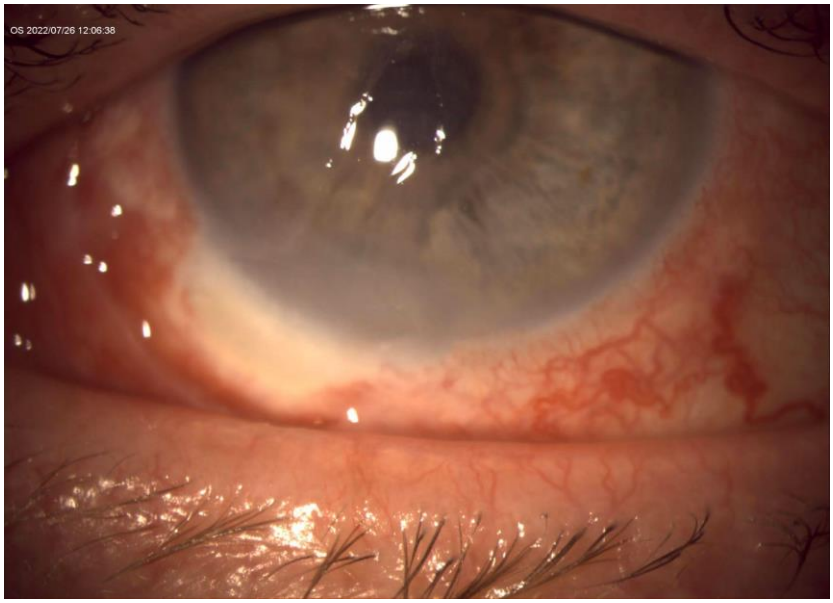


Photograph 7: Postoperative status after layered amniotic membrane transplant, *Photograph by lek. Joanna Bogusławska*

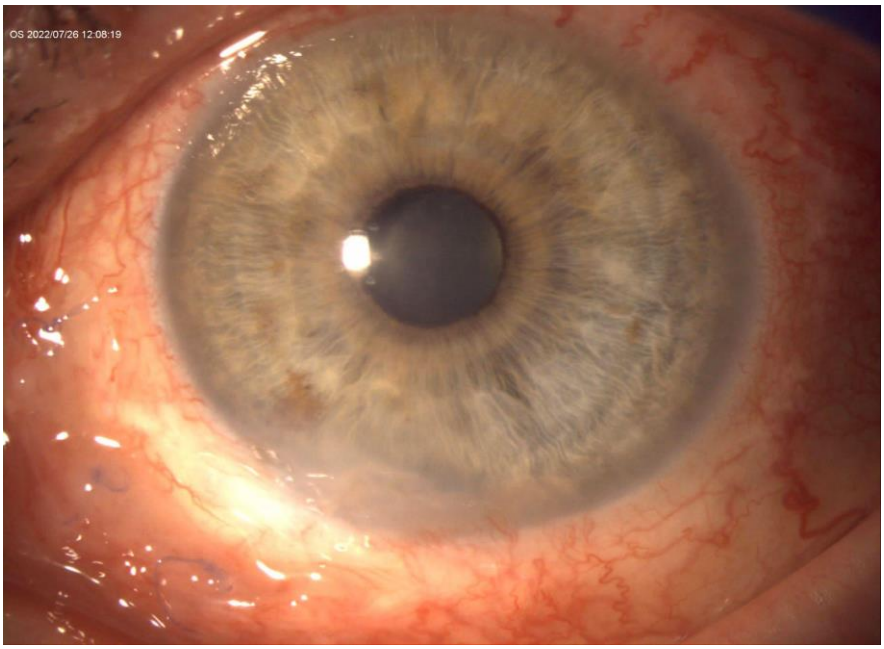
DEBRIDEMENT OF NECROTIC TISSUE

Tenonplasty

In cases of severe burns where the limbal vasculature is significantly damaged, with scleral melting, tenoplasty is performed [34, 35].



Photograph 8: Post-burn defect of the ocular conjunctiva with exposure of the sclera at the site of previous limbal anemization and centrally located vertical erosion of the cornea, *Photograph by lek. Joanna Bogusławska*



Photograph 9: Condition after conjunctiva repair and amniotic membrane transplantation, *Photograph by lek. Joanna Bogusławska*

It has been reported that tenoplasty reliably repairs the necrotic area of the conjunctiva. The procedure involves debridement of necrotic tissues, dissection of the layer of vascularized Tenon tissue and overlapping it on ischemic sclera. In extensive burns, Tenon's capsule might be impaired, thus denying this procedure

LSCT

Ocular burn can result in limbal stem cell deficiency (LSCD). LSCT is conducted in order to restore stem cells on the surface of the eye and provide a healthy support tissue for keratoplasty. If one eye is injured, an autograft from the second eye is possible. In the case of bilateral lesion, the allograft technique is performed. The failure of LSCT can develop during the first year after transplantation [36].

Keratoplasty and Keratoprosthesis

The aim of keratoplasty is to restore the proper visual function of the patient. It can be performed alone or in combination with AMT. Keratoplasty is considered if a patient has visible scarring of the stroma and multiple perforations. Depending on the type and depth of lesion, penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK) can be performed. It should be considered individually which one is more optimal. DALK is performed exclusively in cases that affect the middle stromal layer. Furthermore DALK has a lower likelihood of rejection in comparison to PK. The indication for Keratoprosthesis is multiple failed keratoplasty procedures and if the probability of performing a new successful keratoplasty is low [18].

CONCLUSION

A corneal burn is an emergency in ophthalmology. Quick implementation of adequate treatment can protect the patient against the development of late eye complications, including corneal blindness or even loss of the eye. In topical and general therapy, the ophthalmologist has a wide range of options at his disposal.

The recipe for therapeutic success is an optimal response to the local and general condition of the patient.

The first stage of the therapy is managing the inflammation, which is induced by any type of corneal burn.

Then individualized therapy will bring the best possible therapeutic effect.

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Microinvasive glaucoma surgery - what is it?

Maciej Dyda[1], Justyna Pilch[1], Kamila Łachut[1], Izabela Kudaj[1], Kaja Sladkowska[1], Andrzej Dłubak[1], Paweł Skowron[1], Aleksandra Sadowska[1], Hanna Zając- Pytrus[1,2]

1. Wroclaw Medical University, Wrocław, Poland
2. Department of Ophthalmology, Wroclaw Medical University, Wrocław, Poland

List of abbreviations

MIGS – Microinvasive glaucoma surgery
GFD - Glaucoma Filtration Device
BAGS- blebless ab externo glaucoma surgery
ABiC- Ab-interno canaloplasty
ECP- Endoscopic cyclophotocoagulation
IOP- intraocular pressure
OAG- open-angle glaucoma
SMD- standard median deviation
FDA- U.S. Food and Drug Administration
TM- trabecular mesh
AC- anterior chamber
POAG- primary open angle glaucoma
PDG- pigmentary glaucoma
PXG- pseudoexfoliative glaucoma
UVG- uveitic glaucoma
JVG- juvenile glaucoma

WHAT IS MIGS?

For years the management of glaucoma has been split up into different steps regarding the invasiveness, starting with pharmacotherapy and proceeding to a surgical approach only in

case of failure of non-invasive methods. This cautious step-by-step management of glaucoma is being performed these days due to the high risk of sight-threatening complications associated with performing trabeculectomy, which has been a surgical gold standard in the management of glaucoma since its first description in the late 1960'.

In response to the need for safer methods of glaucoma treatment, in the 1990s' Stegmann et al. and Kozlov et al. described non-penetrating procedures which resulted in minimal blebs. Although these methods had a better safety profile, the lowering effect on intraocular pressure is assessed only as moderate [1,2].

Their research was followed by the introduction of the Ex-Press Glaucoma Filtration Device, (GFD) which, when implanted under a modified trabeculectomy-like scleral flap, reduces the outflow by standardizing the size of the wound and decelerating the flow by channeling it through a cylindrical implant. Procedures involving GFD create minimal blebs and cause fewer complications in comparison to trabeculectomy, however, their major contribution to glaucoma treatment development seems to be the initiation of a generational shift in the design of surgical instruments, reflected in the development of BAGS = blebless ab-externo (outside-in) and MIGS = minimally invasive glaucoma ab-interno (inside-out) procedures refined in collaboration with ophthalmologists [1,2].

All of the procedures included in MIGS criterium share a common mechanism - they improve the outflow of aqueous humour out of the eyeball but in three different ways: conventional trough Schlemm's canal (iStent, Hydrus, Trabectome, Ab-interno canaloplasty - ABiC, ELT), to the suprachoroidal space (CyPass, I-stent supra) or into the subconjunctival space (XEN). The only procedure that uses a different mechanism is ECP the aim of which is to decrease the production of aqueous humour [1,2].

Unlike their predecessors, MIGS are bleb-independent and therefore have a better safety profile. This is a result of using ab-interno access, which does not require any conjunctival incision. As a consequence, the risk of scarring and secondary ineffectiveness of these procedures is significantly lower when compared with traditional methods. Moreover, due to the fact that MIGS do not disturb the conjunctiva, they also do not impede future filtration.

In terms of effectiveness - micro-invasive glaucoma surgeries allow surgeons to treat patients in the early stages of the disease as there is no need to wait for the disease to progress to an advanced stage in order to perform the surgery. Even though the efficacy in reducing IOP is not as high as with trabeculectomy and long-term results are still to be seen, MIGS should be considered as a more convenient alternative in glaucoma treatment due to the fact that they have a better safety profile, can be introduced in the early stages of the disease and effortlessly

combined with cataract extraction, in which case the whole procedure is lasts only 15 minutes longer. Certainly, the expenses of this therapeutic approach should be taken into consideration, especially in developing countries. Nonetheless, from the patient's point of view, MIGS not only improve the quality of life by decreasing IOP values and in consequence also the number of taken medications but also accelerates post-surgery visual rehabilitation [1,2].

ENDOSCOPIC CYCLOPHOTOCOAGULATION

Endoscopic cyclophotocoagulation (ECP) is a unique minimally-invasive procedure designed to lower intraocular pressure through the reduction of aqueous humour production. ECP uses a focused diode laser that emits pulsed continuous energy to selectively ablate the ciliary body processes. The coagulative necrosis of the ciliary body epithelium and stroma decreases the amount of aqueous inflow, which is considered to be the most important explanation for the IOP reduction seen after the procedure. Another possible lowering effect may be due to increased uveoscleral outflow through the areas of damaged tissue.

From its initial use in refractory glaucoma, the indications for ECP have expanded broadly. The procedure has been used to treat many types of glaucoma across the spectrum of disease severity, including primary open-angle, pigmentary and neovascular, chronic angle closure, and normal tension glaucoma as well as post penetrating keratoplasty and iridocorneal syndrome. Absolute contraindications have not been reported [3].

ECP is an efficacious tool for the treatment of glaucoma and is becoming widely utilized as a straightforward and safe procedure. In contrast to other minimally-invasive techniques, ECP lowers intraocular pressure through aqueous suppression and does not require device implantation or conjunctival disruption. In patients with coexisting cataracts and glaucoma, ECP may be easily combined with phacoemulsification to reduce IOP and medication burden. Combination with procedures that enhance the outflow of aqueous humour, such as iStent, is possible and currently being investigated for long-term outcomes [4].

The results of ECP are encouraging, but potential postoperative complications may be significant. Among the most common is fibrin exudate in the anterior chamber, hyphema and cystoid macular oedema. There are also case reports of visually devastating complications, including persistent hypotony and phthisis, although they were often reported in eyes with advanced diseases [3,5]. Although ECP may be a preferable surgery in cases of refractory glaucoma with relatively intact vision, it might not be recommended for patients with very poor vision, since it would unnecessarily expose them to such potential complications [5].

ENHANCING OUTFLOW OF AQUEOUS HUMOR THROUGH SCHLEMM'S CANAL

One of the approaches in MIGS involves enhancing the outflow of aqueous humor through Schlemm's canal. This is achieved by reducing trabecular meshwork's resistance as it is identified to be the main factor affecting the resistance of aqueous outflow[6]. In this approach iStent trabecular micro-bypass implant, Hydrus microstent, Trabectome, ELT, and Ab Interno Canaloplasty are used to achieve increased outflow and hence decreased IOP.

iStent Trabecular Micro-Bypass Stent System (Glaukos Corporation, San Clemente, CA) was the first MIGS implant to be approved by the FDA in 2012. This L-shaped device consists of a 1 mm body containing 3 retention arches and a 0.25 mm snorkel. The arches ensure the body remains in place when implanted into Schlemm's canal [7].

The single-use sterile injector is used to implant the iStent. After implantation, the lumen of the snorkel enables the outflow through the device from the anterior chamber through Schlemm's canal and subsequently aqueous veins and episcleral veins [8].

iStent Inject (Glaukos, Laguna Hills, CA) is the new generation of trabecular meshwork bypass stent that was approved by the FDA in 2018 [8]. It consists of a head residing in Schlemm's canal, a thorax held by the trabecular meshwork, and a wide flange residing in the anterior chamber. The device is 360 μm in height and 230 μm in diameter. A central inlet and multiple flow outlets are meant to optimize the outflow through the natural physiological pathway. The injector in this case is provided with two pre-loaded devices which should be placed 2-3 clock hours apart at the nasal angle. It can be performed through the phaco incision [9].

A review by Yu-Yen Chen et al. aimed to analyze the data on the use of iStent as a standalone procedure and its effects on the patient with OAG, based on 17 studies and 978 eyes evaluated. First-generation iStent was used in 599 (61.2%) eyes, and second-generation iStent was used in 379 (38.8%) eyes. All studies reported a reduction in IOP after iStent implantation. The pooled result demonstrated a significant SMD of −2.64 (95%) confidence interval (CI): −3.21 to−2.07). The majority of studies reported a reduction in the number of medications at the endpoint compared to that at baseline with an overall SMD was −1.71 (95% CI: −2.18 to −1.24). Yu-Yen Chen at al. pointed out that IOP ≤18 mmHg at the end point was achieved by 88.7% (95% CI: 81.5% to 93.4%) of eyes and 86.0% (95% CI: 73.7% to 93.1%) of eyes had a 20% or greater reduction in IOP at the endpoint. Most of the studies had a complication rate of less than 20% with some including progression of cataract and elevated IOP, however iStent

obstruction or iStent malposition were not common and only occurred in two and three studies, respectively [8]. Chen et al. report that the benefit of iStent persisted for up to 42 months as this was the longest follow-up duration and that more iStents (2 or 3) would reduce more IOP. Moreover, both first- and second-generation iStents reduced IOP significantly.

Hydrus® Microstent (Ivantis, Inc., Irvine, CA) is a part of the MIGS category of devices bypassing trabecular outflow and was approved by FDA in 2018. It is a flexible aqueous drainage device designed to be placed ab-interno where it bypasses the trabecular meshwork and dilates approximately three clock hours of Schlemm's canal [10]**.** The micro stent is 8 mm or 15 mm long and 290 μm in diameter consisting of three windows and an inlet residing in the anterior chamber. This device covers 90 degrees of trabecular meshwork while the 1–2 mm inlet segment is left to reside in the AC. It is not only allowing the bypass outflow but also enhances Schlemm's canal patency [10]. A review by Samet et al. summarized the results of outflow facility and resistance experiments. Gulati et al. [11]. conducted a study on freshly enucleated pairs of human donor eyes. In the study 26 pairs of donated eyes were divided into two groups, receiving 8-mm Hydrus Microstent implantation and sham procedure respectively. There was no significant difference in the outflow facility at baseline between the two groups ($P = 0.27$). The results were Hydrus Microstent significantly increased outflow facility from 0.33 ± 0.17 μL/min/mm Hg to 0.52 ± 0.19 μL/min/mm Hg ($P < 0.001$) in implanted eyes while the change in the outflow from the sham surgical procedure in control eyes was not statistically significant ($P = 0.82$). . Outflow resistance was significantly reduced from 4.38 ± 3.03 mm Hg/μL/min at baseline to 2.34 ± 1.04 mm Hg/μL/min ($P < 0.001$) with the microstent [11].

Ahmed et al. [12] compared the efficacy of iStent and Hydrus in terms of reducing IOP and medications in OAG. The study showed the Hydrus Microstent had an advantage over the 2-iStent Trabecular Bypass device in terms of reducing medication use and surgical success in OAG patients at 1 year postoperatively. Medication use was reduced by a greater margin or eliminated more frequently in the Hydrus group than in the 2-iStent group (46.6% to 24.0% respectively). Considering eyes without medication, Hydrus achieved IOP ≤18 mmHg more often (30.1% to 9.3%).

Trabectome is a surgical system developed by NeoMedix (Tustin, CA) used to perform ab interno trabeculectomy. It was approved by the FDA in 2004. It works by removing a strip of TM and an inner wall of Schlemm's canal to create a direct pathway for aqueous humor outflow from the anterior chamber to the collector channels in Schlemm's cana [7]**.**

A single-used, disposable device allows performing electrocautery, irrigation, and aspiration. The device is controlled by a foot pedal 3-position foot pedal (position 1: irrigation,

2: aspiration, 3: cautery) [7]. Before the procedure is started, both the head and a microscope are tilted to give a good view of the angle, with a combined tilt of 60-80 degrees. To make a near limbal, temporal corneal incision 1.7 mm keratome is used. Lidocaine 1% followed by 2% hydroxypropyl methyl-cellulose viscoelastic may be injected. After that the handpiece of Trabectome is inserted in the AC and advanced nasally with the infusion on and help of gonioscopy lens. When the pointed tip of the footplate reaches Schlemm's canal both electro-surgical and aspiration should be used by the surgeon. The strip of TM and the inner wall of Schlemm's canal is ablated and removed. Following that, the formation of the ‚cleft' must be verified and the angle is checked for evidence of blood reflux from Schlemm's canal [7].

Canaloplasty ab interno is a highly effective, minimally invasive procedure involving microcatheterization and viscodilation of the entire length of the Schlemm's canal. It is performed to reinstitute the natural aqueous outflow and lower the resistance, which in open-angle glaucoma tends to be abnormally high [13] and causes increased intraocular pressure. Microcatheter provides additional channels for aqueous outflow by clearing the mechanical obstructions. Viscodilation increases the diffusion through the proximal system into the distal system by creating microperforations within the inner wall of Schlemm's canal. Moreover, ab interno canaloplasty is a procedure performed to avoid scleral incisions and spare conjunctiva [14]. The patients treated with ab interno canaloplasty experienced a statistically significant reduction in mean intraocular pressure. Average reduction in IOP was 36.2%-41.0% [15,16].

Canaloplasty is as effective as trabeculectomy in lowering intraocular pressure and reducing dependence on medications [17]. The main side effects of canaloplasty are the inability to cannulate Schlemm's canal, Descemet's membrane detachment, and improper microcatheter passage. However, compared with trabeculectomy, canaloplasty has no filtering bleb formation, no antimetabolites, rapid visual recovery, fewer complications, simple postoperative nursing, and stable postoperative intraocular pressure[18].

Excimer laser trabeculectomy is a glaucoma surgery that creates multiple laser channels through the trabecular meshwork using a cold laser system, which minimizes tissue fibrosis and aids in bypassing the main area of resistance to aqueous outflow. The surgery is performed in order to lower the intraocular pressure. The laser operates at a wavelength of 308 nm, which allows it to ablate the trabecular mesh without damaging the outer wall of Schlemm's canal or inducing thermal side effects [19]. The laser probe is inserted into the eye with a tip up to 2 mm from the trabecular meshwork, and the indirect view goniolens is placed on the cornea. The aiming beam is directed almost perpendicularly to the eye walls. Then 8 laser spots, distributed equally 500 m from one another, are delivered to the anterior trabeculum [20].

The main advantages of using excimer laser technology are great precision, minimal thermal damage, very low tissue penetrance, and non-lethality to adjacent cells [21].

Long-term efficacy of excimer laser trabeculectomy on elderly patients with median age of 75 years and a median follow-up of 656 days shows that 66%-87% of patients did not need another intraocular pressure-lowering intervention. The intraocular pressure could be lowered by almost 30% within 1 year postoperatively from 25.50 to less than 18.00 mmHg. IOP-lowering medication could be reduced for the first year after surgery but increased again after 2 years of follow-up [22].

SUPRACHOROIDAL MIGS

The iStent Suprachoroidal Bypass System (iStent Supra) and the CyPass MicroStent are designed to reduce intraocular pressure by accessing the suprachoroidal space in the eye.

The iStent Supra is a 4 mm long microstent made of biocompatible polyethersulfone and titanium, with an internal lumen of 165 μm in diameter covered with heparin [23]. During gonioscopic visualization, it is placed through a 1-mm incision of the cornea behind the trabecular mesh in the super vascular space[12]. The iStent Supra is still undergoing investigation.

The CyPass MicroStent, despite receiving FDA approval in 2016, after results from a post-marketing study showing accelerated endothelial cell loss was withdrawn from the market in 2018 [24]. At present, there are no suprachoroidal devices clinically available[25].

SUBCONJUNCTIVAL MIGS

Contrarily to the MIGS devices that allow outflow of aqueous humour through the Schlemm's canal or the suprachoroidal space, the subconjunctival route is fundamentally non-physiological as aqueous humour does not naturally flow into the sub-Tenon’s space [26]. The XEN Gel Stent is currently one of the subconjunctival MIGS techniques that last years have been getting increasing in popularity.

THE XEN® GEL STENT

The XEN® Gel Stent is intended for the treatment of primary open-angle glaucoma (POAG) in patients who have previously failed medical treatment, as well as for patients with

pigmentary glaucoma (PDG) or pseudoexfoliative glaucoma (PXG) who are unable to be treated with maximal tolerable medical therapy. It is also effective in the treatment of uveitic (UVG) and juvenile glaucoma (JVG). The device is CE marked in the European Union and has received FDA approval in the United States. Turkey, Switzerland, and Canada have all been granted permission to use it [27].

The XEN® Gel Stent is an ab interno collagen implant with a durable and flexible design that drains aqueous fluid from the anterior chamber through the scleral canal into the subconjunctival space. The Hagen-Poiseuille equation is the foundation for the implanted mechanism. According to this formula, the flow is determined by inner diameter, tube length and low viscosity. Assuming laminar flow through the implant, this equation can be used to compute the stent's resistance as well as the quantity of flow that should pass through the implant's inner lumen. Based on the dimensions of the device, a filtration rate of 2-2.5 ml/min was calculated [28].

Initially, three types of the implant were designed, each 6.0 mm in length: Xen140, Xen63, and Xen45 with 140, 63, and 45μm internal lumen diameters, respectively, to control intraocular pressures at different levels. Apart from the geometric variations to the implant, all XEN models use the same materials, production techniques, and implantation procedures. The current commercially available version of the implant is Xen 45 [29].

It is produced from porcine gelatin cross-linked with glutaraldehyde [29]. Animal studies have demonstrated the stability and biocompatibility of the material with minimal tissue reaction. The XEN® Gel Stent remains tough when dry and tender and elastic when moistened, making it adaptable to surrounding tissues [30].

As the stent passes through the scleral canal, it forms an S-shaped arch, which reduces the chance of migration. Once the implant exits the sclera, it gently curves down under the conjunctiva. As the surgeon pushes the implant through the conjunctiva and Tenon, a natural bend of approximately 35 degrees is created.

SURGICAL TECHNIC OF SUBCONJUNCTIVAL MIGS

The XEN® Gel Stent is usually inserted through an ab interno approach. The steps of the implantation are the following: 2.5 mm from the limbus, the superior nasal conjunctiva is marked. To reduce the risk of subconjunctival fibrosis, the procedure is augmented with an injection of mitomycin C, a drug that inhibits fibroblast proliferation [31]. The anterior chamber is filled with a cohesive viscoelastic after clear corneal incisions (main and side-port) are made.

The needle is introduced into the main corneal incision and guided across the anterior chamber to the superonasal quadrant. While the second device is placed into the paracentesis to assist in stabilizing the eye, the needle is moved through the sclera into the subconjunctival space. Once the bevel is visible, leaving the sclera into the subconjunctival area, the XEN® Gel Stent is released and the injector is withdrawn from the eye. After that, the viscoelastic is washed out of the anterior chamber, forming an early bleb and proving the device's patency [32].

EFFICACY AND SAFETY OF SUBCONJUNCTIVAL MIGS

Studies with an annual observation found it to be effective in dramatically lowering IOP and reducing the number of hypotensive drugs taken, with a minimal number of complications or serious side effects. Galal et al [33]. made a prospective, interventional study, where 13 eyes with primary open angle glaucoma underwent XEN implantation with subconjunctival MMC under general anesthesia. Complete success was classified as a 20% reduction in IOP from preoperative baseline after 1 year without the use of any glaucoma medicines, while qualified success was defined as a 20% decrease in IOP after one year with medications. Their overall success percentage was 41.7 percent, with a qualified success rate of 66.7 percent.

Pérez-Torregrosa et al [34]. coupled XEN Gel Implant surgery with phacoemulsification in their study. In agreement with earlier clinical research [35], treatment effectiveness was defined as an IOP reduction of ≤18 mmHg without medicines. The success rate was 90% (27/30 patients) after 12 months of follow-up. Two of the remaining patients needed antihypertensive drugs to keep their IOP under 18 mmHg, while the other one needed three medications to keep their IOP under 21 mmHg. None of the patients reported reduced visual acuity as compared to preoperative levels.

COMPLICATIONS OF SUBCONJUNCTIVAL MIGS

Grover et al. reported in their study that the most common complications of the XEN® Gel Stent implantation were temporary hypotony <6 mmHg (24.6%), flat anterior chamber (9.2%) and mild hyphema (4.6%). In one year they discovered six leaks as a consequence of the conjunctival incision for MMC application (9%) and four cases of impaired visual acuity (12). In terms of significant consequences, Schlenker et al. [36] noted four cases of malignant glaucoma (0.4%), and Mansouri et al. reported [37] one cases of retinal detachment (0.1%).

SUMMARY

The number of MIGS approaches has expanded rapidly in the past decade. A heterogeneous group of technics used in the treatment of glaucoma gives a possibility to choose personally tailored therapy for each patient. Micro-invasive glaucoma surgery methods are characterized by high safety profile and they effectively reduce IOP, being a good option for patients with mild and moderate glaucoma [25]. They also offer to reduce the medication burden for patients.

However, there are some concerns about MIGS procedures. One of them is the long-term IOP lowering effect of MIGS, because most of them have been commercially available for less than 5 years now, so there is not enough evidence of the possible failure of a device over time. Another issue involves the lack of randomized clinical trials comparing different MIGS technics with one another and with standard therapy options [16].

Further prospective randomized trials are needed to form good evidence-based guidelines that will enable clinicians to assess the best therapeutic method for their patients. Nevertheless, with the growing popularity and demand for new therapeutic options, new instruments will be probably developed in upcoming years, combining existing methods or giving an all-new approach.

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Keratoprosthesis

Aleksandra Jany[1,2], Julia Górczyńska[1,2], Michał Gebuza[1,2], Agnieszka Kowal- Lange[3], Magdalena Targońska[3], Joanna Bogusławska[3], Jan Gnus[1,3]

1. Wroclaw Medical University, Wrocław, Poland
2. Students' Research Group of Ophthalmic Surgery, Wroclaw Medical University, Wrocław, Poland
3. Regional Specialist Hospital in Wroclaw, Research and Development Center, Wrocław, Poland

List of abbreviations

OOKP- Osteo-odonto-keratoprosthesis
PKP- Penetrating keratoplasty
SJS- Stevens-Johnson syndrome
MMP- Mucous membrane pemphigoid
BKPro- Boston keratoprosthesis
USA - United States of America
PMMA- Polymethyl Methacrylate
IOP- Intraocular pressure
MOOKP- Modified Osteo-Odonto-Keratoprosthesis
RPM- Retroprosthetic membrane
PHEMA- Polyhydroxyethylmethacrylate

INTRODUCTION

In 2020, it was estimated that 43.2 million (55% women-23.7 million) were blind, and 295.3 million had moderate or severe visual impairment. By 2050 the number of blind people is estimated to reach up to 895.5 million. With the world population aging we face significant challenges in preventing visual disabilities. Visual impairment and blindness are associated with reduced economic, educational and vocational opportunities and an increased risk of death. In addition, in old age, visual impairment significantly affects quality of life especially

in the elderly causes an increased incidence of depression, intensifies associated diseases such as cognitive impairment and risk of falls. One of the causes of visual impairment and blindness is corneal diseases. Knowing that the world's population is aging this problem will intensify with the passage of time [1]. Corneal diseases are the second leading cause of blindness in most developing countries. There are estimated 4.9 million bilaterally corneal-blind people in the world for which a corneal transplant could potentially restore sight. This represents 12% of the 39 million blind, using 2010 WHO data on global blindness and 2002 WHO sub-regional causes (updated with 2010 data). Based on India's prevalence ratio of bilateral and unilateral corneal blindness of 0.1% to 0.56%, it is estimated that unilateral corneal blindness affects 23 million people worldwide [2].

Keratoprosthesis commonly referred to as artificial corneas implants provide a great achievement in the world of medicine to prevent vision loss caused by corneal diseases. This treatment method was pioneered by French ophthalmologist Guillaume Pellier de Quengsy in 1789 [3]. They are used when penetrating keratoplasty (PKP) has been unsuccessful or has little chance of success, including eye trauma, herpetic keratitis, Stevens Johnson syndrome (SJS), mucous membrane pemphigoid (MMP), severe eye burns and pediatric corneal diseases [4]. The scarcity of donor corneas in many regions of the world means that traditional keratoplasty cannot have a significant impact on corneal blindness where its prevalence is the highest. Many studies have shown that keratoprosthesis implantation is very effective in restoring vision with very good short-term results. They are used in "last eyes" [5].

GENERAL INFORMATION

Keratoprosthesis are artificial corneal implantations which are used to replace a patient's diseased cornea [6]. Keratoprosthesis are made of transparent plastic with excellent tissue tolerance and optical properties [3]. There are also Osteo-Odonto-Keratoprosthesis (OOKPs) constructed from the patient's dental root and alveolar bone to support a central optical cylinder. They are most often covered with a mucosal graft taken from the buccal [7].

Four models are currently in use: the Boston keratoprosthesis, OOKP, AlphaCor and the KeraKlear artificial cornea, of which the Boston keratoprosthesis (BKPro) type 1 is the most widely used [8]. As of January 2019, more than 19,000 BKPro type 1s had been implanted worldwide, making it the most commonly used artificial cornea in history [5].

Its counterpart, the BKPro type 2, is used much less frequently. It is mainly used in dry, keratinized eyes with extensive eyelid abnormalities [8].

The best prognosis for keratoprosthesis implantation is for non-scarring conditions such as dystrophies, degeneration, bacterial and viral infections, while the intermediate prognosis is for aniridia, keratosis herpetiformis, chemical trauma, chemical burns while the worst prognosis is for Stevens Johnson syndrome (SJS) and autoimmune diseases.

Occasionally impairment of visual acuity is observed after implantation of a keratoprosthesis the cause of which is the development and progression of glaucoma. Reducing the development and progression of glaucoma as well as reducing the risk of other complications, can be achieved by combining pars plana vitrectomy with implantation of a glaucoma restraint device and BKPro [9].

BKPro

The pioneer of the BKPro usage in ophthalmology was Dr. Dohlman in the 1970s [5]. They are primarily used for patients with wet blinking eyes and without eyelid anomalies [10].

The front plate is made of medical-grade polymethylmethacrylate (PMMA). It consists of a front plate with an optical stem, a corneal allograft button and a back plate. The front plate is made of medical-grade polymethylmethacrylate (PMMA). The power of the device is determined by the radius of curvature of the optical surface, which is 3.5-3.7 mm in central diameter and 5 mm including the anterior plate. The edge of the anterior plate is refined so that the patient cannot feel foreign bodies and to ensure a smooth connection with the donor cornea. The central stem is built with an intraocular part and a blocking interface so that the light rays do not bend. The back plate is available in two versions: the original PMMA and the newer titanium. PMMA is a well-tolerated material that can be safely used intraocularly for a long time. Titanium provides excellent tissue tolerance in biological implants and also has high corrosion resistance, lightness and strength. It has no magnetic properties making it safe for patients to receive MRI scans. The back plate has sixteen round holes (each 1.17 mm in diameter) measuring 8.5 mm and eight round holes (each 1.3 mm in diameter) measuring 7.0 mm, which allows the flow of aqueous fluid into the graft. These holes reduced keratolysis to about 10% of cases.

Currently, produced are the inexpensive Auro KPro artificial cornea models manufactured by Aurolab in India and the Lucia keratoprosthesis whose radial aperture design

and brown color improve cosmetic appearance [5]. Before implanting the BKPro device patients' social and personal conditions should be taken into consideration. It is important that patients use well-fitting contact lenses to improve hydration and reduce the formation of epithelial defects and keratolysis. They should also remember not to use toxic eye drops too often. Contact lenses should be regularly replaced and disinfected. Patients who do not use lenses after BKPro surgery show an increased risk of postoperative complications including infection. The top priority is the prevention and treatment of glaucoma. They require lifelong follow-up and close monitoring to prevent complications. If patients do not adhere to medication or follow-up appointments they are not good candidates for surgery.

After surgery the presence of symptoms such as infiltrates on the recipient could indicate possible infection and air bubbles under the anterior plate as a sign corneal tissue loss should be carefully evaluated. Currently, diagnostic imaging is of great value to follow up patients with BKPro especially diagnostic posterior endoscopy, ultra-wide-field imaging and optical coherence tomography [8]. It is important to remember that patients with established glaucoma are at higher risk of permanent irreversible vision loss after KPro implantation therefore require close monitoring and aggressive treatment after the procedure [11]. Traditional intraocular pressure measurement is impossible in patients with a K-Pro implant. In the author's experience the best way to keep IOP under control is to perform eye biometry - changes in the axial length of the eye are the best correlation of increased or lowered intraocular pressure.

Indications

BKPro should be implanted only in wet and blinking eyes.

- Bilateral limbal stem cell deficiency
- Hypotony
- Silicon oil-filled eyes
- Extensive corneal neovascularization
- Neurotrophic keratitis
- Multiple graft failure
- Severe keratitis
- Stevens-Johnson syndrome
- Ocular cicatricial pemphigoid
- Aniridia

- Chemical injury
- Herpes keratitis
- Primary congenital glaucoma with concomitant corneal edema or opacities
- Iridocorneal endothelial syndrome
- Gelatinous drop-like dystrophy
- Extensive deep corneal stromal neovascularization [4,5,8,12].

Contraindications:

- ➢ Infants, young age
- ➢ Patients with good vision in one eye (~20/50 or better)
- ➢ Eyes with end-stage glaucomatous visual loss
- ➢ Severe optic neuropathy
- ➢ Chronic retinal detachment
- ➢ Macular scar
- ➢ Chronic cystoid macular edema

Complications:

- ➔ Retroprosthetic membrane (RPM)
- ➔ Corneal melt
- ➔ Chronic hypotony
- ➔ Retinal detachment
- ➔ Sterile keratolysis
- ➔ Leakage of aqueous and frank extrusion of the device
- ➔ Glaucoma
- ➔ Infectious Keratitis
- ➔ Endophthalmitis
- ➔ Sterile vitritis
- ➔ Vitreoretinal complications (choroidal/suprachoroidal/vitreous hemorrhage, cystoid macular edema, choroidal effusion, and epiretinal/preretinal membrane) [5,8].

OOKP

OOKP was first performed in Italy by surgeon Dr. Benedetto Strampelli in 1963 and modified later by Dr. Falcinelli (MOOKP) [13].

Strampelli noted that gutta-percha would remain in the root canal of a tooth indefinitely but if implanted into the soft tissues it would be rejected. Therefore, the idea developed that if a plastic acrylic implant could be placed in a piece of the patient's tooth and bone and the whole placed in the corneal envelope the tooth and bone would form a stable autograft frame for the acrylic. The procedure has been improved over the past few years and the new changes have been described as the Rome-Vienna protocol [5,14].

OOKP has an excellent profile in terms of long-term retention especially for patients with severe ocular surface disease, severe dryness, poor vision, missing eyelids, absent lids, eyelid anomalies in which BKPro cannot be used [9].

It is characterized by the greatest permanency of all available keratoprosthesis. It is important to remember that a multidisciplinary approach and involvement of an ophthalmologist, oral surgeon, and radiologist is very crucial [14].

It is made of a synthetic optical medium placed inside an alveolar lamina covered by the buccal mucosa. The alveolar plaque is usually taken from a canine of the patient so it is important to carefully evaluate the condition of the oral cavity. Canine is the best tooth by having the longest and largest root and the best quality alveolar bone. The function of the buccal mucosa is to protect physically and supply nutrition to the bone part of the lamina. OOKP being a biological tissue has excellent integrity of the synovial membrane and the benefits are incomparable to any synthetic material. Surgery with OOKP is performed in one eye-with the best visual potential-or in the only eye. The second eye can be treated as a backup in case of failure of surgery in the first eye [14,15].

Patients who have no teeth or whose condition prevents donation can benefit from an OOKP or KPro tibial bone allograft transplant. Allografts are taken from living related donors or after compatibility testing unrelated donors. However, when the above options are used retention results in some centers are poorer than with autografts [15]. The buccal mucosa and lamina should also be observed after the operation.

Local and systemic antibiotics are required for OOKP as well as oral GCS. Systemic immunosuppression should be administered after allografts and acetazolamide should be administered in the final stage until the intraocular pressure (IOP) normalizes. Crucially, the patient should use an overnight ointment with a broad-spectrum antibiotic for the rest of life. The optic cylinder should be cleaned with the juice of a freshly cut lemon using a sterile cotton-tipped applicator.

Indications

The patient should fulfill all of the following criteria:

- Severe dry eye and/or severe irreversible eyelid damage
- Poor prognosis for conventional keratoplasty with high risk of rejection
- Severe visual loss due to corneal opacity uncorrectable (<6/60 in eye with better vision)
- Severe Sicca syndrome
- Limbal stem cell deficiency

Common indications:

- Chemical injury
- Thermal injury
- Mucous membrane pemphigoid
- Trachoma
- Stevens-Johnson syndrome
- Corneal failure after vitrectomy with silicone oil filling that can't be removed safely,
- Lyell Syndrome
- Loss of the lids (e.g. Crouzon disease)
- Uveitis
- Graft versus host disease

Contraindications:

- ➢ Age under 18
- ➢ No light perception in qualified eye
- ➢ Advanced glaucoma
- ➢ Vision >6/60
- ➢ Eyes with no perception of light
- ➢ Phthisis bulbi
- ➢ Severe damage to the optic nerve
- ➢ Severe retinal detachment
- ➢ Tuberculosis
- ➢ Disapproval on the part of the patient for lifelong follow-up, cosmetic appearance of the operated eye, risk of complete loss of vision in the operated eye and complications, multi-stage follow-up and repeat surgeries [14,15,16,17].

Complications:

- ➔ Mucous membrane overgrowth occluding the optic
- ➔ Ulceration
- ➔ Exposure of the lamina
- ➔ Intraocular infection
- ➔ Vitreous hemorrhage
- ➔ Choroidal detachment
- ➔ Loss of laminar volume and integrity
- ➔ Aqueous leak
- ➔ Risk of damage to the parotid duct during preparation of the mucous membrane covering
- ➔ Oromaxillary fistula formation, fracture of the mandible, and damage to the adjacent teeth during preparation of the lamina
- ➔ Retroprosthetic membrane formation

The above method has very good results and patients can achieve visual acuity up to 6/4 [14,15]. It should be remembered that surgical revisions are necessary in every patient and the OOKP itself requires a long-term commitment from the patient to maintain. Patients therefore require specialized care. The cumulative cost of maintenance and surgical revisions is a major disadvantage of OOKP [10].

Complications are a danger often involving abnormal IOP, buccal mucosa, plaque, or retina [15].

However, they are more rarely reported with OOKP than any other material. In recent years researchers have focused on discovering new materials that can replace the tooth while increasing the adhesion between the optic cylinder and surrounding tissues in the eye. Significant improvements in long-term outcomes can be achieved through improvements such as the use of mitomycin C to prevent epithelial proliferation over the prosthesis. For OOKP we can expect the best long-term results in the treatment of severe end-stage uveitis or ocular surface inflammation. After surgery, limited peripheral vision is observed, but the ability to move, read, recognize faces, eat and dress independently is coming back [14].

Unfortunately, few places in the world perform this procedure due to among other things the complexity of the procedure and cost [9].

AlphaCor

It is the latest synthetic keratoprosthesis measuring 7.0 mm in diameter and 0.5 mm in thickness which was approved by the FDA in 2002 for adult patients with corneal blindness at high risk of having a PKP surgery [18]. Inflammation must be excluded and the presence of a satisfactory tear film must be demonstrated [19].

It consists of a peripheral part composed of a porous layer of synthetic polymer poly[2-hydroxyethyl methacrylate] (PHEMA) with a transparent central optical core that forms a hydrogel throughout [17,20]. The pores allow biointegration into the surrounding corneal tissue. The device is currently available in two strengths: AlphaCor-A for patients with aphakia and AlphaCor-P for patients with aphakia or pseudophakia [19].

The operation consists of two stages. In the first stage the central posterior corneal lamina is removed and an intraocular cavity is created, into which an AlphaCor sizer instrument is placed to measure size and centration. In the next step the posterior disc is removed via a 3.5 mm intrastromal trephine. Subsequently, the device is inserted and the incision is closed, often also covering the surface with a Gundersen conjunctival flap, especially in cases where the ocular surface and limbal stem cell function are compromised. An amniotic membrane graft may also be used in addition. Contact lenses with high oxygen transmission also have their uses. Stage two is performed after about 3 months in which the central 4 mm of the conjunctival flap and anterior corneal lamina are trephined thereby removing the suprachoroidal conjunctiva formed by the Gundersen flap [17,19].

Indications:

- Patients that are not candidates for traditional penetrating keratoplasty
- Severe, debilitating corneal disease causing blindness
- Healthy eyelid
- Good tear film
- Absence of active inflammation
- Blindness in the 20/200 – light projection range in the eye to be operated
- Most recent graft > 12 months ago
- Evidence of functioning retina

Contraindications:

- ➢ Ocular cicatricial pemphigoid (relative contraindication)
- ➢ Severely dry eyes

- ➢ Disordered eyes
- ➢ Inflamed eyes
- ➢ Stevens- Johnson syndrome
- ➢ Uncontrolled IOP
- ➢ Smoker unwilling to stop
- ➢ Children or patients unable to provide informed consent
- ➢ Patient unable to tolerate a general anesthetic lasting 1–2 h

Complications:

- ➔ Corneal Melt
- ➔ Retroprosthetic membranes (RPM)
- ➔ optic deposition
- ➔ aqueous leakage
- ➔ endophthalmitis
- ➔ extrusion
- ➔ surface spoliation [17,19,21,22].

Unfortunately, the surgeries are performed in only a few centers. The purpose of the AlphaCor artificial corneas was also to avoid the threatening complications that occur as after PKP - progressive glaucoma, intraocular inflammation and retinal detachment. They are flexible and have the right shape which allows for a relatively non-invasive implantation procedure. Very important for the success of the procedure is the proper selection of patients for AlphaCor implantation. HSV infection previously considered an exclusionary factor for AlphaCor is now not a risk factor for melts. The glaucoma and drainage devices have no effect on retention. Implantation does not appear to impair glaucoma control [19].

Currently, gelatin is being considered for the AlphaCor, the purpose of which would be to increase the biointegration of the device. Also under study is the addition of a commoner that protects against UV radiation. This would avoid UV-related retinal damage. Other studies are focusing on the use of a comonomer that would prevent calcification, reducing the risk of deposits within the optic [20].

For long-term maintenance of the AlphaCor, it is crucial to achieve complete and stable epithelialization of the entire device and proper biointegration into the corneal stroma. Constant

follow-up is very important for AlphaCor implantation. Unfortunately, post-implantation care is challenging and time-consuming [19].

KeraKlear

It is a single-piece non-penetrating artificial cornea without a back plate or locking ring the purpose of which is to create a clear window in the non-illuminated cornea [19]. It is indicated to exclude inflammatory forms of corneal blindness such as keratoconus, corneal dystrophies, corneal scarring and corneal edema. It is made of a transparent, biocompatible polymer. Measuring 7 mm in diameter with 4 mm central optics. Its capability is to replace between 200 and 700 μm of corneal tissue in 100 μm intervals. There are six different models on the market: the XT200, XT300, XT400, XT500, XT600 and XT700. The names represent the amount of tissue to be replaced. It is recommended that the surgeon leave about 100 μ of corneal tissue behind the pocket during surgery. The artificial cornea is positioned inside the patient's cornea on a thin layer of the recipient's posterior stroma. The prosthesis is fixed inside the corneal socket through a peripheral flap containing holes through which partial-thickness sutures are passed. During the operation, a femtosecond laser is used. KeraKlear is implanted using a non-penetrating technique in contrast to other available artificial corneas. It is available in 44 diopter (D) phakic and 60 D aphakic versions.

The unquestionable advantage of KeraKlear is the short learning curve for the procedure. It is well tolerated and provides similar improvements in visual outcomes compared to PK and other available KPros. It provides rapid visual recovery with improved vision visible immediately after leaving the surgical table and stabilization in a few weeks. No increase in intraocular pressure or worsening of glaucoma has been observed after surgery with KeraKlear. Another advantage is that the number of patients can also be expanded due to the ability to reduce the need for corneal transplant tissue and the use of both sterile operating rooms and clean surgery rooms [23,24,25].

Indications

- Corneal blindness VA of 20/200 or worse
- Noninflammatory anterior corneal disease
- Eyes in patients who have declined to have standard penetrating keratoplasty performed with donor tissue

Contraindications:

- ➢ Stevens- Johnson syndrome
- ➢ Ocular cicatricial pemphigoid
- ➢ Atopic keratoconjunctivitis
- ➢ Full thickness opacity
- ➢ Severe dry eyes with a Schirmer test score of less than 3 mm at 5 minutes with anesthesia
- ➢ Uncontrolled ocular inflammation
- ➢ Active infection
- ➢ Corneal thickness less than 300 microns anywhere on the cornea
- ➢ Inability to receive eye drop medications on a daily basis
- ➢ Allergy to acrylic materials
- ➢ Inability to protect the operated eye from trauma
- ➢ Continual exposure to cigarette smoke

Complications:

- ➔ Corneal melting
- ➔ Extrusion of the artificial cornea
- ➔ Retroprosthetic opacity
- ➔ Infection occurring months or years after implantation
- ➔ Opaque deposits within the optic
- ➔ Discoloration of the optic [19,23,24].

CONCLUSIONS

In selected patients, implantation of keratoprosthesis can be an effective and often the only option for visual rehabilitation. A special group to dedicate keratoprosthesis are patients for which corneal transplantation from a deceased donor is not possible. The last decade has seen a rapid increase in the number of Kpro procedures performed worldwide [26]. Although they are often used to treat bilateral corneal blindness, they can also be used to recover binocular vision in unilateral blindness [15]. Preparation of the ocular surface in severely damaged eyes is an important step that increases the success of surgery. A very crucial role to consider is postoperative care, which should be carried out by a multidisciplinary team. Glaucoma, which limits outcomes, remains a challenge for years to come, so it is very important to focus on new studies toward precise devices that control

the intraocular pressure [5]. A multidisciplinary team is needed to provide the best care for patients [27].

Keratoprosthesis are constantly being developed with newer generation materials, but the cost of surgery is very high which may be the biggest problem at the moment. The knowledge of keratoprosthesis and the experience of surgeons are expanding every year, leading to an expansion of indications while giving many patients a chance to see [9].

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Summarized pathology and retinal manifestation management of Herpesviridae

Maria Kręcicka[1], Julia Drewniowska[1], Magdalena Góral[1], Hanna Zając - Pytrus[1,2]

1. Wroclaw Medical University, Wrocław, Poland
2. Department of Ophthalmology, Wroclaw Medical University, Wrocław, Poland

List of abbreviations

AIDS-acquired immunodeficiency syndrome

ARN- acute retinal necrosis

CMVR – Cytomegalovirus Retinitis

DNA- deoxyribonucleic acid

HIV - human immunodeficiency virus

NHR- Necrotizing herpetic retinopathies

PCR – Polymerase Chain Reaction

PORN- progressive outer retinal necrosis

RD- retinal detachment

INTRODUCTION

Herpesviruses are prevalent and major-league group of pathogens which cause infections in many animal species. Among people these viruses lead to multiple syndromes, starting with common skin-mucosal lesions and ending with life-threatening infections. It is confirmed that they may have an impact on carcinogenesis [1–3].

In this review general pathogenesis of herpesviruses, diagnostics and treatment in both immunocompetent and immunodeficient patients will be presented. Our goal is to define current knowledge of the clinical course of eyes' diseases caused by herpesviruses, especially the herpes simplex virus, the varicella zoster virus and the cytomegalovirus.

SYSTEMATIZATION

Herpesviridae family includes 8 types of viruses which can infect people

SUBFAMILY	VIRUS	ABBREVIATION
Alphaherpesviridae	Herpes simplex 1	HSV-1
	Herpes simplex 2	HSV-2
	Varicella-zoster	VZV
Betaherpesviridae	Cytomegalovirus	CMV
	Human betaherpesvirus 6A/B	HHV-6
	Human betaherpesvirus 7	HHV-7
Gammaherpesviridae	Epstein-Barr virus	EBV
	Human gammaherpesvirus 8	HHV-8

Table based on the International Committee on Taxonomy of Viruses (ICTV) regulations.

They have a similar structure. Their DNA (dsDNA, linear) is packed in icosahedron-shaped capsid which is covered by a glycoprotein-lipid sheath. Between the capsid and the sheath characteristic amorphous protein layer called tegument can be found. Tegument's proteins are fundamental to identifying the type of virus [4].

Furthermore, there are differences in the genomic frame – HSV-1 with HSV-2 are known for their unique long and short coding sequences with regions of repeating segments [5]. HSV-1 infections affect mostly the upper part of the body [5]:

- oropharyngeal cavity,
- brain,
- cerebral meninges,
- eye,
- also skin or even genitals (this one is usually caused by HSV-2).

In this review only ophthalmic complications will be discussed.

These are nine times out of ten initiated by HSV-1 and include for example herpes, conjunctivitis, keratitis, disciform keratitis, iritis, iridocyclitis, and acute retinal necrosis (ARN). Another virus, the cytomegalovirus, might be transmitted in early life stages by the

placenta or later for example by sexual contact or kisses. CMV infections usually are asymptomatic in immunocompetent individuals [6].

However, in patients with AIDS, or patients during immunosuppressive therapy, CMV is responsible for opportunistic retinitis (cytomegalovirus retinitis) [7].

Another member of the Herpesviridae family, the varicella zoster virus, is the main factor causing ARN in immunocompetent patients and progressive outer retinal necrosis (PORN) in patients with immunodeficiencies.

Herpes viruses have a special common denominator – the ability to latency. It allows them to induce silent infections. In this paper the focus will remain on retinal manifestations caused by viruses mentioned above.

PATHOGENESIS ON THE EXAMPLE OF HSV - 1

There are two ways of entry into the host cell – endocytosis or fusion between viral envelope and cell membrane. In processes of adsorption and entering glycoproteins like gB, gD, and complex of gH/gL are crucial, glycoprotein gC is not necessary but its absence reduces the strength of the bind virus-host cell [8].

The portals of entry are mucosal surfaces, especially the oropharyngeal mucosa[9]. The virus propagates, which causes lysis of cells and the formation of bubbles filled with numerous virions. Once replication begins, the viruses travel to the spinal ganglia in the posterior roots via the sensory nerves supplying the area.

THE SLEEPING VIRUS

Primary infections of the facial region are associated with the trigeminal ganglion – where the latent virus harbours [9]. Viral DNA is integrated into neuronal DNA. After weeks or months, HSV-1 reactivates – this may be brought on by sunlight, menstruation or operative procedure.

Primary infection of VZV, which results in chickenpox, may be associated with leaving the latent form of the germ hidden in the cerebral or posterior root ganglia. Renewed activation might happen even several decades later and be manifested by ophthalmological symptoms.

CMV infects from 50 to 80% of people, usually during early life. It remains latent for the life of most individuals [10].

If it reactivates in a healthy carrier, there might be no symptoms present, as it is normally controlled by the immune system. However, in patients who failed to generate the primary T-cell response, for example after an organ transplant or with existing disorders, CMV can cause serious damage [11].

CLINICAL ANALYSIS OF RETINAL DISORDERS

Necrotizing herpetic retinopathies (NHR), such as ARN and PORN, include several entities which are caused by VZV, HSV 1 and 2, CMV, and rarely EBV. They are relatively seldom, but if occurred, must be treated as absolute emergencies, requiring urgent antiviral therapy. A spectrum of clinical pictures depends on the specificity of the virus and, what is essential, the host's immune status.

DIAGNOSIS OF VIRAL RETINITIS

When the clinical examination indicates ARN, further methods confirming the diagnosis are advised. Some of said laboratory methods include serum or intraocular fluid antibody testing, retinal biopsy, viral culture, and immunocytochemistry[12], however, they are often found limited by lack of availability and risk to the patient.

PCR

The diagnostic procedure proves highly precise in identifying viral DNA from small aqueous or vitreous samples using Polymerase Chain Reaction. PCR enables us to determine the specific virus type in ARN cases. Correct conduct of laboratory testing is crucial, as acute retinal necrosis may present with clinical features resembling other disorders. A negative PCR result suggests other causes. There is no definitive proof of significant difference when using aqueous or vitreous samples [12].

PCR is crucial in differentiating by which form of the virus the retinitis was caused - HSV, VZV, CMV. It can also help eliminate the suspicion that the changes were caused by other pathogens, such as Toxoplasma gondii [13].

Clinical examination

- **ARN** - The majority of patients present with symptoms such as pain, redness, photophobia, floaters, and blurred vision. During slit lamp exam, careful examination

of the anterior chamber will reveal unilateral anterior uveitis with or without granulomatous or stellate appearing keratic precipitates. As the disease progresses and cellular immunity to the virus is stimulated, dense vitritis may develop. Ultrasonography can let us see beneath the haze of vitritis and may be useful for assessing the onset of retinal detachment. Upon fundoscopic examination, multiple focal, well-defined areas of whitening in the peripheral retina will be present. If treatment is not initiated in time, areas of retinal whitening and necrosis may become confluent and progress to involve the posterior pole [14].

- **VZV -** The diagnosis of PORN caused by VZV includes some specific clinical features, such as the appearance of outer retinal opacification, minimal or absence of ocular inflammation, bilaterality and multifocality. Subtle whitening of the posterior pole of the retina is often observed. The clinical term “cherry red spot” is used here to explain the visible effects of ischaemia, retinal edema, or retinal artery occlusion. In this case, the swelling and loss of transparency in the macula are detected [15].
- **CMV -** One of the features that allow recognizing CMVR from more aggressive HSV, is the slow replication rate of CMV (about every 18 hours) [16]. CMV initially infects the retinal vascular endothelium and later spreads into the surrounding retina. That is the probable cause of distinctive, superficial, granular appearance and pattern of spread. The classic arc-shaped patch of retinitis is most likely produced by the infection of one of the major vascular arcades. This variant is called ‘fulminant’ retinitis. CMVR can also present as ‘indolent’ - infection of small vessels leads to multiple, inner retinal, small, peripheral lesions [16].

Further testing

Viral meningoencephalitis has been reported in association with ARN. In patients presenting neurological symptoms, it is advised to continue further testing, such as a lumbar puncture, magnetic resonance imaging and computer tomography [14].

ACUTE RETINAL NECROSIS IN IMMUNOCOMPETENT PATIENTS

Acute retinal necrosis is a viral-induced retinitis syndrome. Not immediately treated ARN leads to vision loss and retinal detachment (RD). VZV and HSV are the most common causes. CMV and EBV may also lead to ARN, although less frequently [17].

Treatment

It is important to note, that in patients with suspected ARN, treatment should not be delayed by waiting for the PCR results.

In order to stop the progression of the disease in the affected eye and prevent it from spreading to the fellow eye, the treatment with intravenous acyclovir was initially described. Methods additional to antiviral medication include aspirin, corticosteroids, laser retinopexy and vitrectomy [17].

Recent reports have presented the benefits of administering intravitreal antiviral agents. The most common initial treatment of ARN is intravenous acyclovir and oral valacyclovir. Intravitreal foscarnet or ganciclovir may be administered as adjuvant local therapy, however, they cannot be used alone - they leave the fellow eye at risk of developing the disease [14].

In immunocompetent patients acyclovir-resistant HSV strains are very rare. Recently, oral antiviral therapy with intravitreal foscarnet has become a more popular option than intravenous acyclovir, as it does not require hospital admission [14].

Systemic antivirals have known adverse effects, for which patients require routine monitoring [14].

Geriatric and renal patients require dose adjustments and it must be placed under careful attention, whether the patient is taking other nephrotoxic medications [14].

In order to decrease the severe inflammatory response associated with ARN, corticosteroids can be administered, both topically and orally [14].

Systemic Therapy

Palay et al conducted a study of ARN treatment with acyclovir in immunocompetent patients [14].

Out of the 54 patients with unilateral disease, 31 were treated with intravenous acyclovir 1500mg/m2/day for 7-10 days and then oral acyclovir for 2-4 weeks (unknown dose and frequency) and the remaining 23 patients were observed [14].

Of the treated patients, 87% remained disease-free in the contralateral eye versus 30% of the untreated patients [14].

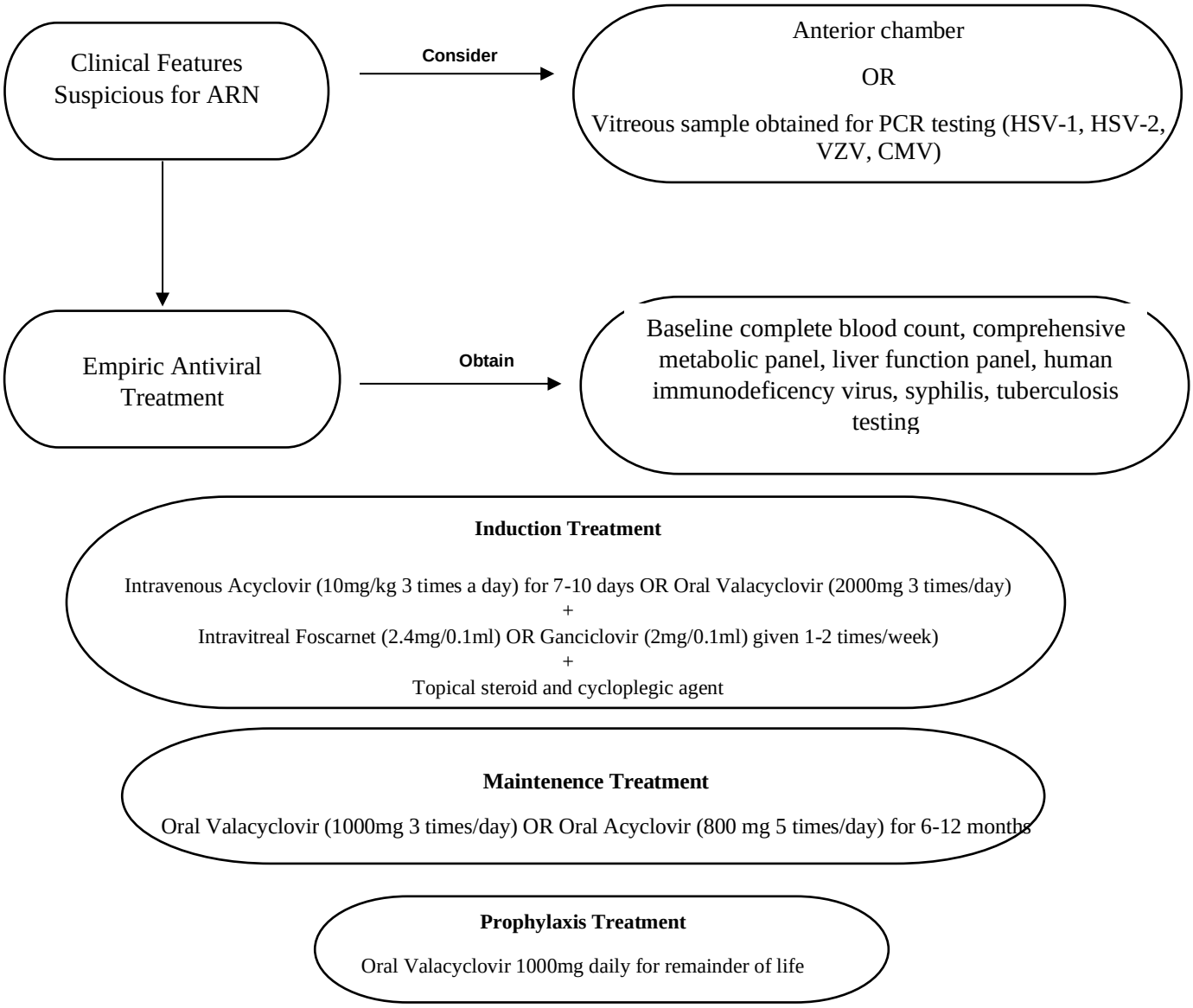

Figure 1. Recommended treatment algorithm of acute retinal necrosis [14]

SECONDARY INFECTIONS CONNECTED WITH IMMUNODEFICIENCY

Having considered the clinical manifestations caused by herpes viruses and the latency of their forms, we should take into account the possibility of developing secondary ocular infections among vulnerable individuals. Opportunistic retinal infections are responsible for morbidity among immunosuppressed or immunocompromised patients, not only those with acquired immunodeficiency syndrome (AIDS) [18].

The most precisely documented disorders in those cases are CMV retinitis and progressive outer retinal necrosis (PORN), although retinopathies are typically associated with immunocompetent states, such as acute retinal necrosis (ARN), which are also described in some clinical examples[19]. Conversely, PORN detected in HIV – negative patients may be understood as an intermediate form of these two NHRs [19,20].

CYTOMEGALOVIRUS RETINITIS??

There are a lot of different medical reports which connect human immunity conditions with the presence of a reactivated form of CMV, causing a secondary infection known as cytomegalovirus retinitis (CMVR) [18,21].

Typically, CMVR has been associated with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) [22].

Nevertheless, the increasing number of various modern immunosuppressive therapies appears to be one of the most alarming risk factors for CMV reactivation [23].

Through the hematogenous spread, the virus attacks the retina, which is usually manifested by bilateral retinal opacification, local full-thickness necrosis, and oedema. Wedge-shaped areas of whitening, associated hemorrhage, and smaller granular lesions are detected during the fundoscopy [24].

Less typical signs in the vascular type of CMVR may develop as retinal vasculitis, associated with perivascular sheathing (characteristic ‘frosted branch angiitis’). CMV retinitis usually starts in the peripheral area of the retina, progressing to the center and then posterior pole at the rate of more than 2 mm per day. Progressive necrosis involving the macula or the optic nerve leads to serious visual impairment, not rarely resulting in complete loss of vision and irreversible blindness. Exudative retinal detachment is a real threat as well[23]. It is worth mentioning that CMVR is not the only possible entity caused by cytomegalovirus in immunocompromised patients. Distinguished from the aforementioned but equally well–recognized, acute retinal necrosis (ARN) may be that second variant [24].

It most often occurs here as a bilateral syndrome consisting of peripheral necrotizing retinitis, retinal vasculitis, and notable anterior chamber and vitreous inflammation. Polymerase chain reaction studies of the vitreous biopsy might help the specialist to make a correct diagnosis[24] and introduce the proper treatment immediately.

Treatment

The main goal of treatment, which includes oral, intravenous, and intravitreal therapeutic agents, is to prevent further lesions of the retina. The therapy of CMV infection usually consists of 2 phases, the induction phase and the maintenance phase. The first one is usually continued until the first clinical response to the drugs. During the maintenance phase, when the drug dosage is reduced, it is essential to monitor the possible signs of retinitis reactivation.

Ganciclovir

The medicine is being used in intravenous, oral, or intravitreal therapy. Ganciclovir is infused intravenously twice a day at a dose of 5 mg/kg for 2 to 3 weeks. After this time, the drug is given at a maintenance dose of 5 mg/kg daily. If the maintenance therapy is continued for weeks or months, a peripherally inserted central catheter may be a good solution. Lower ganciclovir doses should be applied to patients with renal impairment. Myelosuppression, such as anemia, neutropenia, and thrombocytopenia are the dose-limiting toxicity factors. Clinical research shows that oral ganciclovir is inferior to intravenous ganciclovir because it fails to reach therapeutic serum levels [25]. It has to be taken in high doses, usually at 3000 to 6000 mg per day. The drug approved in the treatment of CMV retinitis is the L-valyl ester prodrug of ganciclovir, valganciclovir, absorbed and hydrolyzed by hepatic and gut esterases into ganciclovir. The induction therapy includes 900 mg of valganciclovir twice daily for 21 days. The proper dose in the second phase is 900 mg once a day. The bioavailability of oral valganciclovir is approximately 10 times higher than oral ganciclovir at the standard doses [26].

Intravitreal ganciclovir therapy enables the drug to concentrate in the retina, without affecting the bone marrow suppression. The safe doses which have been injected without visible retinal toxicity vary from 200 mg/0.1 mL to 2000 mg/0.1 mL per injection [27].

Implant

Ganciclovir intravitreal implant is made of polyvinyl alcohol/ethylene vinyl acetate. It is implanted surgically, by a pars plana incision. The drug is released from a 4.5 mg capsule into the vitreous cavity at a constant rate of 1 μg/hour over 7 to 8 months.

A randomized study by Musch et al was carried out on 188 AIDS patients with CMV retinitis. The patients were randomized to treatment with a ganciclovir implant of 1 mg/hour,

a ganciclovir implant delivered at 2 mg/hour, or intravenous ganciclovir. The study showed that a ganciclovir implant, compared with intravenous therapy, delayed the time of the progression of retinitis. In the 1 mg/hour group the median time of retinitis progression was 221 days, in the 2 mg/hour group - 181 days, and in the intravenous ganciclovir group - 71 days. However, it is important to note, that the treatment with intravenous ganciclovir presented a lower risk of developing extraocular manifestations of CMV disease compared with the ganciclovir implant. Endophthalmitis, rhegmatogenous retinal detachment, cystoid macular edema and vitreous hemorrhage are among the possible complications [27].

Foscarnet

Another method of treatment is the use of foscarnet - a pyrophosphate analog of phosphonoacetic acid. The drug's main task is to inhibit the viral DNA polymerase and reverse transcriptase in patients with AIDS. Foscarnet can be administered intravenously at a dose of 60mg/kg 3 times a day for 3 weeks with maintained therapy at a dose of 90mg/kg daily after. The greatest advantage of using foscarnet is that initially implemented it gives a longer survival rate in patients with AIDS than ganciclovir does[28]. It is necessary to be aware of some side effects of foscarnet therapy. Metabolic and electrolyte abnormalities such as symptomatic hypocalcemia are frequent adverse reactions. Also, nephrotoxicity, tremors or diarrhea can appear [27].

Cidofovir

Cidofovir requires less frequent administration than ganciclovir and foscarnet and it delays the progression of previously untreated retinitis. Induction dosing is 5 mg/kg per week for 2 weeks, after that during the maintenance phase, the advised dose is 5 mg/kg every other week. Cidofovir treatment is also beneficial for patients, for whom ganciclovir and foscarnet therapy was unsuccessful. Mutations of the viral DNA may cause resistance to cidofovir. Long-term use is limited due to the risk of nephrotoxicity [27].

VARICELLA ZOSTER AND PORN

Differentiation of clinical pictures depends on the immune status of the patient. For this reason, VZV secondary infection might develop in several forms. Progressive outer retinal

necrosis (PORN), described first in 1991 [19], is the one affecting immunocompromised hosts, especially those suffering from AIDS [22].

The disease is characterized by multifocal, deep, homogenous necrotic retinal infiltration[19] without the presence of intraocular' inflammation. In some cases, minimal vitreous inflammation can be detected [29]. Extremely rapid progression leads to complete retinal necrosis and gives a rather bad visual prognosis. A lot of new lesions located in the posterior pole and peripheral retina are continuously observed [29]. The optic nerve remains at risk of becoming quickly inflamed and destroyed. A high possibility of retinal detachment is present as well. Patients with PORN usually complain of constriction of their visual field and of complete vision loss afterwards [30]. Keeping in mind the significant improvement of visual prognosis, adequate therapy should be introduced as quickly and decisively as possible.

Treatment

In a case report from 2016 [20] a patient began intensive antiviral therapy with acyclovir. Intravitreal ganciclovir (2 mg/0,1 mL) therapy twice weekly for 3 weeks was added, due to the very rapid progression of the disease with macular involvement. Unfortunately, neither of these treatments was able to prevent the progression of the damage in the eye. This reflects the current ineffectiveness of PORN treatment.

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SELECTED PROBLEMS IN ONCOLOGY

The role of GREM1 expression in pancreatic and gastric cancer

Ewelina Jałonicka

Medical student, Faculty of Medicine, Collegium Medicum Cardinal Stefan Wyszynski University in Warsaw, Warsaw, Poland

PURPOSE

The purpose of this study is to review the scientific literature on the role played by the GREM1 protein in pancreatic and gastric cancer with particular emphasis on potential therapeutic use.

METHODS

The work is of a review nature. Scientific reports on the topic addressed were reviewed. The PubMed search engine was used, with the search terms "pancreatic cancer" AND "GREM1" and "gastric cancer" AND "GREM1". The search results covered the time frame of 2009 - 2022 and 2005 - 2022, respectively. From the results, papers were selected for inclusion in the review. In addition, the publication was enriched with literature outside the above search to supplement the information.

INTRODUCTION

Pancreatic cancer is the leading cause of death among people diagnosed with cancer worldwide with a pathogenesis that is still not fully understood. In 2017, there were 441,000 such cancers diagnosed worldwide. This number is twice as high as two decades ago. By comparison, 196,000 cases of pancreatic cancer were diagnosed in 1990. The 5-year survival rate is still low. However, it has increased - from < 5% in 1990 to as high as 9% in the United States and Europe in 2019 [1].

Pancreatic cancer is characterized by cellular heterogeneity. This appears to be related to paracrine signaling of mesenchymal cells [2].

Gastric cancer is one of the leading causes of death worldwide. Unfortunately, despite the treatment undertaken, up to 30 - 40% of patients have a relapse within 5 years. There are several subtypes of gastric cancer - intestinal, diffuse and histologically indeterminate subtypes [3].

Abnormal Hedgehog gene signaling contributes to the carcinogenesis of many cancers including pancreatic and gastric cancer. Hedgehog signaling induces the process of cell proliferation, and therefore one can attempt to inhibit Hedgehog signaling using appropriate inhibitors. It is believed that in the treatment of cancer, Hedgehog inhibitors should be used together with tyrosine kinase inhibitors, G protein-coupled receptor modulators and/or irradiation of the tumor lesion [4].

The GREM1 protein prevents bone morphogenetic proteins (BMPs) from binding to their receptors, likely plays a significant role in human tissue differentiation, and there is emerging evidence that it is expressed in many malignancies. The results of one scientific study indicate that GREM1 expression correlates with, among other things, smaller tumor size, less lymph node involvement or a higher likelihood of 5-year survival [5].

It therefore seems appropriate to undertake research in the context of GREM1 and such difficult-to-treat cancers as pancreatic and gastric cancer.

WHAT IS GREM1?

GREM1 is an antagonist of BMP proteins 2, 4, 7 and can block the BMP signaling pathway. It plays an important role in organogenesis or tissue differentiation, for example [5, 6].

The GREM1 gene is located on chromosome 15q13-q15. It encodes a glycoprotein capable of inhibiting the BMP pathway - antagonism of BMPs 2, 4 and 7 occurs, which translates into the fact that ligands and receptors cannot interact. This results in inhibition of transforming growth factor beta signaling. It is likely that GREM1 can affect angiogenesis. The activity of this gene is suppressed by promoter hypermethylation in human malignancies [7]. Based on in vitro studies, GREM1 inhibits BMP2-mediated osteoblast differentiation - so it is a BMP2 antagonist. It impairs monocyte chemotaxis (it is an inhibitor of monocytes). In addition, it attenuates BMP4 signaling in a dose-dependent manner [7].

It appears that GREM1 may be associated with mixed polyposis. In the literature, one can find descriptions of families with hereditary mixed polyposis syndrome in which

duplications of the GREM1 gene of 40 kb on chromosome 15 have been detected. Overexpression of the gene allows epithelial cells to retain properties similar to those of stem cells. This can lead to the formation of ecotopic crypts and subsequent neoplastic changes [8]. We assessed what contribution the GREM1 mutation has in familial colorectal cancer in a Jewish Ashkenazi family. Among the 472 individuals with a duplication in the GREM1 region - 194 were found to have familial colorectal cancer, 131 had another type of cancer (endometrial, pancreatic or ovarian cancer) that are nevertheless related to colorectal cancer, and 147 were cancer-free. It seems that genetic testing for GREM1 mutations can help prevent colorectal cancer [9].

GREM1 VS. NOGGIN

Both GREM1 and Noggin proteins are involved in bone morphogenetic protein (BNP) pathway signaling. GREM1 and Noggin inhibit the BMP signaling pathway, which is involved in tumorigenesis, thus these two proteins can be called BMP pathway inhibitors. Laurila et al. examined their expression on healthy and tumor tissues. In most samples, healthy as well as cancerous tissues showed no or weak GREM1 expression. In the case of healthy stomach and skin, clear expression of GREM1 could be found. This was also true for the Noggin protein. For cancer tissue samples, the expression patterns were more variable. However, elevated expression of these two proteins was found in several cases. In the case of GREM1, these included glioma, hepatocellular carcinoma, diffuse B-cell lymphoma, and in the case of the Noggin protein, granular kidney tumor and papillary thyroid carcinoma. In general, BMP antagonists show weak expression on healthy and tumor tissues compared to bone morphogenetic protein 4 (BMP4), but there are examples where their expression will also be higher in certain types of cancer, indicating a potential role in BMP signaling in cancer [10].

PANCREATIC CANCER AND GREM1

Pancreatic ductal adenocarcinoma (PDAC) contains both epithelial and mesenchymal carcinoma cells in its structure. The cellular heterogeneity of PDAC is an important feature in distinguishing this disease subtype. The molecular mechanisms responsible for what cell fate will be in PDAC are still unknown. Lan et al. identified BMP-inhibitor GREM1 as an important factor responsible for the heterogeneity of the structure of this type of cancer in humans and

mice. In the mouse study, inactivation of GREM1 resulted in direct conversion of epithelial cells into PDAC mesenchymal cells. On the other hand, GREM1 overexpression led to almost complete epithelialization of highly mesenchymal PDAC. GREM1 also reduced epithelial-mesenchymal plasticity. Thus, suppression of BMP activity, e.g., by the presence of GREM1, is essential for maintaining epithelial cells in PDAC. We can also conclude that the cellular heterogeneity of pancreatic cancer requires continuous paracrine signaling by a single factor [11].

We investigated the relationship between GREM1 and another protein, the sonic hedgehog homolog (SHH), and what effect GREM1 has on pancreatic cancer. GREM1 protein was found to be overexpressed in pancreatic cancer - particularly in the stroma. GREM1 levels were significantly correlated with survival rates, among other things. In turn, SHH appeared to be a promoter of GREM1 expression. In addition, GREM1-related small interfering RNA (GREM1 siRNA) promoted the proliferation and migration of pancreatic stellate cells. Based on the data obtained, the study found that abnormal GREM1 expression levels in pancreatic cancer were associated with SHH signaling. In turn, GREM1 overexpression enabled pancreatic cancer progression. Thus, abnormal GREM1 protein expression was induced by SHH signaling. The in vitro results also suggest that GREM1 may promote the invasion of pancreatic cancer cells. Thus, it may be a therapeutic target or a potential marker of pancreatic cancer [12]. Chen et al. conducted a study in which they showed that GREM1 promotes angiogenesis in pancreatic endocrine tumors and may also be a new prognostic marker in this type of cancer [13].

GASTRIC CANCER AND GREM1

The role of GREM1 in the development and progression of gastric cancer was studied. Overexpression of the GREM1 gene significantly correlated with a lower chance of survival, and expression of the gene was also associated with tumor growth and lymph node metastasis. In in vitro studies, GREM1 promoted cell proliferation and tumorigenesis. Thus, increased GREM1 expression in gastric cancer is associated with disease progression and poor prognosis, and is likely involved in processes such as angiogenesis and lymphogenesis, for example [5].

Using immunohistochemical methods, the expression and distribution of GREM1 protein in the non-cancerous gastric mucosa of 159 patients diagnosed with gastric cancer. Of the 159 primary tumors, 37% were positive for GREM1 expression. Patients with GREM1-negative results had a lower survival rate than patients with GREM1-positive results.

Corresponding analyses showed that GREM1 expression is an independent predictor of survival in gastric cancer. Thus, the results not only indicate that GREM1 is involved in gastric cancer progression, but may also be a good marker of long-term survival in patients with this type of cancer [14]. Yamasaki et al. conducted a study in an attempt to clarify how GREM1 expression affects gastric cancer clinically and biologically. Out of 232 patients, 117 were classified as GREM1-positive tumor patients, and a positive result correlated with, among other things. with smaller tumor size, less lymph node or vascular involvement. The 5 - year survival rate was higher in the GREM1 - positive group than in the GREM1 - negative group. In the group of GREM1 - positive patients, it was 81%. Expression of GREM1 involved in the BMP pathway may have clinical applications. In particular, it appears to be a good diagnostic tool, being a useful prognostic marker in gastric cancer [15].

Icamp – A POTENTIAL NEW CANCER MARKER

One of the features of cancer is its ability to evade the human immune system. Oncogenesis is also favored by inflammatory processes. The hypothesis has been put forward that cancers, regardless of their histopathology, share a common inflammatory cancer-associated molecular pattern (iCAMP). Rachidi et al. defined such a common pattern for 7 types of epithelial cancer including pancreatic and gastric cancer (the others being lung, colon, prostate and oral cancer). It was also discovered that karyopherin alpha 2 (KPNA2) is significantly associated with poor cancer prognosis. It may be a new prognostic marker and may be useful in individualized patient treatment. The existence of such a pattern as iCAMP also underscores the importance of "onco-inflammation" in the course of ontogenesis. This type of inflammation contributes to tumor characteristics, for example, in the context of cellular proliferation, angiogenesis or the ability to evade apoptosis. The unnatural expression of certain genes in tumors of different histological nature suggests that different tumors may engage the host immune system in the same way so that growth and invasion of tumor cells is possible. [16].

SUMMARY

GREM1 appears to be an interesting therapeutic target that can be used in planning new cancer treatments. It also appears to be a good diagnostic tool and a useful prognostic marker

in gastric cancer, for example. In the case of pancreatic cancer, the results indicate that GREM1 is an important factor responsible for the heterogeneity of the structure of this type of cancer in humans and in mice. Thus, expanding scientific research in this area seems appropriate.

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Assessment of cancer-related fatigue: exploring the screening tools

Tomasz Jurys[1], Michalina Stepanik[2], Martyna Andreew[1,3], Bartłomiej Burzyński[2]

1. Doctoral School, Faculty of Health Sciences in Katowice, Medical University of Silesia in Katowice, Poland
2. Department of Rehabilitation, Faculty of Health Sciences in Katowice, Medical University of Silesia in Katowice, Poland
3. Scientific Study Group at the Department of Internal Nursing, Department of Internal Medicine, Faculty of Health Sciences in Katowice, Medical University of Silesia in Katowice, Poland

List of abbreviations

ASCO – American Society of Clinical Oncology

BFI – Brief Fatigue Inventory

CRF – Cancer-Related Fatigue

CFS – Cancer Fatigue Scale

ESMO – European Society for Medical Oncology

FACT-F – Functional Assessment of Cancer Therapy-Fatigue

FAQ – Fatigue Assessment Questionnaire

FQ – Fatigue Questionnaire

FSS – Fatigue Severity Scale

HPA – Hypothalamic-Pituitary-Adrenal axis

IARC – International Agency for Research on Cancer

MFI-20 – Multidimensional Fatigue Inventory-20 Items

NCCN – National Comprehensive Cancer Network

NICE – National Institute for Clinical Excellence

PFS-Revised – Piper Fatigue Scale-Revised

VAS – Visual Analogue Scale

INTRODUCTION

In 2020, International Agency for Research on Cancer (IARC) stated there were nearly 20 million new cancer cases and 10.0 million cancer death worldwide. Furthermore, worldwide growing of cancer's incidence and mortality was also observed. This leads to a position of cancer as a main cause of premature deaths is strengthened. It requires to create a complex infrastructure for cancer prophylaxis, early diagnosis and effective treatment [1].

The common problem affecting cancer population is chronic fatigue. It has a significant impact on the patient's quality of life, including physical, emotional, psychosocial and economic impairment. In accordance with the definition of National Comprehensive Cancer Network (NCCN): "Cancer-related fatigue (CRF) is a distressing, persistent subjective sense of physical, emotional, and / or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" [2].

PREVALENCE OF CRF

It is difficult to give a clear and detailed information about the prevalence of CRF among cancer population. It is caused by several factors like reporting differently the CFR in different studies. The possible reasons of that phenomenon are using various scales to evaluate the CRF, which are as different from each other as the construction of questions and results interpretation. Equally important, the CRF is subjective sensation which can be modified by the many factors (e.g. social support, own beliefs or personal experience). Study conducted by Ma et al. which is a meta-analysis of 84 studies shows that overall cancer-related fatigue prevalence was calculated to be 52% [3]. More frequently, the CRF affects women, population aged ≥ 65 years or chemoradiotherapy patients. Furthermore, that study presents possible risk of factors for CRF which could be insomnia, depression, poor performance status or even neuroticism [3]. According to an article published in UpToDate database concerning cancer-related fatigue, prevalence of CRF is estimated to 15 – 90% of cancer population and up to 75% of population with advanced cancer or bone metastases [2]. In turn, European Society for Medical Oncology (ESMO) recommendations indicate that cancer-related fatigue affects more than 60% of cancer population, whereby 40% of patients

experience fatigue at the diagnosis moment and up to 90% during radiotherapy and/or chemotherapy [4].

PATHOGENESIS OF CRF

Despite the chronic fatigue is widely reported problem among cancer population, the pathophysiology of CRF is still unclear. The pathogenesis seems to be complex and consists the physical, emotional, social and psychological factors [5]. One of the possible mechanism explaining cancer-related fatigue phenomenon is closely linked to disruptions in the nervous system concerning inflammation, regulation disorders of the hypothalamic-pituitary-adrenal (HPA) axis or reduced energy metabolism. The course and treatment of cancer disease may induce the network of pro-inflammatory cytokines and cause the symptoms of cancer-related fatigue (e.g. pain, insomnia, mood swings or cognitive impairment) through cytokine signalling pathways in the central nervous system. Stimulation of the immune system provokes the HPA axis dysfunction which affects the CRF development [6].

The HPA axis dysregulation causes the cortisol release disruption resulting in lack of the body protection from the immune system overactivity. Loss control of the tissue damage due to excessive inflammation could be linked to physical fatigue, circadian rhythm disorders and sleep deprivation. Physical fatigue could also be a consequence of the reduced energy metabolism. It is related to the sarcoplasmic reticulum and mitochondria impairment [6,7].

DIAGNOSIS

Understanding of the chronic fatigue (including cancer-related fatigue) was observed in the last years. However, the diagnosis process and specific international diagnostic criteria are not still well established. Current diagnostic criteria are proposed by Cella et al. for ICD-10 in 1998 [4,8].

Proposed diagnostic criteria are divided into four main groups (from A to D). Criterion A consists 11 common clinical symptoms observed among cancer population reporting fatigue. Authors proposed to meet criterion A, 6 of 11 symptoms must be present for 2 weeks daily over last month. Criterion B concerns the influence of fatigue on social and occupational aspects of life. Criterion C is designed to ensure that the fatigue symptoms come from cancer

disease or treatment. Finally, D criterion is proposed to exclude that fatigue are not a result of existing comorbid psychiatric diseases [8].

Despite the studies supporting the validity and reliability of the CRF diagnostic criteria, NCCN do not recommend their use [2,4].

Management of CRF

Therapeutic options for cancer-related fatigue consist pharmacotherapy, physical exercise, nutraceutical treatment, mind-body interventions, cognitive behavioural therapy and psychosocial interventions [4,9,10]. Pharmacological treatment is common option for chronic fatigue. Psychostimulants are used to increase the dopamine level in central nervous system, antidepressants for modulate brain serotonin or corticosteroids for pain control [4]. Physical exercise as a non-pharmacological treatment option is strongly recommended for cancer-related fatigue management [4,10]. Types of physical exercise (walking, nordic walking, ergometer cycling), resistance exercise or its combination. It is important that exercise program should be established individually to the needs of patient. Regular physical exercise may improve the functional capacity, cardiorespiratory fitness, increase muscle mass which in turn increase cancer patient's independence [4,11]. As regards the nutraceutical treatment, ESMO guidelines describing l-carnitine, coenzyme Q_{10}, mistletoe and Wisconsin ginseng extracts supplementation to ameliorate fatigue symptoms. However, the panel members recommend only consider using extracts of Wisconsin ginseng and mistletoe in CRF patients of all abovementioned nutraceutical treatment options [4]. Mind-body interventions including e.g. mindfulness-based stress reduction, yoga or acupuncture are also implement for cancer-related fatigue treatment. Mindfulness-based stress reduction programme includes meditation exercises, breath awareness, focusing on body sensations and elements of psychosocial education. Its purpose is increase body consciousness and improvement in fatigue, sleep, anxiety and fear of recurrence [4,10]. Yoga which key elements are physical poses and breath awareness can be proposed for cancer patients with fear of excessive physical exercises or as a starting point for regular training. Yoga also develops body consciousness and reduces stress and fatigue [10]. Finally, acupuncture in CRF management is reliable treatment option. There is recommended 20-30 minutes sessions few times a week for reduce sensation of fatigue and pain [12]. Cognitive-behavioural therapy is used for resolve the problem of fear of cancer recurrence, better control of difficult emotions associated with experience of cancer and also can help with sleep disturbances. Therapy is based on individual behaviour and

patterns of psychological functioning [13]. Psychosocial interventions for CRF treatment includes all methods in order to build self-help and self-care strategies. Its consists of psychoeducation, psychotherapy, relaxation techniques and energy conservation management [4,10].

Justification and aim of the study

The authors of present paper justify the selected topic by fact that using the validated tools for assessment cancer-related fatigue can improve understanding of chronic fatigue phenomenon among cancer population. It can increase the quality of management and treatment of the patients. The aim of the study is conducting a review of the most popular questionnaires assessing cancer-related fatigue.

Assessment of CRF

International guidelines, consensus and recommendations developed by e.g. National Comprehensive Cancer Network or National Institute for Clinical Excellence (NICE) indicate using questionnaires and symptoms-specific scales like supportive tools for assessing patients' expectations and needs [14]. It may include assessment not only physical distress, but also depression, anxiety, cognitive impairment and chronic fatigue caused by cancer or cancer treatment. Moreover, questionnaires allow to know patient's perspective and thus involve them as a active part of decision-making process [14,15].

In accordance with the American Society of Clinical Oncology (ASCO), each patient suffering from malignant neoplastic disease should be examined for the development of CRF during first diagnostic counseling, at the end of basic oncological treatment, and then according to clinical indications. Screening should be performed and described using standardized research tools [2].

VAS (Visual Analogue Scale)

Visual Analogue Scale as universal tool is also used for assess severity of cancer-related fatigue. Usually, VAS for fatigue is composed of 10-cm line with two endpoints: 0 (= no fatigue feeling) and 10 (= worst possible fatigue feeling). VAS for fatigue evaluation is rather used for rapid assessment over a daily period or before/after physiotherapy session [16,17].

BFI (Brief Fatigue Inventory)

An equally popular tool for assessing fatigue is the BFI questionnaire developed in the late 1990s. by Mendoza et al [2,18]. It consists of a total of 10 items grouped into 3 categories. The first is a single, non-scored question as to whether the last week's fatigue was different than usual and the possible answer is “Yes” or “No”. The next category of questions concerns the indication of the intensity of the experienced fatigue: at the moment, average over the last 24 hours, and the strongest over the last 24 hours. The answers to these questions are given by the respondents on a 0 to 10 scale, where 0 means no fatigue feeling, and 10 the strongest imaginable fatigue feeling. The third category brings together questions about the influence of fatigue on different aspects of life: general activity, mood, walking abilities, daily duties (work and home), relations with people and life enjoyment. Likewise, responses are given on an 11th point scale from 0 to 10, with 0 being no impact and 10 being total impact. The total result is the arithmetic mean of all scored responses and is understood as the global fatigue score. A score of 1 to 3 indicates a feeling of mild fatigue, from 4 to 6 a moderate, and a score of 7 to 10 indicates a severity fatigue. The BFI questionnaire is strongly recommended by the National Comprehensive Cancer Network [2].

FSS (Fatigue Severity Scale)

FSS was constructed by Krupp et al in 1989 containing 9 items in the form of affirmative sentences, which the respondents must refer to by marking the answer on a scale from 1 to 7, where 1 means a strong negation, and 7 strong consent [19]. The items relate to the impact of fatigue, including on: the level of motivation to act, physical functioning, fulfilling professional and home duties, family and social life. The result of the questionnaire is the sum of all answers, ranging from 9 to 63 points, where the higher result means the higher level of fatigue [19]. However, it is more and more often proposed that the overall result of the FSS questionnaire should be the arithmetic mean of all responses, which allows the test person to obtain a result in the range of 1 to 7 points. The following interpretation is then proposed: a score below 4 shows a low level of fatigue, between 4 and 5 - a moderate level, and above 5 points - severe fatigue [20].

CFS (Cancer Fatigue Scale)

Another tool developed to assess cancer-related fatigue is the CFS questionnaire, which was developed by Okuyama et al [21]. CFS contains 15 questions that are grouped into

three main domains: physical, affective, and cognitive. Each of the questions contained in the questionnaire is answered on a scale from 1 to 5, where 1 means "No", 2 - "A little", 3 - "Slightly", 4 - "Significantly", 5 - "Strong". The score for individual scales is calculated in accordance with the formulas proposed by the authors and ranges from 0 to 28 for the physical domain and from 0 to 16 points for the affective and cognitive domains - higher score shows a higher level of fatigue [21].

MFI-20 (Multidimensional Fatigue Inventory – 20 Items)

The MFI-20 questionnaire is a tool for measuring the severity of various types of fatigue developed by Smets et al. [22]. The questionnaire consists of 20 questions to which the respondent answers on a scale from 1 to 5, where 1 is the answer that most strongly confirms the statement, and 5 is the answer - the most negative. The questions included in the questionnaire are grouped into five domains: general, physical, and mental fatigue, decreased motivation, and decreased activity. In each of the domains, the obtained result ranges from 4 to 20 points, which is then converted into values in the range from 20 to 100. Obtaining a higher result means a stronger fatigue [22,23].

FAQ (Fatigue Assessment Questionnaire)

Fatigue Assessment Questionnaire originally was developed by Glaus and Miller in 2001, but the current standardized version was established by Beutel et al in 2006 [24]. FAQ consists 20 items grouped into 3 domains: physical domain (11 items), affective domain (5 items) and cognitive domain (3 items), but also single item “sleep disorder” concerning last week. Each of the questions contained in the questionnaire is answered on a scale from 0 to 3, where [24]:

- 0 means “Not at all”,
- 1 – “Hardly”,
- 2 – “Moderately”,
- 3 – “Strongly”.

Obtaining a higher result means a higher level of fatigue [24].

FQ (Fatigue Questionnaire)

Fatigue Questionnaire is a tool for measure the fatigue in general practice settings and was developed in 1993 by Chalder et al [25]. FQ is composed of 11 items grouped into two

domains: physical symptoms of fatigue (items: 1 – 7) and mental symptoms of fatigue (items 8 – 11). Each of the questions contained in the questionnaire is answered on a scale from 0 to 3, where 0 means "Better than usual", 1 – "No more than usual", 2 – "Worse than usual" and 3 – "Much worse than usual". Obtaining a higher result means a stronger fatigue [25].

PFS-Revised (Piper Fatigue Scale – Revised)

PFS– Revised version was developed in 1998 and contains 27 items, 5 of which are additional open-ended items not used to calculate of total fatigue scores. 22 items are grouped into four domains: behavioural/severity, affective meaning, sensory and cognitive/mood [26]. The answers to these questions are given by the respondents on a scale from 0 to 10. The result for individual subscales is determined in accordance with the formulas proposed by the authors and ranges from 0 to 10 for all domains and total fatigue score. Obtaining a higher result means a higher level of fatigue [26].

FACT-F (Functional Assessment of Cancer Therapy – Fatigue)

FACT-F questionnaire is a tool developed in the middle of the 1990s by Yellen et al. [27]. It is consisted of 41 items grouped into 5 subdomains [27]:

- physical well-being (7 items),
- emotional well-being (6 items),
- social/family well-being (7 items),
- functional well-being (7 items);
- fatigue (13 items).

The answers to these questions are given by the respondents on a scale from 0 (= "Not at all") to 4 (= "Very much so"). Obtaining a higher result means a higher level of fatigue [27].

CONCLUSION

Symptom-specific scales and questionnaires are tools to measure various aspects of patients' lives, i.e. quality of life, activity and / or participation limitations. They can be used both for diagnostic and prognostic purposes and in determining the effectiveness of the undertaken therapeutic interventions.

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Physiotherapeutic management of bladder cancer patients undergoing radical cystectomy: a review and account of professional experience

Tomasz Jurys[1], Martyna Andreew[1,2], Monika Dzierzawa-Kloza[3], Kamil Burzyński[4], Bartłomiej Burzyński[5]

1. Doctoral School, Faculty of Health Sciences in Katowice, Medical University of Silesia in Katowice, Poland
2. Scientific Study Group at the Department of Internal Nursing, Department of Internal Medicine, Faculty of Health Sciences in Katowice, Medical University of Silesia in Katowice, Poland
3. Department of Electrocardiology and Heart Failure, Faculty of Health Sciences in Katowice, Medical University of Silesia in Katowice, Poland
4. UROSILESIA Center of Physiotherapy, Zabrze, Poland
5. Department of Rehabilitation, Faculty of Health Sciences in Katowice, Medical University of Silesia in Katowice, Poland

List of abbreviations

CRF – Cancer-Related Fatigue
ERAS – Early Recovery After Surgery
GLOBOCA – Global Cancer Incidence, Mortality, and Prevalence Project
MIBC – Muscle Invasive Bladder Cancer
NMIBC – Non-Muscle Invasive Bladder Cancer
TURBT – Transurethral Resection of Bladder Tumor
WHO – World Health Organization

INTRODUCTION AND AIM

Bladder cancer is one of the most common urological neoplasms, contributing to the deaths of 196,500 people annually worldwide and thus being categorized as the 9th and 19th most frequent cause of cancer-related deaths among men and women respectively.

Epidemiological data on bladder cancer from the last 20 years are, however, difficult to obtain due to the negligible number of literature studies. According to Safiri et al., who refer to the latest epidemiological data from the Global Cancer Incidence, Mortality, and Prevalence Project (GLOBOCAN), there were 524,000 cases of and 229,000 deaths due to bladder cancer in 2019 alone [1]. A study by Teoh et al. contains the most recent data on the incidence of bladder cancer, based on three sources, namely GLOBOCAN, the Cancer Incidence in Five Continents database, and the World Health Organization (WHO). These show that men are more likely to develop bladder cancer as the incidence rate ranges from 1.3 / 100,000 men in South Africa to 26.5 / 100,000 men in Southern Europe while the incidence rate among women is much lower, ranging from 0.8 / 100,000 women in South-Central Asia to 5.5 / 100,000 women in Southern Europe. On average, the worldwide number of deaths among men is 3.2 / 100,000 men, and among women 0.9 / 100,000 women [2,3,4]. Taking into account age, in 2019 the highest incidence rate for both sexes occurred in people aged >95 years: on average, 214.4 cases / 100,000 men (from 168.1 to 243.2) and 63 / 100,000 women (from 46.1 to 73.4). The number of cases was also elevated among people in the age categories 70–74 years and 75-79 years. The highest percentage of deaths was observed among people aged 80-84 [1].

According to GLOBOCAN, the main, confirmed risk factors for developing bladder cancer are smoking and high fasting levels of blood glucose [1].

Further individual factors that may contribute to the development of bladder cancer include age (advanced), sex (male) and race (white). A diet characterized by low levels of hydration, low consumption of citrus fruits, cruciferous vegetables, vitamins A, D, and folate, and high consumption of processed meat can also contribute to the development of bladder cancer. Additionally, environmental factors, such as working or living in industrial areas, which can increase exposure to 2-naphthylamine, benzidine, 4-aminobiphenyl or polyaromatic hydrocarbons, may heighten the risk of disease [6].

The diagnosis of bladder cancer, both Non-Muscle Invasive Bladder Cancer (NMIBC) and Muscle Invasive Bladder Cancer (MIBC), is complex and should be based on comprehensive medical history, cystoscopy, cytological examination of urine sediment, and possibly additional imaging tests (computed tomography, magnetic resonance imaging, ultrasound). An additional diagnostic method is bladder biopsy carried out during the Transurethral Resection of Bladder Tumor (TURBT) procedure [5].

Radical cystectomy is the current gold standard treatment for localized bladder cancer

in patients with pathologies classified as T2–T4a, N0–Nx, M0 [7]. This procedure involves removal of the urinary bladder as well as associated organs (among men – usually the prostate gland, among women – the uterus, ovaries, part of the vagina) and surrounding lymph nodes. As successful employment of minimally invasive surgical techniques has been observed, there is growing interest in robot-assisted and laparoscopy-assisted radical cystectomy. However, in spite of these advances, mortality and morbidity rates remain poor in comparison with those for other urogenital cancers [8].

In recent years, physiotherapy has become an intrinsic element in the management of patients undergoing oncological surgery. It has been successfully employed even before surgery, with the aim of improving the functioning of the patient and preparing the body for the procedure. Physiotherapeutic interventions are also used in the first days after surgery and are aimed at early mobilization and elimination of the effects of immobilization. In the case of bladder cancer, physiotherapy also focuses on the functioning of the pelvic floor muscles which, if compromised, may result in urinary incontinence.

The aim of the our study is to present a review of possible physiotherapeutic interventions which can be applied among bladder cancer patients undergoing radical cystectomy. Due to the dearth of studies dealing specifically with physiotherapy for bladder cancer, we have decided to take into account studies concerning physiotherapy for cancer and cancer surgery more generally. A second aim of the present study is to share our own experiences of physiotherapeutic management of bladder cancer patients.

PHYSIOTHERAPY AS A PART OF PREHABILITATION

Poor preoperative cardiopulmonary fitness, comorbidities and unhealthy habits (smoking tobacco and poor diet) presented by cancer patients are risk factors for post-surgical outcomes, functional capacity and health-related quality of life [9]. Therefore, prehabilitation protocols for improving the health status of patients ahead of surgery are more and more commonly applied in healthcare interventions [10]. Prehabilitation is a collection of interventions which focus, among other things, on pre-surgical nutritional counselling, anesthetic and analgesic care, thrombolytic and respiratory tract infection prophylaxis, pain control management and physiotherapy [8]. Its purpose is to improve surgical outcomes, decrease perioperative complications and shorten recovery times in hospital.

One of the particular objectives of physiotherapy before radical cystectomy is reduction of the consequences of post-surgical immobilization. Prolonged immobilization in a lying position increases the risk of chest immobility and thus the weakening or ineffectiveness of the cough and sneeze reflexes, which may lead to impairment of pulmonary ventilation. A further possible effect of prolonged immobilization after surgery is deep vein thrombosis, which is commonly localized in the lower extremities. Finally, cardiopulmonary immobility may lead to poor wound and tissue healing [11]. Healthcare professionals – in particular physiotherapists – should therefore aim to improve patients' cardiopulmonary fitness in the pre-surgical period through intensive education concerning anticoagulant and breathing exercises and through planning programs of adequate physical activity (type, frequency, and duration). Physiotherapists should also explain and demonstrate to patients how to change position in a manner which avoids or reduces pain, and educate them about how to walk safely with surgical incisions. All of the above taken together can decrease the risk or severity of post-surgical complications. However, the patient's full involvement in the prehabilitation process is essential to the successful achievement of such goals.

PHYSICAL ACTIVITY INTERVENTIONS BEFORE AND AFTER CANCER SURGERY

The impact of physical activity interventions on cancer patients' wellbeing has become a focus of interest in recent years [10,12]. More precisely, physical activity programs for people suffering from cancer at all stages of the disease and treatment pathways have been implemented in order to improve treatment outcomes as well as health-related quality of life. The benefits of exercise programs among cancer patients may result from several potential mechanisms including, among others, improved immune response and vascularization of tumors. Therefore, a growing number of studies have assessed the possible benefits of physical activity as a supportive treatment for cancer. However, a scoping review by Bessa et al. indicates that current recommendations regarding physical exercises for bladder cancer patients are largely based on aerobic/cardiovascular training, while there is a lack of studies on other types of physical activity in relation to different stages of bladder cancer. Studies considering physical activity aimed at strengthening pelvic floor muscles and thereby improving continence are likewise in short supply [12].

Further important but neglected questions include 1. which type of physical activity is to be recommended at particular stages of bladder cancer or of treatment pathways and 2. how to intensify exercises effectively, which is an issue of particular significance as the majority of the relevant cancer population comprises elderly patients presenting high levels of physical inactivity. In summary, the scoping review indicates deficiencies concerning the implementation of physical activity in accordance with global WHO guidelines.

Physical activity programs for bladder cancer patients are recommended even before radical cystectomy due to their positive effects on peri- and postoperative functioning. Programs should consist of aerobic exercises, resistance exercises and flexibility training [13,14]. However, to increase the chances of patients' participation in such programs, exercises should be designed in a clear and enjoyable form [10], and patients should be given a choice of exercise setting, i.e. health center-based or home-based. Due to the current tendency to shorten the length of hospital stays, home-based physical exercises programs are becoming increasingly common as a part of prehabilitation therapy or self-management after cancer surgery. Healthcare professionals may supervise physical activity programs by telephone or by using communication platforms or other long-distance communications devices [15]. Aerobic exercises can be prescribed in the form of moderate-intensity continuous training or high-intensity interval training. A single session of aerobic training (moderate or high-intensity) is typically 20-60 minutes long, although shorter sessions of at least 10 minutes may also be beneficial [10]. Resistance training is also recommended for improving the physical functioning of cancer patients. Exercise programs should comprise major muscle group exercises with equal concentric and eccentric phases, and include antagonistic muscle groups. The planning of adequate rest between repetitions, sets and sessions is also significant [16]. Flexibility training should also be a part of physical activity programs, its aims being to preserve or improve mobility and habits of posture and to contribute to the prevention of injuries [10]. Moreover, a review conducted by Jensen et al. highlights the point that traditional physical exercise programs may also contain specific activities which are dedicated to individual needs, e.g. pelvic floor exercises for urinary incontinence or breathing exercises for heavy smokers [10].
A systematic review conducted by Rammant et al. indicates that exercises during and after bladder cancer treatment can be beneficial, improving health-related quality of life and physical fitness and relieving pain and fatigue. However, this review found only three studies assessing the impact of exercises on patients undergoing radical cystectomy [17].

First study assessed the influence of postoperative training programs consisting of strengthening exercises, mobility training, balance training, endurance training and stretching exercises on health-related quality of life and physical fitness versus standard care. This program was performed twice a week for 45 minutes for 12 weeks and supervised by a physiotherapist. The study showed significant effects of the exercise program not only on physical functioning after 14 weeks ($p=0.031$) but also on walking after 14 weeks ($p=0.013$) and after one year ($p=0.010$).

Second study investigated a 2-week preoperative exercise program including endurance and strength exercises performed twice a day and a 1-week postoperative exercise program consisting of respiratory and circulatory exercises but also muscle strength and endurance training implemented twice a day. The impact of this training program on health-related quality of life, personal activity in daily living, pain symptoms, in-patient satisfaction and mobilization, muscle leg power and walking was assessed. Study found significant differences between baseline and after 4-month follow-up in dyspnea ($p=0.05$), constipation ($p=0.02$), abdominal flatulence ($p=0.05$) and urinary problems ($p=0.05$). Moreover, a significant 7-day postoperative improvement in personal activity in daily life ($p\leq0.05$) and in walking ($p<0.001$) was observed, and muscle leg power significantly increased 14 days after baseline ($p<0.006$).

Final study evaluated the impact on physical fitness of a 4-week preoperative aerobic exercise program using a cycloergometer performed twice a week for 60 minutes with an intensity of 70-80 HR_{max}. The results showed significant improvement for all parameters (VO_{2max}, VO_2, V_E, and oxygen pulse; $p=0.001$, $p<0.001$, $p=0.001$, and $p<0.001$ respectively) except the anaerobic threshold ($p=0.500$).

Due to there being only three such exercise studies, moreover with focus on disparate types of intervention, timing, duration, and assessment of outcomes, it is difficult to arrive at firmly-grounded recommendations for physiotherapeutic practice based on this systematic review [17].

EARLY PHYSIOTHERAPY AFTER SURGERY

Abdominal and pelvic oncology surgery is connected with a significant decrease in physical and psychosocial functioning, leading to lower health-related quality of life and a rise in dependency on other people [18]. Early mobilization after surgery, composed largely of

exercises and education regarding bedside and off-bed activity, can improve functional well-being and expedite postoperative healing by bringing about recovery of cardiopulmonary fitness and muscular strength [18-20].

It is important because delayed activity after radical cystectomy may result in prolonged hospitalization and recovery [19].

In view of the lack of sufficient studies, in terms of both quantity and quality, concerning physiotherapeutic management in the early post-surgical period after radical cystectomy, the decision was taken to incorporate into this paper studies from the broader cancer and surgical physiotherapy literature.

Designed protocols for early physiotherapy after surgery which focus primarily on early patient mobilization are not very widespread on surgery and cancer wards. However, strategies for rapid implementation of single physiotherapeutic interventions postoperatively are becoming the norm. A comprehensive review by Wessels et al. indicates that early mobilization on the day of surgery or the day immediately following it is recommended in 84% of early recovery after surgery (ERAS) protocols (N=21) and is included in their qualitative synthesis [19].

Early postoperative physiotherapies include breathing exercises, anticoagulant exercises, frequent upright positioning, and simple physical activity aimed at the restoration of cardiopulmonary fitness, muscle strength and mobility. Moreover, early physical rehabilitation allows patients to explore and challenge their current functional well-being and to identify barriers which restrict their activity. Physiotherapeutic interventions are also crucial in breaking the harmful downward cycle of weakness, discomfort, insomnia, fatigue, and difficulty with engaging in rehabilitation [21].

An interventional study by de Almeida et al. assessed early mobilization programs among 108 patients after major abdominal cancer surgery. The program implemented in the intervention group consisted of isotonic training, isometric training, core training and gait training versus standard rehabilitative care in the control group. Exercises were performed for 5 days after cancer surgery twice per day for 30 minutes. The findings indicated that physiotherapy focused on physical activity applied in the early post-operative phase enhances patients' health quality of life ($p<0.001$) and decreases symptoms of fatigue ($p<0.05$). Furthermore, a higher number of patients in the intervention group was able to gain walking independence [22].

A pilot study conducted by Silverdale et al. showed promising results in terms of improving well-being and relieving pain symptoms in the acute post-surgical period. Patients (N=38) on day one and day three after radical cystectomy obtained one hour of reflexology, massage, or a combination of both. Before therapy and immediately afterwards, pain and well-being levels were measured, and the intensity of pain symptoms evaluated again in the evenings. Results showed that wellbeing outcomes were significantly increased on day one and day three ($p<0.01$), while pain symptoms were significantly decreased on day one ($p<0.01$) but not day three ($p>0.09$). In this study, no significant differences in relation to the therapy applied (reflexology, massage, or both) were observed. In conclusion, the findings support the benefits of physiotherapeutic intervention in the early post-surgical phase [23].

MANAGEMENT OF CANCER-RELATED FATIGUE

A common and complex problem among cancer patients is cancer-related fatigue (CRF), which is defined as a disturbing, persistent, subjective feeling of physical, emotional and/or cognitive fatigue or exhaustion related to the course of treatment that is not proportional to activity undertaken and significantly disrupts everyday functioning. Cancer-related fatigue is distinguished from fatigue that accompanies everyday life in that the latter is usually temporary and relieved by rest [24,25]. It is estimated that CRF affects between 15 and 90% of cancer patients and, among patients with a malignant neoplasm or distant metastases, the percentage can be as high as 75% [24,26].

Providing active physiotherapy for those suffering from cancer-related fatigue can be difficult since patients often give up physical activity for fear of worsening symptoms. Patients notice the fact that, as a consequence of the disease and its treatment, they lose muscle mass, become weaker, and recover more slowly after physical exertion. Therefore, the undertaking of regular physical activity should be preceded by proper preparation of patients for a given load of physical exercise. Physiotherapists should teach patients how to plan activities and rest between them. It is equally important to skillfully formulate recommendations for patients, as this increases the effectiveness of physiotherapy and builds a sense of independence [27,28]. Initially, in order to build confidence in physiotherapy and prepare the motor system for physical exercise, it is recommended that selected elements of myofascial therapy be used because, for a patient with significantly reduced physical capacity and a negative attitude, this may be an especially engaging form of commencing physiotherapy [28]. The use of passive

techniques during the first physiotherapeutic consultations is an opportunity to change the attitude of cancer patients to regular physical activity, and it is also the appropriate time to conduct educational activities that build patients' awareness of their health condition and the possibility of self-help [28-30]. Classic massage also seems to be a promising physiotherapeutic intervention in the initial phase of physiotherapy. Research by Kinkead et al. conducted on a group of 57 oncological patients showed that a 6-week cycle of classic full-body massage, which was performed once a week for 45 minutes, reduced feelings of fatigue and improved quality of life [31]. In the course of individual myofascial therapy, the physiotherapist may gradually incorporate active therapy techniques and simple motor tasks. Such action is aimed at recreating correct movement patterns, learning to plan physical activity, and learning active relaxation. Thanks to this, a space is created for the transition from passive to active physiotherapy, which will be focused on building physical capacity, improving muscle strength and, consequently, increasing patients' motor independence [30].

The basics of aerobic and strength training, as well as their combinations, are used in the conduct of physical exercises in patients suffering from cancer-related fatigue. The benefits of regular aerobic training for people suffering from cancer include not only improving the values of cardiovascular and respiratory parameters but also reducing the intensity of fatigue, regulating the circadian rhythm, and improving the quality of sleep. It is worth noting that planning of aerobic training should be based on the results of functional tests, endurance tests, consultations with the attending physician, and conversations with patients [27,32]. Strength training is used to improve muscle strength, muscle trophies and bone density. To generate resistance in strength training, specialized equipment, elastic bands, weights or even the patient's own bodyweight may be used [27,33]. The load should be adjusted individually to the functional state of the patient, their needs and the goals of the physiotherapy. Many studies show that regularly performed strength training reduces the negative effects of oncological treatment, improves quality of life and increases the sense of motor independence [27-29]. A combination of aerobic and strength training is equally effective in the treatment of cancer patients. Research shows that either aerobic and strength training, or a combination of both, reduces feelings of fatigue and improves quality of life. It is recommended that training sessions last at least 20 minutes, usually 3 times a week, for a period of several weeks [32]. In patients suffering from cancer-related fatigue, yoga can also be a new and interesting form of activation. It does not require any special equipment or space, and today many free instructional materials and videos present and teach the basics of yoga. The benefits of regular yoga include improving

mobility, improving muscle strength, reducing feelings of fatigue, learning proper breathing, increasing body awareness, learning active relaxation, reducing levels of perceived stress, and improving quality of sleep [27,34].

OUR OWN EXPERIENCE

There are but few mentions of pelvic floor physiotherapy for the bladder cancer population in the available literature. Studies indicate possible benefits, in general, of pelvic floor exercises for incontinence after radical cystectomy and/or orthotopic bladder substitution [35], but there are no large-scale studies focused on the use of physiotherapeutic methods for bladder cancer patients in particular. The authors of the present study have therefore decided to share their own experiences in connection with functional diagnosis and physiotherapeutic management of bladder cancer patients.

Surgical treatment of bladder cancer and orthotopic bladder substitution require physiotherapeutic treatment focused on urinary continence. A crucial element of such physiotherapy is performing a functional diagnosis of the pelvic floor muscles, the lumbopelvic hip complex muscles and the abdominal muscles, as well as the genitourinary system. This diagnosis begins with anamnesis and questions concentrating on urinary and fecal continence. The key point of physical examination is the assessment of bladder substitution volume and the ability of the bladder to empty itself, that is, post-void residual volume. We would draw particular attention to the problem of the difference in feeling of bladder pressure before and after radical cystectomy and bladder reconstruction. Our patients commonly report a feeling of bladder pressure, which could be characterized a slight pain in the underbelly area, and the use of the abdominal muscles to empty the bladder. At our physiotherapy facilities, we use ultrasonography to assess pelvic floor muscle functions because we find that the elevation (lifting during volitional tension) of these muscles is crucial for improvements in urinary continence. Moreover, we use electromyography for both functional diagnosis and therapy in order to assess times of pelvic floor muscle tension and release. For this purpose, two-channel electromyography is used: one channel monitors pelvic floor muscle tension while the other assesses the peripheral muscles (e.g. the abdominal or gluteal muscles), which should not be activated during tension of the pelvic floor muscles. The electrode monitoring the pelvic floor muscles activity is commonly placed rectally, although it is also possible to place the self-adhesive electrodes perineally . Application of electrodes is also useful for electrostimulation

therapy. The parameters depend on the patients' clinical condition as well as on the aim of the therapy (e.g. strengthening or building awareness of pelvic floor localization). The number of physiotherapy sessions (using ultrasnography, electromyography and electrostimulation) is dependent upon the degree of urinary incontinence, the balance of the pelvic floor muscles in relation to the abdominals, and the functioning of the genitourinary system. Decisions regarding the number of sessions, the parameters of pelvic floor muscle training, and other physiotherapeutic methods (e.g. manual or physical therapy) are made individually in consultation with the patient.

As stated previously, physiotherapeutic management after radical cystectomy is focused on pelvic floor muscle function and urinary incontinence. However, we would also recommend the performance of therapy of the abdominal wall tissues by means of myofascial relaxation techniques or manual therapy, and that patients receive education concerning physical activity after cancer surgery and the phenomenon of cancer-related fatigue.

CONCLUSIONS

Physiotherapy is an integral part of comprehensive care for people with bladder cancer who have undergone radical cystectomy. Physiotherapeutic activities are carried out in many areas, as they focus both on improving the functioning of patients before surgery, but also on educating them and preparing them for the first days after radical cystectomy. In the later postoperative period, physiotherapy is used in the event of fatigue related to cancer and is also used to reduce the effects of long-term immobilization.

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Prophylactic mastectomy

Maja Mielczarek[1], Jan Sroczyński[1]

1. Faculty of Medicine, Faculty of Medicine, Medical University of Silesian Piasts in Wrocław, Wrocław, Poland
2. Faculty of Medical Sciences and Health Sciences, Faculty of Medicine, University of Technology and Humanities Casimir Pulaski in Radom, Radom, Poland

List of abbreviations:

BPM- Bilateral Prophylactic Mastectomy

HBOC- Hereditary Breast and Ovarian Cancer

NSM- Nipple-sparing Mastectomy

SSM- Skin-sparing Mastectomy

INTRODUCTION

Breast cancer is one of the most common cancers among women all around the world. According to WHO in 2020 2.3 million of women were diagnosed with breast carcinoma and 685 thousand died because of it. Thanks to the evolution of treatment methods as well as the spread of social awareness, by the end of 2020 there were almost 8 million women living with breast cancer, diagnosed in the previous 5 years [1].

In modern medicine there are various medical approaches to reducing the risk of developing the cancer as well as in managing it after it develops. Knowledge about genetic predisposition syndromes and testing people with high risk of having inherited mutations like BRCA1 or 2 allows them to receive careful monitoring and early detection of cancer, as well as education about possibilities of reducing the risk of breast carcinoma [2].

There are many treatment options including chemotherapy, radiotherapy or surgery. Mastectomy is both therapeutic and a risk-reducing procedure. Rates of mastectomies have been growing over the decades. It is a breast removal operation that can be either uni- or bilateral. There are different types of this surgery, depending on the extent of the invasive breast cancer. They include: radical mastectomy, modified radical mastectomy, simple or

total mastectomy, skin-sparing mastectomy and nipple-sparing mastectomy. Prophylactic mastectomy carried out in order to minimize the risk of cancer [3].

INDICATIONS

Prophylactic mastectomy is the most effective risk-reducing option for patients at high risk of developing breast cancer [4]. In the past it could be performed on women with painful breasts, cancer-phobia, any family history of breast cancer or history of breast biopsies [5].

Currently it concerns mostly women with hereditary breast and ovarian cancer syndrome (HBOC), who are carriers of BRCA1 or 2 gene. HBOC syndrome is associated with significantly higher lifetime risk of developing breast carcinoma (55-85%) [4].

More over breast carcinoma is often bilateral and multicentral in BRCA carriers [6].

Contralateral prophylactic mastectomy is an option for women who already have cancer in one breast and want to reduce the risk of developing it in another one. It also has some indications due to reconstructive consideration like symmetry and balance as well as for women with difficult surveillance because of dense, cystic and difficult to examine breasts or mammographically occult cancer [3].

The PROSE Study Group performed a research on BRCA ½ carriers after bilateral prophylactic mastectomy, controls being women with the same mutation without prior BPM surgery witha mean follow-up of 6.4 years. It found out that breast cancer was diagnosed in only 1.9% of 105 tested women after bilateral prophylactic mastectomy and 48.7% of 378 matched controls. The surgery reduced the risk of breast carcinoma by 95% in women with prior oophorectomy and 90% in women with intact ovaries [7].

Another study performed in 2001 by Meijers-Heijboer on 139 women with BRCA mutation, 76 of which have gone through BPM. Results have shown 100% reduction of breast cancer incidence in the group of women after breast removal after 2.9 years [8].

Similar outcomes have been reported by Hartmann and his study group on follow-up after 13.6 years on 26 women positive with BRCA gene that have undergone BPM [9].

Apart from significantly reducing the risk of developing cancer, prophylactic mastectomy has a positive effect on anxiety and fear of getting sick that often strongly compromise quality of life of BRCA carriers [6].

PROCEDURE

There are various technical approaches to risk-reducing mastectomy. As mentioned before it can be either bilateral or contralateral. Gold standard in surgical techniques currently seems to be nipple-sparing mastectomy (NSM) thanks to its ability to optimize oncological and aesthetic results [6].

NSM is based on removing all of the breast tissue including the ductal tissue with preservation of the nipple-areolar dermal layer. This allows the skin envelope of the breast to be intact, and leaves a good base for following breast reconstruction. There is a small risk of ischemic complications following nipple-sparing mastectomy leading to complete (2% of cases) or partial nipple necrosis (9.1% of cases) [3].

Another often used technique is skin-sparing mastectomy (SSM) that is very similar to NSM. In this case as well most of the skin is preserved and forms a pocket, facilitating immediate breast reconstruction [10].

The only difference is that SSM does not save the nipple-aureola complex, which gives it slightly better cosmetic outcome, sexual functioning and body image [11].

The nipple sensitivity, appearance and feeling of mutilation is noted to be more satisfactory after NSM [12].

BREAST RECONSTRUCTION

Breasts are widely considered a symbol of woman's femininity, sexuality and beauty. They are important part of motherhood and used for feeding infants [13].

That is why most women decide on performing breast reconstruction. Both skin-sparing mastectomy and nipple-sparing mastectomy require immediate breast reconstruction, because formed skin envelope tends to be shrinking with time. It can be performed with autologous tissue or implants [4].

There are various methods of breast reconstruction depending on the type of mastectomy and patient's needs [14].

Although the procedure takes place just after mastectomy, total completion of breast reconstruction may take up to 1-2 years, because of aesthetic corrections like nipple reconstruction or lipofilling [4].

It is also an invasive and major operation commonly associated with some adverse effects. Up to 40% of women may experience complications after mastectomy with reconstruction. In some cases it can require re-operation [15].

PSYCHOLOGICAL IMPACT

Regardless of possibilities formed by an advance in breast reconstruction surgery techniques, mastectomy still results in permanent change in body appearance of women [13]. Majority of women choose prophylactic mastectomy, based on emotional reasons. In a study evaluating psychosocial burden of positive BRCA gene status, results were clear that after diagnosis of hereditary breast and ovarian syndrome many women experience increased distress, symptoms of depression and anxiety in the first twelve months [16].

Evaluation of psychosocial effects of bilateral prophylactic mastectomy has shown that only around 5% of women were dissatisfied with their decision about undergoing BPM and it was reported to be more common among those that had the idea originated form physician's advise. Majority of women would choose BPM again and had no regrets about their decision [17]. Most of them would also recommend the surgery to other women in this situation [18].

Majority of women perceive their breasts as a very important part of their body image. The scale od psychological reaction to losing breasts is closely linked to an emotional value attached to them by woman [19].

Satisfaction with the cosmetic effects is usually based on an outcome of breast reconstruction. In a study performed in 2000 by Frost, around 70% of women were satisfied or very satisfied with cosmetic outcome of their bilateral prophylactic mastectomy.

Body image and sexuality after BPM has also been evaluated in multiple studies with various results. Some of them stated no change in sexual functions of questioned people [21] when the others claimed that up to 23% of participants have experienced adverse effects in their sexual relationships [20] and 31,7% worsening of their sexual lives [18]. 23% of women were feelings changes in their femininity [20].

In the same study there has been reported diminished level of fear about developing cancer in 74% of women after BPM and neutral or favorable influence on emotional stability in 91% [20]. Majority of women claimed to have lower cancer-related anxiety. The quality

of life of women after BPM, based on the Quality of Life Index, is slightly better than this of the general population [22].

Professional psychosocial support provided after surgery is a really important issue that plays a major role in the future recovery of the patient and may positively influence their feelings and emotions about new body image [23]. A patient should be able to address her concerns and emotional burdens to someone that can help them resolve these problems and prevent them from affecting future life of the patient.

CONCLUSIONS

Higher levels of education, social awareness and general improvement in society's interest about health lead to rising popularity of prophylactic mastectomy. More people are likely to have undergone genetic counselling and testing which gives them a closer look at their personal risk of breast cancer [3]. Positive diagnosis with BRCA gene is connected with huge emotional burden and stress. Because of that many women decide to perform ether bilateral or contralateral mastectomy [16]. According to research the surgery is able to lower the risk of breast carcinoma up to 90% [7]. It is a difficult decision based mostly on emotional reasons like fear and concern about developing cancer among women [16]. Nevertheless the positive risk-reducing and psychosocial effects of the procedure it should be remembered that it should be considered only among those at very high risk of disease. It is an invasive procedure and as in every operation it has a risk of complications [5]. There are multiple options and techniques of performing breast reconstruction and plastic surgeons are able to suit the preferences of patients and make them look desirable and realistic [4]. Women often experience changes in multiple areas of their lives like sexuality, body image and general life quality, but overall most of them do not regret the decision about breast removal and would advise to to other women in the same situation [18,19].

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Rectovaginal fistula - a consequence of radiotherapy in pelvic malignancies - how it should be diagnosed and treated?

Małgorzata Satora[1], Klaudia Żak[1], Milena Leziak[1], Krzysztof Kułak[2]

1. Student Research Group at the Clinic of Oncological Gynecology and Gynecology, Medical University of Lublin, Poland
2. The Clinic of Oncological Gynecology and Gynecology, Medical University of Lublin, Poland

List of abbreviations

RVF - rectovaginal fistula

TEM - endoscopic microsurgical treatment

INTRODUCTION

A rectovaginal fistula (RVF) is an abnormal canal lined with epithelium between the rectum and the vagina. Fistulas should be differentiated according to their diameter or location. There are many causes of RVF [1].

The fistula resulting from the treatment of advanced pelvic minor tumors with radiotherapy is particularly difficult to treat [1].

Sick patients struggle with passing feces through the vagina, which significantly worsens their quality of life [1].

Despite medical advances, there is still no specific treatment algorithm for RVF due to the complex etiology of this pathology. After irradiation, RVF is extremely difficult to treat due to poor blood supply to the tissues and a high risk of disease recurrence [1].

In the medical literature, many different methods are used in the treatment of RVF after radiation, which will be analyzed in this review [1].

The problem of fistulae needs to be raised in order to find the optimal treatment for RVF and improve the quality of life of patients.

RECTOVAGINAL FISTULA

The process of fistula formation is initiated by radiation inflammation, which leads to swelling of the rectal mucosa and subsequent fibrosis of its walls. Increasing ischemia impairs the healing of the resulting fistula. The rectal mucosa ulcerates [1,2]. In patients, passing feces from the rectum through the vagina is a burden that hinders everyday functioning and the comfort of life. The literature proposes several proposals for the classification of rectovaginal fistulas. Due to the diameter, the RVF is divided into small (<0.5 cm in diameter), medium (0.5-2.5 cm) and large (> 2.5 cm). There is also a classification that takes into account the topography of the fistula in relation to other anatomical structures. Due to their anatomical location, fistulas can be divided into: low - located above the teething line with the vaginal opening; high - vaginal openings behind or near the cervix and middle - when the fistula is between high or low locations. Classification according to morphology and etiology divides RVF into simple, secondary to infection, and complex, which are caused by inflammatory bowel disease or by radiation [3].

ETIOLOGY

RVF are a group of complex anatomical disorders caused by a variety of etiological factors, such as: obstetric trauma, prolonged labor or episiotomy due to difficult childbirth; inflammatory diseases of the digestive tract, e.g. ulcerative colitis or Crohn's disease; operations of the pelvic organs; tumors of the vagina, cervix, rectum and anus; infections, abscesses and ionizing radiation.

It is important to distinguish between spontaneous RVF after radiotherapy and postoperative RVF [4]. Studies show that fistulas after radiotherapy heal poorly in cancer patients [5].

RADIATION REACTION AFTER TREATMENT WITH RADIOTHERAPY

Radiotherapy used in the treatment of pelvic tumors is used in the form of both teleradiotherapy and brachytherapy. Studies show that around 85% of patients diagnosed with cervical cancer are treated with radiation therapy, which in most women leads to complications called radiation exposure [6,7]. Its intensity depends on the total and fractional radiation dose. Irradiation complications may be mild, of an early type, which may heal or resolve

spontaneously. An early reaction may occur during or shortly after irradiation. It mainly covers the intestinal mucosa in the gastrointestinal tract. Such complications usually do not have serious consequences for the patient and require only symptomatic treatment. Late reaction, including radiation rectovaginal fistula, may appear up to 2 years after the end of radiotherapy treatment. Gagliardi and Pescatori published a study in 2005 according to which radiation RVF accounted for 7% of all RVF [8].

Late reaction involves changes in the intestinal submucosa that can lead to stricture, haemorrhage and perforation [6].

RVF DIAGNOSTICS

Correct diagnosis of a RVF is necessary to determine the location of the fistula orifices, as well as the course, topography and branches of the canal. The basis is collecting a personal history, in which the patient reports passing stools or gases through the vagina. The presence of RVF may also suggest foul odors during vaginal examination, vaginal bacterial infections, and urinary tract infections. There may also be patients who are asymptomatic and RVF is found on proctology for a different reason [6,9].

A physical examination of a patient with suspected RVF should include a gynecological examination in which the rectovaginal fistula is a small depression in the vaginal mucosa in the vaginal speculum [1,9-11].

Rectoscopy and colonoscopy are useful in assessing the orifice of the fistula and the mucosa in order to detect inflammatory changes in Crohn's disease or neoplastic changes [1,9-11].

When diagnosing inflammation, it is also helpful to perform a general urine test and determine the level of leukocytes in the blood. Equally important for the diagnosis of a rectovaginal fistula is the transrectal ultrasound examination and the transvaginal ultrasound examination [1,9-11].

The tampon test involves inserting a vaginal tampon and injecting methylene blue into the rectum. The discoloration after 20 minutes of the tampon confirms the presence of a rectovaginal fistula in the patient. This technique does not allow the location of the fistula to be assessed. Additional tests are also a histopathological biopsy that allows to exclude neoplasms or inflammations, computer tomography and magnetic resonance imaging. In the

case of a biopsy, material should be taken from the edge of the fistula in order to exclude local recurrence [1,9-11].

PREVENTION RECTOVAGINAL FISTULAS

Preventive treatment of RVF can be effective in people with small fistulas, minimal symptoms, and no irradiation of the pelvis. In the literature, descriptions of preventive methods used to reduce the formation of RVF can be found. These methods include substances such as metronidazole, mesalazine, sucralfate and steroids. In persistent bleeding, coagulation or argon plasma can be used. Some data suggest that the administration of intravenous coagulation factor XIII is effective in promoting fistula healing. Small fistulas can heal on their own in 6 to 9 months. In the literature, the diameter of the RVF associated with spontaneous healing was not greater than 1 cm [12,13]. Despite the advances in medicine, effective methods of preventing fistulae have not yet been described. There are reports in the literature on the surgical treatment of rectovaginal fistulas caused by radiotherapy. The article includes descriptions of surgical techniques used in the treatment of irradiated complex fistulas published in recent years.

TREATMENT OF RADIATION RVF

When choosing a method of surgical treatment of RVF, many factors should be taken into account, such as the patient's age and general condition, etiology, location and dimensions of the fistula, and the course of communicating organs and systems. Preparation for the surgical treatment of a rectovaginal fistula involves thorough preparation of the large intestine and vaginal irrigation with a baptide solution, which will prevent risky infections [14,15].

Before attempting to surgically repair of RVF, it is necessary to ascertain whether there is an infection or local inflammation. Then, antibiotic therapy or drainage seton should be implemented to eliminate the infection. Bidhan et. described the usefulness of drainage setons in complex, tall fistulas, selectively for untreated sepsis or for pain control [15].

An important factor qualifying for surgery is the time since the first symptoms of the fistula appeared. In RVF, consideration should be given to the reduction or termination of tissue inflammation, which may take a year. Minimizing this condition enhances the treatment success of surgical reconstruction and fistula recurrence.

In preparation for surgical treatment, not only anti-inflammatory treatment may be helpful, but also anti-diarrheal treatment, hyperalimentation or exclusion of the rectum from the passage of the intestinal contents. Mechanical cleansing of the large intestine, vaginal disinfection and bladder catheterization are immediate preparation before surgery.

The technique of the surgical treatment of a rectovaginal fistula depends primarily on the location of the RVF. Low and middle fistulas should be operated from the transvaginal and transrectal access from the perineum. High fistulas, in turn, should be operated from the abdominal approach, in this case classical and laparoscopic techniques can be used [16].

STOMA

In a patient diagnosed with RVF, the first step is to select an artificial rectum. A stoma is used in complicated cases and in larger fistulas. Surgery with the emergence of the final stoma improves the patient's quality of life and facilitates the maintenance of daily hygiene, as well as improves the quality of sexual function. Publications do not indicate that the creation of a redirection stoma affects the results of treatment or recurrence of rectovaginal fistulas. The decision to choose a stoma should be based on the size of the fistula and the patient's workload [16,17].

PARKS' COLOANAL SLEEVE ANASTOMOSIS

In 1978, Parks described the principles of treating RVF resulting from radiation therapy. The technique of the procedure consists in removing the mucosa altered by radiation and filling the fistula site and its surroundings with well supplied tissues that have not been irradiated. The colon is then anastomosed to the rectum. The Parks technique spares the sphincters. The abdominal and perineal access is recommended for high and large fistulas, and the transrectal approach for low and small fistulas. Park's coloanal anastomosis maintains the correct stool holding mechanism and eliminates the need for dissecting the lower rectum. This method also gives good results in rectal reconstruction in the treatment of radiation RVF [2,18].

Already in 1985, Gazet applied the Parsk technique to 11 patients. 7 patients underwent surgery after treatment of rectal cancer, 2 patients after treatment of cervical cancer, 1 patient after treatment of uterine cancer, 1 patient after treatment of ovarian cancer, 1 patient after treatment of seminoma and 1 patient after treatment of bladder cancer. 1 patient died due to

pulmonary embolism on the 7th day after surgery. In the rest of the patients with colorectal anastomosis, successful closure of the temporary colonostomy occurred within one to six years. All patients underwent repair due to an ileo-colonic fistula. No cases of fistula recurrence have been reported. The newspaper concluded that Parsk's procedure avoids the extremely difficult dissection of the lower rectum and the separation of radiation-damaged tissues, which allows it to be used in patients with radiation injuries to the rectum [19].

Nowacki et al. described 15 cases of colorectal sleeve anastomosis in order to repair radiation rectovaginal fistula. All patients had previously received radiotherapy for cervical cancer. There has been 1 postoperative death. The results were good in 11 patients, and surgical curettage was performed in 7 patients due to difficult removal of the rectal mucosa. A few years later, Nowacki published another study on 24 patients who had also been previously irradiated due to cervical cancer. 1 postoperative death was observed, and of the 23 surviving patients, 18 had good functional outcomes. Surgical curettage was performed in 16 patients [20,21].

San Martin in 1995 evaluated the effects of the Parks technique in the treatment of severe radiation proctitis. San Martin reviewed the clinical histories of 35 patients with cervical cancer, 5 with endometrial cancer, and 1 with vaginal cancer who had received radiation therapy. About 2 years later, 19 of them developed fistulas, and the remainder developed rectal bleeding, strictures and ulceration. All of them underwent Park's surgery after a mean interval of 1.6 years. In the study group, the temporary colostomy was closed about 3 months after the operation. Functional outcomes were reported as good in 30 cases during the follow-up till the 64th month after surgery. 1 patient died due to complications, 2 patients developed colon necrosis, which made post-treatment evaluation impossible [22].

GRACILIS MUSCLE INTERPOSITION

The effectiveness of gracilloplasty in the treatment of rectovaginal fistula was assessed by Hotoraus et al. in the years 1980-2013. The aim of the study was to evaluate the use of slender femoral transposition in the surgical treatment of RVF and the effect of this technique on the number of relapses.

The authors analyzed 17 studies involving 106 patients, of which 11 were caused by radiation. The patients had previously undergone an average of 2 repair procedures, and the fistula returned. The median cure rate over the two-year follow-up was 33-100% of cases. In 13 cases, no serious complications were noted. The authors believe that the slender femoral

transposition has a reasonable success rate in rectovaginal fistula repair and can therefore be considered as a treatment option for recurrent RVF [22].

MISCELLANEOUS PROCEDURE

This procedure is mainly used in patients with defects in the rectal wall as a result of chronic inflammatory bowel disease or after radiotherapy. It is a highly invasive procedure involving resection of the distal part of the rectum. After the area with the fistula is removed, re-anastomosis is performed with manual transrectal sutures [24].

SURGISIS MESH

In 2009, Schwandner et al. analyzed the effectiveness of the use of the Surgisis mesh in the closure of RVF. Patient inclusion criteria for analysis included RVF in the lower two-thirds of the rectovaginal septum. The operation consisted of a combination of transrectal and transvaginal fistula excision and transvaginal placement of a Surgisis mesh. The internal openings as well as the anus and vagina were closed. 21 patients were qualified for the analysis, 18 of whom had recurrent rectovaginal fistula. In 9 patients, the cause of RVF was Crohn's disease, in 6 RVF was caused by an iatrogenic cause, and in 2 patients the cause was radiation. 2 patients had a fistula caused by obstetric trauma and 2 due to idiomatic reasons. The success rate after the primary surgery was 71%. The rest of the patients with fistula failure or recurrence were repaired. 4 of the 6 who were repaired were cured. Schwandner et al concluded that the technique using the Surgisis mesh to close RVF is promising [25].

ENDOSCOPIC MICROSURGICAL TECHNIQUE

Endoscopic microsurgical technique (TEM) is a technique proposed by D'Ambrosio and others in the 1980s. TEM is a method used in the treatment of rectal cancers and rectal polyps. This method recommends the insertion of a surgical rectoscope through the anus, creating a positive pressure in the presence of carbon dioxide. Then the vision track is introduced and microsurgical tools are used for the operation. Full-thickness resection consists in full-wall excision of lesions below the peritoneal crease. In order to close the defect, the wall is sutured intracorporeally.

D'Ambrosio et al. Applied the TEM technique to 13 patients with RVF. RVF was healed in 90% of patients, and fistula recurrence in 1 patient.
The advantage of the TEM technique is the avoidance of surgical incisions in the perineal area, which prevents damage to the anal sphincter and pain [26].

PALIATIVE TREATMENT

Due to the spread of cancer and the poor general condition of the patient, which excludes other methods of treating the rectovaginal fistula, palliative treatment is used. Laura A Sonoda et al. In 2012 proposed a stool collection system placed vaginally in a 75-year-old patient with advanced cervical cancer and RVF [27].

DISCUSSION

RVF is definitely a dangerous and life-difficult complication after radiotherapy, which in 52% of patients is used as the optimal treatment in gynecological neoplasms [28]. It is difficult to estimate the actual number of patients struggling with radiation RVF due to the lack of registers and failure to perceive the enormous scale of the problem, which is the fistula. Zelga et al. in 2017 reported fistulas in 50 patients with endometrial or cervical cancer out of 1725 patients treated with radiotherapy within 10 years , which is a challenge for modern medicine [7].

Articles on RVF can be found in the medical literature, but there is a lack of knowledge in the subject of radiation-induced RVF’s treatment. The above-mentioned studies described many methods of treatment of fistulas, but the question is, which of them should be the option of choice. The creation of a stoma seems to be a helpful step in the treatment of a fistula, as it reduces the risk of fistula recurrence, may cause its spontaneous healing and it alleviates symptoms [7].

The Park's method is still popular, and has been used by Polish doctors for years in the treatment of RVF from the pre-abdominal approach. The Parks technique maintains proper stool holding mechanisms and eliminates the necessary separation of previously irradiated tissues. Studies by San Martin et al. show that the Park's method allows for good functional results up to 64 months after surgery in 75% of patients treated with this method [22].

Techniques of interposing the perfused tissues are used in the prevention of RVF recurrences. The technique of a flap displaced from the bulbar-cavernous muscle from one labia appears to be promising with an efficiency of 60% to 94% [1].

Gracilloplasty used by Hotoraus et al. may actually be a treatment option for radiation RVF in the treatment of relapses, after other failed treatments. Hotoraus's anal shows that this method does not cause any serious complications [23].

Less preferred techniques that are alternative treatments for radiation RVF are the Miscellaneous procedure, Surgisis mesh and TEM. The Miscellaneous procedure is a highly invasive method that is only used in patients with severe rectal wall defects, so it is not a recommended technique for the standard treatment of RVF [24].

Outstanding results in the treatment of RVF have been achieved with the use of the Surgisis mesh. The cure rate with this method in the treatment of combined RVF was 71% based on short-term follow-up. Only long-term follow-up makes it possible to assess healing indicators, which may be dynamic, especially after radiotherapy or in the course of Crohn's disease. This technique can therefore be an alternative to slender muscle transposition [25].
TEM is certainly a very precise technique due to the use of both hands and the three-dimensional view of the operating field. This technique avoids surgical cuts that could damage the anal sphincters. The disadvantage is that the operation takes longer time, and the sutures are difficult to put on. This technique is used in the treatment of rectal cancers or rectal polyps. This technique avoids surgical cuts that could damage the anal sphincters [26].

In the treatment of RVF, the best method seems to be the Park's technique, which is a good treatment of radiation fistulas involving also the retroperitoneal part of the rectum. The Parks method is a good method used in the treatment of high, complex fistulas, which include radiation RVF. A stoma is definitely a method that prevents pain and many inflammations. This is the first stage of the surgical procedure. However, it is a method that in 24% of patients requires the implementation of an additional form of radiation RVF treatment due to the low probability of spontaneous closure of the fistula after using only a stoma. Then the operative method can be the use of the Park's technique.

CONCLUSIONS

Radiation RVfs are definitely one of the problems that significantly worsens the quality and hygiene of the patient's life and prevents her from fulfilling social roles.

Radiation-induced RVFs are particularly problematic due to the poor quality and vascularization of the tissue and the risk of intraoperative complications and fistula recurrences.

There is still no specific treatment algorithm for RVF caused by radiation. It is important to respect the patient's rights to maintain good quality and hygiene of life and to select a stoma, which improves the patient's daily functioning. This method prevents the unpleasant symptoms of the fistula, but only slightly increases the likelihood of spontaneous closure of the fistula, which forces doctors to implement other surgical procedures.

Preventive treatment of radiation RVFs, which belong to complex fistulas, is not possible. There are many methods related to tissue reposition that appear to be effective. The fistula treatment algorithm requires individualization due to the different location and rarity of occurrence. The problem of rectovaginal fistula seems to be ignored in the literature and medical literature. Research into the development of effective RVF treatments needs to be continued, allowing patients to return to their daily duties and functions in society.

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SELECTED CLINICAL AND THERAPEUTIC PROBLEMS

Severe eosinophilic asthma and the prospects for its biological treatment

Kamila Florek[1], Michał Błaszkiewicz[1], Agata Walulik[1], Krzysztof Gomułka[2]

1. Student Scientific Group of Adult Allergology, Wroclaw Medical University, Wroclaw, Poland
2. Department of Internal Medicine, Pneumology and Allergology, Wroclaw Medical University, Wroclaw, Poland

INTRODUCTION

Asthma is a worldwide non-communicable disease which affects all age groups (children and adults as well). According to GINA (Global Initiative for Asthma) "*It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation"* [1].

Major part of the affected young generations are boys, whereas in adults women suffer from asthma more often than men. Estimated number of people suffering from asthma reaches 241 million [2].

Our society is still challenged with a high prevalence of asthma. During the last few years we can observe a descending trend in some high-income countries but the number of cases in low and middle-income communities is still rising [3].

The genesis of this disorder is heterogeneous. Current methods of studies and research should focus on crucial environmental and genetic factors, which can help to distinguish various pathomechanisms of asthma inflammations and to separate different clinical manifestations of each type [4]. The most prevailing phenotypes listed by GINA are:

- allergic asthma,
- non-allergic asthma,
- adult-onset (late-onset) asthma - eg. work or age related asthma,
- asthma with persistent airflow limitation,
- asthma with obesity.

MAKING THE DIAGNOSIS

To make the proper diagnosis it is crucial to base on precise respiratory symptoms patterns and expiratory airflow limitations which are specific for asthma. The main point of the analysis should be focused on the pattern of the symptoms because separated manifestations can be caused by many other diseases. Respiratory symptoms strongly suggesting asthma are:

- wheezing, shortness of breath, cough, chest tightness,
- experiencing more than one of upper phenomena,
- manifestations stronger during the night or in the early morning,
- various time and intensity of the symptoms,
- symptoms triggered by infections, exercise, allergens, weather changes, laughter, irritants such as car fumes, smoke or strong smells [1].

TREATMENT

GINA differentiates five steps of the therapeutic process of asthma. The schemes of the therapy on each step depend on the characteristics of each patient. The main scheme for the adults presents the two possible ways based on the type of inflammatory realiever - LABA (Long-acting β-agonist) or SABA (Short-acting β-agonist) and inhaled corticosteroid (ICS) [1]:

- Step 1: Manifestations less than twice a month.
- Step 2: Manifestations twice a month or more but less than 4-5 days a week.
- Step 3: Manifestations most days or waking due to the symptoms at least once a week.
- Step 4: Daily manifestations, waking at least once a week and low lung functions.
- Step 5: Persistent manifestations or exacerbations despite correct treatment in the previous step.

EOSINOPHILIC ASTHMA

Eosinophilic asthma is one of asthma phenotypes defined as an inflammation of the basement membrane in the airways and eosinophilia in the sputum and blood. Furthermore, other the most common features of this asthma phenotype are:

- mainly adult onset - 63% of patients who developed asthma in adulthood had eosinophilia [5]

- late onset makes allergic background less likely,
- elevated level of total IgE,
- sensitivity to NSAIDs (Nonsteroidal anti-inflammatory drugs) - e.g. ASA (Acetylsalicylic acid),
- chronic rhinosinusitis with nasal polyposis,
- airflow limitations not fully reversible with bronchodilators,
- may be steroid - resistant or the response to glucocorticoids may be reduced [6].

Eosinophilic asthma has three distinct presentations: allergen-exacerbated asthma - with early onset, idiopathic eosinophilic asthma - adult onset, nonatopic patients, ASA-exacerbated respiratory disease- adult onset, nonatopic patients [7].

The diagnosis of eosinophilic asthma is made on the basis of sputum eosinophils but the sputum sample is not so easy to collect so sometimes in clinical practice we use surrogate markers - such as:

- blood eosinophils,
- FeNO,
- serum IgE,
- periostin.

The demonstration of eosinophils in sputum is no guarantee for response to treatment with current biological agents targeting type-2 inflammation because there are several molecular pathways that may lead to eosinophilic inflammation [8].

The most likely diagnosis of eosinophilic asthma, using blood test results, is possible when the total count of peripheral blood eosinophils is higher than 400 cells per microliter. There is a need to consider if there is no different cause of the increased level of eosinophils, such as other eosinophilic disorders: parasite infection, allergic disease, hematologic or neoplastic disorders, immunologic disease, lupus, or EGPA (eosinophilic granulomatosis with polyangiitis). EGPA is a disease which has to be considered in patients with eosinophilic asthma, because of its common clinical manifestation at the early stages of EGPA. In EGPA there are distinguished 3 stages of disease: allergic, eosinophilic and vascular. Two first steps are characterised by the same manifestations which we can observe in the eosinophilic asthma but that vascular stage can be presented about 3 years later than other symptoms so it is crucial to observe patient with eosinophilic asthma if there are no signs of EGPA, because it is common to develop the cardiovascular complications in patients with that disease [9]. Perspective for 50% of patients suffering from severe eosinophilic asthma is worse than for other patients with

asthma, as well the control of disease is harder. Level of blood eosinophilia in majority is connected to severity of asthma, as well sputum eosinophilia is related to number of exacerbations [10]. T2-high eosinophilic asthma is characterized by infiltration of airways with those granulocytes, where they produce different cytokines and inflammation mediators that play a pivotal role in the pathogenesis of bronchial inflammation and remodeling [11].

PATHOMECHANISM OF ASTHMA

We can distinct two molecular mechanisms of asthma [12]. Type 2 asthma is characterized by increased levels of Th2 cytokines such as: IL-4, IL-5 and IL-13. That result is caused by the following mechanism. The dendritic cells present the environmental factor to the naive T helper cell, which activates Th2 cells and they produce IL-4 and IL-13. Those cytokines activate lymphocytes B and stimulate them to produce IgE. IgE bind to the mast cells, when the invading antigen binds to the IgE connected with the mast cell it triggers degranulation of the mast cell - release of mediators hidden in the mast cell such as histamine, prostaglandin, leukotriene and several cytokines: IL-8, IL-13, tumor necrosis factor α (TNF-α) and chemokine (CeC motif) ligand CCL2. Th2 cells secrete IL-5 responsible for eosinophil activation and recrutation. ILCs2 - type 2 innate lymphoid cells as well produce IL-13 and IL-5 responsible for eosinophils recruitment and expansion. Those cells are suggested to play the main role in the non-allergic eosinophilic asthma pathogenesis- they are activated by IL-25, IL-33 and prostaglandin D2 [13]. In allergic eosinophilic asthma the same interleukins and thymic stromal lipoprotein (TSLP) are involved in its mechanism - the cascade of action starts with the TLR (Toll-like receptor) stimulation with the aeroallergen. In the consequences of this process we can observe increased mucus production, bronchoconstriction and leukocyte migration. Hours after contact with the antigen, the late phase of the reaction starts with IEos (inflammatory eosinophils) - induced in the lungs during inflammation, cytokines and pro remodeling factors (TGF-β, MMP-9, TIMP-1, VEGF, and bFGF) production which cause advanced bronchoconstriction, cell damage and airway hypersensitivity and hyperresponsiveness what leads to the remodeling of the airway tissue [6]. The other non-type 2 also known as non eosinophilic or T2-low asthma is characterized by neutrophilic inflammation. To confirm T2-low asthma we need to check the cytokines profile in the sputum, bronchoalveolar lavage or blood samples and usually base on clinical manifestations. The detailed mechanism of neutrophil recrutation is not understood yet but is connected with activation of Th1 and Th17

cells via toll - like receptor activated by irritants. Non-type 2 asthma is characterized by higher severity and lower response to glucocorticosteroids due to their inhibiting impact on neutrophil apoptosis.

The crucial particle in eosinophil activation, differentiation, growth, recruitment, degradation and survival is IL-5 and the treatment of eosinophilic asthma is mainly focused on it.

TREATMENT

The long-term goals of treating asthma are risk reduction and symptom control. The main aim is to reduce exacerbations, airway damage and medication side effects. It is very important to take into consideration a patient's individual risk factors and comorbidities while treating asthma. The latest guidelines of GINA recommend that every adult and adolescent suffering from asthma should receive inhaled corticosteroid (ICS) as a controller medication to reduce risk of exacerbation and reliever inhaler for as-needed use, either low dose ICS-formoterol or short-acting β2 agonist (SABA). With symptoms increasing it is recommended to add long-acting β-agonists (LABA) and alternative therapies such as theophylline or cromolyn. A biological treatment with monoclonal antibodies against key asthma mediators is recommended and used as the fifth level of the step-wise approach in medication therapy for patients with severe symptoms despite use of high doses of controller medications [1].

Omalizumab

The real game-changer for patients suffering from severe asthma was the introduction of the first biological treatment Omalizumab in 2002, firstly approved in Australia, followed by the United States, the European Union and Japan [14]. It was registered to treat adults and children ≥12 years old with moderate to severe persistent allergic asthma resistant to treatment by high doses of ICS and lately for children aged ≥6 years with a total serum IgE level between 30 and 700 units/mL and a positive allergen test [15,16]. Since 2014 it is also approved as a treatment of chronic idiopathic urticaria [17]. Omalizumab is a recombined, humanized kappa IgG1 monoclonal antibody produced by DNA technology which selectively binds to Cε3 domain of the Fc region of human IgE in blood and interstitial fluid, thereby binding to free IgE and as well the membrane-bound form of IgE on the surface of B lymphocytes. Using the described mechanism Omalizumab inhibits the interaction between IgE and FcεRI leading to

decreased levels of free IgE in circulation [14]. Thus, it inhibits the activation of basophils and mast cells, decreasing the release of histamine. Administered subcutaneously every 2-4 weeks based on IgE serum level, Omalizumab improves the quality of life, pulmonary function and reduces exacerbations by approximately 43% [18]. Serious side effects are rare but may occur and include eosinophilic granulomatosis, cardiovascular events, such as transient ischemic attack and ischemic stroke and anaphylaxis [16].

Mepolizumab

Another biological drug used for treatment of severe asthma is Mepolizumab - humanized kappa IgG monoclonal antibody targeting IL-5 [19]. Registered in 2015 as an add-on treatment, among other in patients ≥6 years old with severe eosinophilic asthma, in adult patients for eosinophilic granulomatosis with polyangiitis, hypereosinophilic syndrome (HES) in patients aged 12 and older with eosinophilia persistent for at least six months without an identifiable non-hematologic secondary cause. As an interleukin-5 receptor agonist, it binds to the IgG1 kappa region and reduces the eosinophil count in both blood and sputum [20]. Clinical studies showed that after subcutaneous administration repeated every 4 weeks, significant improvement in symptom control is observed, exacerbations compared with placebo are reduced by 66%, thus patients may take reduced doses of ICS while taking Mepolizumab [21]. Unlike Omalizumab no significant effects on FEV1 (forced expiratory volume in the first second) and PEF (peak expiratory flow) are found [22]. Common side effects include headaches and injection site reaction [16].

Dupilumab

Dupilumab is a human monoclonal antibody of the immunoglobulin G4 subclass that binds to the IL-4 receptor, inhibiting the receptor signaling pathway [23]. It is a new treatment option, approved in 2017 for patients with moderate to severe asthma ≥12 years old, ICS-dependent asthma or asthma with severe atopic dermatitis or chronic rhinosinusitis with nasal polyps [24]. As an interleukin-4 receptor α-antagonist, Dupilumab inhibits the cytokine-induced inflammatory responses such as interleukins, chemokines, IgE, nitric oxide release [23]. Since Dupilumab works to suppress the immune system response, it reduces exacerbations by approximately 50%, improves FEV1 and reduces the dose of oral glucocorticoids [16]. Common side effects are injection site reaction, conjunctivitis and nasopharyngitis [25].

Reslizumab

Reslizumab is another humanized IgG4 kappa monoclonal antibody IL-5 receptor antagonist. It is indicated as an intravenous add-on drug in ≥ 18 years old patients with severe eosinophilic asthma inadequately controlled with ICS [26]. By binding to the IgG4 kappa region it inhibits IL-5R receptor binding, it prevents the ability of eosinophils to mature and proliferate and promotes programmed cell death [20,27]. Clinical trials showed improvements compared to placebo in FVC, FEV1 measures, quality of life and reduced exacerbations after 16 weeks of treatment. Adverse effects of the therapy may include injection site reactions, oropharyngeal pain, transient increased creatine phosphokinase, anaphylaxis and myalgia [16,28].

Benralizumab

The last FDA (The United States Food and Drug Administration) - approved in 2017 biological drug used to treat patients with eosinophilic asthma is Benralizumab - a humanized recombinant monoclonal antibody of the IgG1 kappa immunoglobulin that specifically binds to the interleukin 5 receptor (IL-5R) expressed on eosinophils and basophils [29].

It is indicated as a maintenance treatment for patients ≥12 years old with severe asthma and an eosinophilic phenotype [16]. Its mechanism is to inhibit the binding of IL-5 and hetero-oligomerization of the alpha and beta subunits of the IL-5R, thus blocking signal transduction. Moreover it has high affinity for the receptors in neutrophils, macrophages and natural killer cells [29].

DISCUSSION

Almost 241 people worldwide suffer from asthma. There are different phenotypes of asthma but their clinical manifestations may be similar. Although they are presented by various pathomechanisms. One of asthma types is eosinophilic asthma which should be considered by doctors as a diagnosis if the disease does not respond to GINA recommended treatment with glucocorticoids, LABA and SABA. Even though the glucocorticoids relieve the symptoms, the therapy is not effective and the exacerbations are frequent, there should be a diagnostic for eosinophilic asthma - in clinical examination there may present chronic rhinosinusitis with nasal polyposis. The diagnostic testing shows elevated levels of total serum IgE and total eosinophil count in the sputum or serum but there are also more surrogate markers. The diagnosis is crucial to apply the proper treatment. The chance for patients with eosinophilic asthma is biological

treatment. The medications approved for that type of asthma is Omalizumab leading to decreased levels of free IgE in circulation, medications targeting IL-5 or its interactions with receptor, such as: Mepolizumab, Reslizumab, Benralizumab and IL-4 binding drug - Dupilumab. The development of biological therapies of severe asthma has changed the quality of life of many patients for whom traditional methods of pharmacological treatment had not brought the expected results. Using subsequent antibodies able to target other molecules involved in asthma pathophysiology, made a possibility to treat patients with "tailored-made" drugs which significantly increases their effectiveness. Clinical studies reveal benefits, such as reduction in asthma exacerbations, improvement in pulmonary function - FVC (Forced vital capacity), FEV1, PEF, decreased hospitalization number and higher health-related quality of life.

Further monoclonal antibody development is recommended. It is important to establish agents that can be used regardless of age, administered less frequently, subcutaneously and at home. These factors would significantly affect accessibility to treatment options. A greater focus on long-term efficacy, cost-effectiveness, and drug–drug comparison studies are also recommended.

The most important aim of this study is to focus on the diagnosis of eosinophilic asthma in patients and treat them with the most efficient biological medications. As new drugs, the results of long-term treatment are not conclusive but there is no doubt biological treatment is revolutionary. As well, the crucial issue is to make those drugs easier to use at home.

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Interleukin 5 and its role in allergic diseases

Kacper Brzdąk[1], Katarzyna Antosz[1], Aleksandra Kozioł[1], Wiktor Woźniak[1], Krzysztof Gomułka[2]

1. Student Scientific Group of Adult Allergology, Wroclaw Medical University, Wroclaw, Poland
2. Department of Internal Medicine, Pneumology and Allergology, Wroclaw Medical University, Wroclaw, Poland

Interleukins are secreted proteins which regulate intracellular communication and keep many cellular functions under control, especially in terms of the immune response. Human genome encodes over 50 interleukins and proteins related to them. In 1979 during The Second International Lymphokine Workshop in Switzerland the name “interleukin” was chosen in order to systematise medical nomenclature concerning this expanding group of cytokines [1,2].

Interleukin 5 (IL-5) is a 115-amino acid long cytokine, which in its active form is a homodimer. Along with IL-3, IL-4, IL-9, IL-10, IL-13 it is produced by Th2 lymphocytes. Other sources of it are mastocytes, basophils, and eosinophils. Production of this interleukin-5 can be stimulated by superantigens such as ones secreted by *Staphylococcus aureus* [3]. It plays a crucial role in immunological response, first of all in parasitic infestations. This T-cell-derived cytokine works synergistically with IL-3 and granulocyte-colony stimulating factor and erythropoietin (GM-CSF) is responsible for terminal differentiation, activation, and survival of committed eosinophil precursors. It coordinates diversifying and releasing of eosinophils into the circulation and extends its lifespan. It cooperates with granulocyte colony-stimulating factor (G-CSF) and has an impact on lymphocytes B, intensifies proliferation and differentiation of basophils, promotes class switching of immunoglobulins to IgA. Furthermore, it stimulates wound healing along with soft tissue remodelling [4].

IL-5 acts on target cells by binding to its specific IL-5 receptor (IL-5R) which belongs to type I cytokines` family. It consists of the IL-5 receptor α subunit (IL-5Rα) and the receptor

β subunit (IL-5Rβ). IL5Rα is also known as a cluster of differentiation 125 (CD125). It is located on chromosome 3p26-p24 and expressed predominantly on eosinophils. The β chain is bigger, contains a large cytoplasmic domain and is crucial for signal transduction. Although playing immeasurably different roles, they are both required to activate a successful IL-5 signal. Triggering of a signal is followed by its transduction which runs as per few major transduction pathways (JAK-STAT pathway, mitogen-activated protein kinase pathway - MAPK/ERK pathway, phosphatidylinositol 3-kinase pathway - PI3K pathway) [4].

The JAK-STAT signalling pathway communicates information from the outside environment to the nucleus of the cell. It activates genes through transcription using three main components: Janus kinases, signal transducer and activator of transcription proteins and receptors binding chemical signals. When a ligand binds to the receptor and phosphates are added by JAKs, STAT proteins bind to these phosphates and form a dimer during a process called phosphorylation. Then the dimer goes to the nucleus, binds to DNA and transcription of specific genes begins. The disruption of JAK-STAT signalling may result in disorders concerning the immune system such as asthma [5].

The MAPK/ERK pathway communicates a signal from the outside of the cell, using a receptor on its surface, to the nucleus. The pathway consists of many mitogen-activated protein kinases which communicate using phosphate groups that are added to other proteins. The function of this pathway involves cell cycle regulation, cell migration, wound healing, and tissue repair. It also stimulates angiogenesis. Although the dysregulation of this pathway is mostly known to cause cancer, it may result in inflammation or developmental disorders.
The PI3K pathway is an intracellular pathway related to growth, differentiation, proliferation, motility, and the cell cycle in general. PI3Ks are intracellular enzymes capable of phosphorylating and signal transducing. Some isoforms of PI3K regulate immune response and disturbance of this process results in immune diseases [6].

IL-5 plays a crucial role in pathogenesis of many allergic diseases such as asthma and atopic dermatitis. There is a significant increase in the number of eosinophils in blood, respiratory tract tissue and sputum in the process of these afflictions. Inhibition of this interleukin, using anti-IL-5 therapy agents such as: benralizumab, mepolizumab and reslizumab, can be used for the treatment of eosinophilic diseases described in the following paragraphs [7].

ROLE OF INTERLEUKIN 5 IN ASTHMA

2021 The Global Initiative for Asthma (GINA) Guidelines define asthma as a “Heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation”. There are several phenotypes of asthma: allergic asthma, non-allergic asthma, adult-onset (late-onset) asthma, asthma with persistent airflow limitation, and asthma with obesity.

The role of interleukin 5 focuses mainly on severe asthma connected with an eosinophilic phenotype, in which T-helper lymphocytes and innate lymphoid cells erect type 2 cytokines: IL-4, IL-5, and IL-13 [8,9]. In the case of severe asthma, interleukin-5 works in the bone marrow and bronchial mucosa, which increases the production of eosinophils from CD34+ hematopoietic progenitor cells. When eosinophils arrive in the lung tissue, they have the main role in type-2 inflammation because of eosinophil's innate and adaptive immune response [10]. IL-5 is responsible for the reduction of eosinophil apoptosis, and the level of IL-5 was inversely proportional to the level of apoptotic eosinophils in people with exacerbation and stable asthma [11]. Induce sputum of a patient with allergic asthma contained raised levels of IL-5, eosinophil progenitors, and mature eosinophils [12]. In addition, interleukin-5 and eotaxins attract eosinophils to the respiratory tract [13].

Apart from promoting eosinophilic inflammation, interleukin-5 participates in the remodelling of the bronchial mucosa. The remodelling of the airways involves the basal reticular membrane and the bronchial submucosa and is based on an increased deposition of extracellular matrix proteins. They are procollagen III, proteoglycans, tenascin, and lumican. The function of extracellular matrix proteins is not only limited to changing the structure of the airways but also influencing function, adhesion, differentiation, and cell survival. In addition, remodelling increases the mass of smooth muscles, goblet cell hyperplasia, and angiogenesis [14]. The interleukin-5 gene deletion in the mice genome caused a decrease in the concentration of eosinophils and airways rebuilding [15]. Patients' biopsy with anti-IL-5 antibodies therapy reflected the results of animal studies. Anti-IL-5 treatment reduced accretion of extracellular matrix proteins such as procollagen III, tenascin, and lumican. It reduced the thickness of the reticular basement membrane [16].

ROLE OF INTERLEUKIN 5 IN ATOPIC DERMATITIS

The key to understanding the issue of atopic dermatitis (AD) is the unbalance between lymphocytes Th1 and Th2. As a very first sign of acute disease a high level of Th2 is excepted, as well as a high level of Th1 in the chronic ones. Likewise, the profile of secreted cytokines is different in the acute and chronic stages of the disease [17]. In the acute phase of AD, there is an early phase of the IgE-dependent immune response, dominated by Th2 lymphocytes, subsequently an increase in the synthesis of interleukins: IL-2, IL-4, IL-5, IL-6, IL-10, IL-13, IL-21, and IL-31 is observed [18].

Based on the topic of this work it is easy to predict that the major attention is going to be given to interleukin 5. In AD an increase in IL-5 expression induces chemotaxis of eosinophils, then extends their survival time and, what is noticeable at first glance, it leads to the development of inflammation of the skin. As it is already known, peripheral and cellular eosinophilia occurs in AD, therefore using immunohistochemical techniques it is possible to visualize the layer of proteins derived from degranulated eosinophils.

It is worth emphasizing that AD can be divided into two groups of high and lower levels of IgE. IgE is estimated to be increased in 70% of patients – and this is the group where the treatment with IL-5 manipulations can be effective [19,20].

Along with the increasing impact of therapy in asthma that is based on using anty-IL-5 recombinant humanized monoclonal antibody mepolizumab, the idea of using it on AD patients had been started. However, since 2005 the study in this field has remained almost unchanged.

The above-mentioned work by Oldhoff et al. seem to be still one of the most mentioned in this field [21]. Even last year's publications such as paper by Bieber et al. still is referring to that one [22]. In research by Oldhoff et al. was trying to indicate the effectiveness of asthma therapy in the AD’s ones. The idea of this new application was based on the significant role of eosinophils concerning not only asthma pathogenesis but also AD, in that, both biomolecular mechanisms IL-5 is indispensable for eosinophils growth, differentiation and migration. Also, what is quite important to highlight – this should work only in the IgE-depended AD. However, their study showed that even though reducing purposefully peripheral blood eosinophil numbers was observed after mepolizumab treatment compared with placebo, nonclinical success was reached [21]. Moreover, no clinical improvement was

seen since [23]. There are some different explanations for why anti-IL-5 drugs do not appear as efficient in AD as they are for asthma treatment. Firstly, the studies have shown that the peripheral blood eosinophils level has decreased after treatment, but it may have no connection with eosinophils level in skin tissue or that noticeable reduction of tissue eosinophils may take a much longer amount of time. Additionally, even with the reduced blood level of eosinophils, they still can migrate to the skin due to the chemotaxis. While eosinophils carry the CC chemokine receptor 3 (CCR3), the combination of therapy of IL-5-antagonist and CCR3 antagonists may be the more effective solution. Finally, the proper doses or details of treatment also should be taken into consideration in order to establish the suitable level of peripheral eosinophils blood level in which the clinical effect will be seen [24].

Nowadays in dermatology and allergology lots of attention is given to IL-31, which is suspected to be the main interleukin that causes itching, or IL-4 and IL-13, especially in AD e.g., dupilumab (an antibody against a subunit of the IL-4/13 receptor) [25]. The treatment with anti-IL-5 antibodies can be considered as the missing accompaniment in resistant and complex causes of AD, but it still needs lots of afford to be defined and set the medical guidelines.

ROLE OF INTERLEUKIN 5 IN CHRONIC SPONTANEOUS URTICARIA AND CHRONIC RHINOSINUSITIS

While still staying in the matter of allergic diseases – other applications of anti-IL-5 drugs had and have been sought.

For example, in chronic spontaneous urticaria (CSU) treatments that are aimed at reducing eosinophil accumulation and activation, using biological drugs such as mepolizumab, reslizumab, and benralizumab (IL-5 antagonists), seems to be able to reduce CSU symptoms. Even when CSU is featured as a mast cell-driven disease, the role of eosinophils is started to be analyzed. Mainly because of the interactions between both kinds of blood cells, e.g., the cytokine cross-talk, mediators release, and due to the fact that mast cell degranulation is the result of the chain reaction that involves activation of proteins of the coagulation pathway by eosinophils. Even when there are only asthma-connected cases of

CSU confirmed that go on anti-IL treatment, the promising examinations are undoubtedly worthy of attention [26,27,28].

Other promising results are received in the case of eosinophilic chronic rhinosinusitis. Mepolizumab is seen as the cause of decreasing proportion of patients who required surgery and lowered the nasal polyp score in patients with chronic rhinosinusitis with nasal polyps (CRSwNP). Following the newest studies, in which CRSwNP is divided into 10 different clusters, six of which had high concentrations of IL-5 as well as IgE, IL-5 seems to be the main aim.

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Erectile dysfunction in diabetes mellitus – the pathogenesis, the frequency, and the treatment

Olgierd Dróżdż, Michał Bolek, Anna Dobrowolska, Michalina Grzelka

Wroclaw Medical University, Wrocław, Poland

List of abbreviations

ACEI – angiotensin-converting enzyme inhibitors,

AGE – advanced glycosylation end-protein,

ARB – angiotensin receptor blockers,

cAMP – cyclic adenosine monophosphate,

cGMP – cyclic guanosine monophosphate,

CAD – coronary artery disease,

CVD – cardiovascular diseases,

DAN – diabetic autonomic neuropathy,

DM – diabetes mellitus,

ED – erectile dysfunction,

ET-1 – endothelin-1,

NO – nitric oxide,

OFR – oxygen free radicals,

MARD – mild age-related diabetes,

PAI – plasminogen activator inhibitor,

PGE1 – prostaglandin E1,

SAID – severe autoimmune diabetes,

SIDD – severe insulin-deficient diabetes,

SIRD – severe insulin-resistant diabetes,

CD – vacuum constriction device

Erectile dysfunction in diabetes mellitus – the pathogenesis, the frequency, and the treatment

INTRODUCTION

Diabetes mellitus (DM) is a serious condition affecting approximately 537 million adults [1]. As it has many complications, erectile dysfunction (ED) is one of life's most embarrassing and deteriorating qualities [2]. Moreover, it is a complication occurring up to 2-3 times more often in diabetics than in the healthy population and up to 15 years earlier than in healthy people [3]. In most cases they appear periodically, especially when the glucose levels are uncontrolled – that is also the main reason for the fact, that correct treatment of DM could improve the patient's condition [2]. It is predicted that by the year 2025 the estimated number of people suffering from ED would reach 322 million [3].

DEFINITION

According to NIH (National Institute of Health), erectile dysfunction is a persistent inability to achieve or maintain an erection, which is needed for satisfying intercourse [4].

PATHOGENESIS

The pathogenesis of erectile dysfunction in DM is multifactorial. There are five main causes – psychogenic, organic, environmental, hormonal [2] and the effect of the drugs [5].

ORGANIC FACTORS

The main organic factor is angiopathy, which is the most common complication of diabetes itself. It can be divided into two groups – macroangiopathy and microangiopathy [2]. Microangiopathy includes retinopathy and nephropathy, whilst macroangiopathy refers to coronary artery disease or vascular conditions of the brain, pelvis, arteries of the lower extremities, and carotid arteries [5]. When describing the problem of erectile dysfunction, the attention will be focused on vessels that provide blood to the corpus cavernosum of the penis and their endothelium. In general, angiopathy and endothelial dysfunction is strictly connected with hyperglycemia [6]. An HbA_{1c} value of more than 8,1% increases the risk of developing ED three times [7]. Increased level of glucose in the blood leads to its transformation into sorbitol – a substance that can raise osmotic pressure. High osmotic

pressure leads to a reduction of phosphatidylinositol, which results in a lower activity of the sodium-potassium pump and electrolyte disturbances [2].

Moreover, hyperglycemia causes the formation of AGE (advanced glycosylation end-protein), which are the abnormal proteins (e.g. collagen) made in non-enzymatic glycation. AGE are prone to building up in vessel walls, especially in the corpus cavernosum, changing their properties. It is possible, because of forming the covalent bond with vascular collagen [8]. Other important compounds in damaging the vessel walls are oxygen free radicals (OFR), which are formed during the autoxidation of glucose [2]. OFR and AGE cause impairment of vascular endothelium and function of NO (nitric oxide). Decrease of NO and increase of endothelin 1 (ET-1) cause the remodeling of the vessel. NO insufficiency results also in a decrease of cGMP (cyclic guanosine monophosphate) [8], which is responsible for vascular smooth muscle relaxation and their proper filling during erection [9]. On the other hand, elevated ET-1 levels predispose to increased contractility of the penile vessels [8]. Furthermore, DM is also related to coagulation disorders. It is mainly because of the impairment of endothelium, but also reduction of C-protein, which functions as a clotting inhibitor and increases the concentration of fibrinogen and PAI (plasminogen activator inhibitor) [2]. Also, hyperinsulinemia has a severe impact on angiopathy. A high level of insulin, associated with DM type 2 leads to the intensification of lipids biosynthesis, myocyte proliferation, and increased activity of PAI. The combination of increased aggregation and adhesion of platelets with endothelial dysfunction is a serious factor in the development of angiopathy, which manifests as a reduced inflow of blood into the corpus cavernosum of the penis, called penile hypotension [2].

Naturally, angiopathy is not the only reason for failure to achieve a proper erection. The other important factor is diabetic autonomic neuropathy (DAN) [10], especially disorders of the parasympathetic system [11]. Nerve endings in this system secrete acetylcholine – its deficiency causes a decrease in NO concentration [9]. Apart from DAN, diabetes is also associated with peripheral neuropathy [8]. It presents its contribution to ED through impairment of sensory impulses from the shaft and glans of the penis, which are transferred to the reflexogenic erectile centre, and also through abnormal innervation of the ischiocavernosus and bulbocavernosus muscles, which contraction is required for an erection to maintain [8]. According to Bleustein et al., neuropathy of the penile nerves may precede the onset of neuropathy in other peripheral nerves [12]. The other components of the metabolic syndrome – hypertension and atherosclerosis – are also important organic factors in

the processes leading to ED, as well as cardiovascular diseases (CVD) related to them [3]. The connection between ED and CVD works both ways – both CVD contribute to ED [8], and ED may be a predictor of upcoming disorders [13], including myocardial infarction or heart failure [14].

HORMONAL FACTORS

The main hormonal factors that influence the development of erectile dysfunction in DM are hyperprolactinemia, hyper- and hypothyroidism [5], and hypogonadism [8]. The latter has a particular effect on ED occurrence [15]. It is believed that it is due to the low concentration of sex hormone-binding globulin, which carries the testosterone. Visceral adiposity is also associated with hypogonadism. It is because of the aromatase – enzyme, which is produced in adipose tissue and can convert testosterone into estradiol [8]. Moreover, a low testosterone level activates lipoprotein lipase, which acquires free fatty acids, causing further development of adipose tissue [16].

PSYCHOGENIC FACTORS

Erectile dysfunction in patients with DM is often called a silent complication. The main reason for that name is because the patients are too ashamed of this condition, therefore they do not speak about this problem, even with their doctor. Dembe and al. pointed out that every third patient does not admit to this problem. So it is not surprising that emotions and the psychological sphere are significant factors as well. Depression and anxiety caused by not only this condition but also by diabetes itself seem to worsen the patients' problems [2]. Anderson et al. in their meta-analysis pointed out that DM may double the chance of depression [17]. The influence of fear of not getting an erection may be strong enough to cause this condition even without any other factors [9].

ENVIRONMENTAL FACTORS

The environmental influence on erectile dysfunction is mainly due to smoking [18], alcohol consumption, and drug abuse [5]. Reduced physical activity and a sedentary lifestyle

has also an effect on it [19]. It leads to an increased deposition of adipose tissue, which inter alia disturbs the testosterone metabolism [8].

EFFECT OF THE DRUGS

There is no doubt that patients with diabetes have to take more drugs than the general population. Among the medicines that are considered negatively affect the achievement of a full erection, there are drugs such as anticholinergic drugs, antidepressants, β-adrenolitics, cimetidine, metoclopramide, reserpine, and thiazides [5]. Drugs that have the most serious effect on erectile dysfunction are diuretics – in Dembe et al. and Kalter-Leibovici et al. research it was shown that they were taken much more often in patients with erectile dysfunction [5,20]. Their harmful effect most likely consists in disturbing the function of vascular smooth muscles or abnormal response to catecholamines [5]. Another significant group of drugs is β-adrenolitics, which lowers libido and disturbs erection [21]. This effect has been proven especially for atenolol [22] and metoprolol [23].

THE FREQUENCY OF ERECTILE DYSFUNCTION OVER THE YEARS

The study performed by Dembe et al. shows that erectile dysfunction is the most common complication – nearly 70% of respondents (total number of respondents was 6670 males between 18-91 years) suffer from it [5]. There is also a positive correlation with the age of patients, duration of DM, cigarette smoking, complications of DM such as macroangiopathy, microangiopathy and polyneuropathy, and hypertension. Problems with erection had started approximately 3 years after diagnosis of diabetes and appeared sooner in DM type 2 [2]. Therefore, it is justified to pay attention to erectile dysfunction in a newly diagnosed diabetic [9]. Moreover, Dembe et al. noticed that erectile dysfunction may be the first symptom of DM – nearly 20% of respondents (which is represented by 885 people) had this condition before diagnosing DM [2].

On the other hand, Kouidrat et al. performed a meta-analysis with over 140 studies, in which the overall prevalence of ED in diabetes was 59,1%. Distinguishing between two types, the prevalence of ED in type 2 was around 66%, while in type 1 was significantly lower – 37,5% [3].

Furthermore, Bahar et al. showed that the risk of ED among diabetic patients above 50 years old was 11.21 times higher than for patients under 50 years of age [24].

According to a systematic review and meta-analysis conducted by Shiferaw et al., if a patient's BMI exceeds 30 kg/m^2 there was a 1.26 times more chance to develop ED, and if the HbA_{1c} level was <7% there was a 7% less chance to develop ED [25]. In addition, the prevalence of ED is correlated with the type of DM [26]. Men with severe insulin-resistant diabetes (SIRD) show the highest risk of ED (52%), men with severe insulin-deficient diabetes (SIDD) – 31%, men with mild age-related diabetes (MARD) – 29%, men with mild obesity-related diabetes (MOD) –18%, whereas men with severe autoimmune diabetes (SAID) presents the risk on level 7% [26].

Otherwise, patients with a prolonged DM presented more serious symptoms of ED than patients with a relatively short duration of disease. This relationship between the duration of DM type 2 and the severity of ED was described by Mushtaq et al. in their work. The mean duration of DM in the research group was 8.3 ± 5.1. Mild ED occurred in 19 patients, mild to moderate in 15 patients, moderate in 42 patients, and severe in 24 patients (11.9%, 9.4%, 26.2%, 15.0% respectively) [27].

Generally, many patients are ashamed of ED and they do not report the problem, also many doctors grudgingly ask patients about their sexual health, so it is difficult to research the actual number of people who struggle with ED [28].

PREVENTION AND TREATMENT

A very effective action in the prevention of erectile dysfunction is a proper correction of glucose levels, especially in DM type 2 [29]. In the case of DM type 1, Enzlin et al. showed in their study, that there is no correlation between the metabolic control of diabetes and the sexual dysfunction of patients [30]. Moreover, a change in lifestyle that involves quitting smoking, reducing alcohol consumption, giving up on drugs, losing weight, and exercising is beneficial for the improvement of erection [31]. It is most likely due to the increased availability of NO. In addition, it should be mentioned that the loss of excess body weight helps to improve the function of the penis by affecting the patient’s well-being and reducing the activity of aromatase synthesized in adipose tissue [8].

There are some medications that, when given for a different purpose, can improve the condition of patients. The main examples are ACEI (angiotensin-converting enzyme

inhibitors), which are used in hypertension (which often coexists with diabetes) and improve the function of the endothelium – probably by reducing the degradation of bradykinin [22]. Other drugs are ARB (angiotensin receptor blockers) – especially losartan [32] – and nebivolol [33].

Drugs aimed at preventing ED in type 2 diabetes are neurotrophic factors – NTF-3 (neurotrophic factor 3), NGF (nerve growth factor), GCLDNF (glial cell line-derived neurotrophic factor), and BDNF (brain-derived neurotrophic factor). It was noticed that within 5 weeks after induction of DM in animal models there was a significant decrease in the major pelvic ganglia, which resulted in ED [34].

Selective PDE5 inhibitors – sildenafil, and tadalafil – are the first line of ED treatment [8]. Their activity is based on preventing the breakdown of cGMP. Nevertheless, while sexual stimulation is required, these drugs cannot induce an erection on their own [8]. Admittedly, the effect of their action is stronger in patients without diabetes, however, in studies sildenafil improved erection in 63% of diabetics [35]. The most common side effects of these drugs are headaches, facial flushing, and visual disturbances [8]. It is also important to be careful about the interactions of PDE5 inhibitors with nitrates and alpha-blockers, which are often used in coronary artery disease (CAD) frequently associated with diabetes [36,37]. Nonetheless, PDE5 inhibitors have a beneficial effect on the condition of patients with CAD, inter alia, by reducing the incidence of cardiovascular events [8].

Intracavernous injection of alprostadil is the second-line treatment. Alprostadil, which is a PGE1 (prostaglandin E1), increases the level of cAMP (cyclic adenosine monophosphate) by influencing the enzyme that produces it – adenylate cyclase [8]. As a consequence, the smooth muscles of the vessels relax, dilate, and prevent platelet aggregation [38]. With this type of treatment, it is important to teach the patient how to inject correctly [8]. The effectiveness of this method is estimated at 74% [39]. A combination of alprostadil and phentolamine may increase efficacy by up to 90% [8]. Major side effects include penile pain, prolonged erections, and priapism [40]. Another way to administer prostaglandins is by an intraurethral suppository [8]. It is a method that is easier for the patient to self-administer and has fewer side effects than its injection. It is also the first-line treatment in patients with contraindications to the use of PDE5 inhibitors [41].

Another way – this time with the use of instruments – is a vacuum constriction device (VCD). It is a device that creates negative pressure to fill the cavernous bodies with venous blood. It is especially effective for older men [42]. The main issue when using this method is

the presence of a special ring needed to insert the device. It causes discomfort with ejaculation and pain [8]. The last resort in treating ED is the use of a penile implant [8]. Supportive measures include alpha-lipoic acid and benfotiamine [43].

Apart from pharmacological treatment, a holistic approach to the patient and cooperation with a psychologist is important [3].

CONCLUSION

Our society is aging more and more, which also affects more and more cases of diabetes in the world. It is expected that by the year 2045 the total number of people with diabetes will exceed 745 million [1]. Therefore, diagnosing and treating ED is a serious problem in modern medicine. Due to the quickness and prevalence of this complication in the population, general practitioners, urologists, and diabetologists should pay special attention to this condition, which cannot be achieved without an honest conversation with the patient under conditions conducive to confidentiality. It should not be forgotten that the correct approach to the problem from the psychological point of view is as important as drug treatment, hence the participation of a psychologist in the treatment process is so significant.

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Antibiotics resistance - modern medicine issue

Katarzyna Gadżała[1], Agata Magierska[2], Olga Ptak[2], Krzysztof Gomułka[3]

1. Student Scientific Group of Vascular Surgery, Wroclaw Medical University, Wroclaw, Poland
2. Student Scientific Group of Adult Allergology, Wroclaw Medical University, Wroclaw, Poland
3. Department of Internal Medicine, Pneumology and Allergology, Wroclaw Medical University, Wroclaw, Poland

INTRODUCTION

The discovery of antibiotics is considered as one of the greatest achievements of 20th century medicine. Today, antibiotics are widely used in hospitals, homes and infirmaries. They are used prophylactically in the perinatal and perioperative periods, in the prevention of infections during oncological treatment and transplantations. They are also used in veterinary medicine and industry. It should be noted that the use of antibiotics in food processing is significantly greater than the use for therapeutic purposes. Over time the effectiveness of antibiotics began to decline due to increasing resistance of the microbes. The intensification of antibiotic resistance may lead to the emergence of new epidemiological outbreaks that are difficult to control and stop, threatening the health and life of people all over the world. This problem has been recognized by the World Health Organization (WHO) and the European Commission (EC) as one of the greatest threats to public health. The greatest risk is posed by multidrug-resistant microorganisms because infections they cause are severe, difficult to control, sometimes leading to the death of the patient. Time of treatment for patients infected with drug-resistant strains is increasing and costs are rising. Acquired antibiotic resistance has been divided by the European Center for Disease Prevention and Control (ECDC) and the US Centers for Disease Control and Prevention (CDC) into three subgroups:

1. MDR (*multidrug-resistance*) - acquired insensitivity to at least one drug in three or more antimicrobial categories,

2. XDR (*extensively drug resistant*) - insensitivity to at least one factor in all but two or less categories of antimicrobial agents,
3. PDR (*pan drug resistance*) - lack of sensitivity to all available, registered antibiotics in all groups used for a given species of microorganism.

The excessive, inadequate and careless use of antibiotics is the ground of the problem of multidrug resistance. The way of acquiring and developing resistance by microorganisms is not understandable to a significant part of society, including people from the medical community. Patients take antibiotics off-label or without medical indications, doctors prescribe inadequate pharmaceuticals and pharmaceutical companies have reduced the production of new antimicrobial drugs in favor of more cost-effective, long-term medications. In Poland an additional problem is the predominance of treatment over prophylaxis and microbiological diagnostics, laboratories do not belong to hospitals, they are separate units, which generates additional costs and excludes microbiologists from the empirical treatment process [1,2,3].

EPIDEMIOLOGY AND MORTALITY

The spread of multidrug-resistant bacteria is now a major public health threat worldwide. The increase of infections correlates with higher hospitalization costs, prolonged hospital stay, and increased patient mortality. Among hospitalized people, the most vulnerable are those in intensive care units, undergoing oncological treatment, the elderly and newborns. Infection with antibiotic-resistant bacteria doubles the probability of developing a severe form of the disease and threefold increases the risk of death. Currently, 700 000 people worldwide die every year due to infections with drug-resistant microorganisms. It is estimated that around 10 million people worldwide will die as a result of infection with antibiotic-resistant microbes by 2050 if rational and effective measures are not taken.

Among gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) are currently the most dangerous species. Hospital-MRSA (HA-MRSA) is one of the most common infections acquired during hospitalization. This pathogen is responsible for 25-50% of nosocomial infections. Cases of infections are reported all over the world, the most vulnerable are patients with intravenous catheters, patients with ulcers, after surgery and on a ventilator. HA-MRSA poses many clinical problems, it is resistant to most classes of antibiotics, with the exception of ceftobiprole and cefazoline generating more of previously mentioned issues. Studies have shown that HA-

MRSA infection was twice as likely to lead to patient death than infection with MSSA. Vancomycin-resistant *Enterococcus* is also most common in hospitals, especially in intensive care units (responsible for 25% of infections with multi-drug resistant bacteria). In the MDR studies of bacteria, it has been shown that 30% of patients infected with VRE die within one month of the onset of infection. In case of sepsis caused by *Enterococcus* resistant to vancomycin the mortality rate is up to 50%.

Among Gram-negative bacteria associated with nosocomial infections the most dangerous are pathogens of the genus *Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter* and *Clostridium difficile*. Strains that are widespread in the community outside the hospital include *Escherichia coli* and *Neisseria gonorrhoeae*. The incidence of *P. aeruginosa* infections is increasing worldwide, and resistant strains are now considered to be responsible for 15-30% of nosocomial infections (depending on the geographic region). Mortality within a month of infection reaches 30%. In Poland particular attention is paid to *Acinetobacter baumannii* (ACI) infections, which are particularly resistant to commonly used antibiotics. Studies in the south of the country showed that more than 75% of these pathogens isolated from patients with pneumonia were resistant. About 50% of the cases resulted in the patient's death within a month [4,5,6].

TO WHICH PATHOGENS ANTIBIOTICS RESISTANCE IS INCREASED

Although drug resistance is a current problem, it has not been discovered recently. Penicillin was discovered in 1928 but by then it had already been noticed that some colonies' growth was not inhibited by it. That led to discovering and identifying bacterial penicillinase in 1940 [7]. That may indicate that bacteria always had an ability to develop antibiotic-resistance but the ability only revealed itself when we started using antibiotics on a much bigger scale.

Since then, the modern medicine world has been flooded with news of newly appearing strains of bacteria that have become drug-resistant. One of the worst case scenarios is when a pathogen becomes multidrug-resistant (MDR). Commonly, they are known as superbugs. They are especially prevalent in nosocomial infections caused by *Acinetobacter baumannii, Burkholderia cepacia, Campylobacter jejuni, Citrobacter freundii, Clostridioides difficile, Enterobacter spp., Enterococcus faecium, Enterococcus faecalis, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella spp., Serratia spp., Staphylococcus aureus, Staphylococcus epidermidis,*

Stenotrophomonas maltophilia, and *Streptococcus pneumoniae* [8]. Most of these pathogens are Gram-negative and some of them can be found in the human microbiome. They are extremely common, infectious and difficult to treat.

LAST LINE OF DEFENSE

Since the initial boom with discovering antibiotics in the 1900s there has been a decrease in development of new pharmaceutics and an increase in evolution of bacterial defense mechanisms. In many clinical facilities carbapenems are still considered "last line" antibiotics used for MDR microorganisms especially in empiric therapy. However, there has been a steady increase in carbapenem-resistant pathogens which produce enzymes in many variants that render the drugs useless. These strains are closely monitored and under great scrutiny but unfortunately they still managed to spread around the globe [9]. That has prompted researchers to seek other possible therapy options. The strategies include: developing new chemotherapeutics, researching possible modifications and alternative uses of known antibiotics and also inventing new non-antibiotic preventions. One of the first modifications to the treatment plan was including inhibitors of beta-lactamase's while administering beta-lactams. Nowadays, physicians are recommended to use a combination of different types of antibiotics to fight the infection. In 2007 World Health Organization WHO put polymyxins as a treatment option for MDR organisms. This event has anewed an interest in already discovered chemotherapeutics which were earlier put aside because of serious side effects. However, in 2015 the first polymyxin resistant gene in bacteria was discovered [10].

Nonantibiotic prevention includes using immunogenic mechanisms and microbiologic options to limit infection and inhibit colony growth. Immunogenic strategy uses vaccines and immunostimulants against MDR bacteria [11]. On the other hand, microbiology strategy involves bacteriophages which are bacterial viruses to treat the infection [12]. Both of those methods are still in the research phase but in the future they might be an option for immunocompromised patients.

ANTIBIOTIC RESISTANT PATHOGENS IN THE WORK ENVIRONMENT

Among the professional groups particularly exposed to contact with multidrug-resistant microorganisms are: food industry workers (especially employees of slaughterhouses), farmers,

cattle and poultry breeders, doctors, nurses, orderlies, medical students, veterinary doctors and students, laboratory technicians and people working in the waste disposal. People from a close environment of exposed workers are also at increased risk of infection. In hospitals the greatest threat is infection with methicillin-resistant *Staphylococcus aureus* strains - MRSA, *Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli, Clostridioides difficile, Acinetobacter, Streptococcus pneumoniae* and *Enterococcus* bacteria. Nosocomial infections are caused by insufficient hygiene, resistant strains transmitted mainly on the hands, gloves, clothes, personal belongings of hospital staff, as well as through inaccurate disinfection and cleaning of utility surfaces. *Staphylococcus aureus* - MRSA and strains of the genus *Enterococcus* can survive in unwashed spaces for several months. A single skin contact with a contaminated area causes the transmission of 100 to 10 000 bacteria, it is estimated that each person then transmits the pathogens to 5 or 14 consecutive people. *Staphylococcus aureus, Escherichia coli* and pathogens of the genus *Enterococcus* present in raw meat, dairy products and animal faeces pose the greatest risks for food industry workers and farmers. Infection with multidrug-resistant microorganisms occurs most often during direct contact or through air-droplets, the microorganisms enter the body through contact with the mucous membranes of the mouth, nose and eyes [13,14].

APPROACH IN THE CONTEXT OF POLAND

In Poland, the monitoring of antibiotic resistance within the EARS-Net is financed from the funds at the disposal of the Ministry of Health. It is a part of the implementation of the health policy program called the National Antibiotic Protection Program [15]. In Poland, total consumption of antibiotics is one of the highest among all European countries. [16,17]. Moreover, between 2007 and 2016, there was an increase in the consumption of antibiotics by 8% [18].

Individual bacteria have different susceptibility to antibiotics. In Poland, the following antibiotic resistance is monitored (data for 2019):

1. *E. coli*:

- Ampicillin - 62%,
- 3rd generation cephalosporins - 17,1% (an increase compared to 2015 by about 6%),
- Fluoroquinolones - 33% (an increase compared to 2015 by about 6%),
- Aminoglycosides - 12,6%,

- MDR (to 3rd generation cephalosporins fluoroquinolones, aminoglycosides simultaneously) - 9,3% (an increase compared to 2015 by about 3%, fifth worst result in Europe - after Slovakia, Hungary, Italy and Bulgaria).

2. *K. pneumoniae*:
   - Aminoglycosides - 47,5%,
   - Fluoroquinolones - 61,3%,
   - 3rd generation cephalosporins 58,3%,
   - Carbapenems - 7,7% (there has been an increase in resistance in recent years - from 0,5% in 2015 - connected with spread of *K. pneumoniae* strains producing carbapenemases),
   - Colistin - 5,8%,
   - MDR (to 3rd generation cephalosporins fluoroquinolones, aminoglycosides simultaneously) - 45%.
3. *P. aeruginosa*:
   - Aminoglycosides - 19,7%,
   - Fluoroquinolones - 34,1%,
   - Piperacillin / tazobactam - 28.3%,
   - Ceftazidime - 20.1% ,
   - Carbapenems - 24.0%,
   - Colistin - 0.0%,
   - MDR (simultaneously to three of the following antibiotics: piperacillin/tazobactam, ceftazidime, fluoroquinolones, aminoglycosides and carbapenems) - 22.6%.
4. *Acinetobacter spp*.:
   - Carbapenems - 71%,
   - Aminoglycosides - 80,9%,
   - Fluoroquinolones - 85,5%,
   - MDR (simultaneously to carbapenems, aminoglycosides and fluoroquinolones) - 63,2% - that is twice the European population weighted average.
5. *S. aureus*:
   - Methicillin - 14,9% (population weighted European average is on a comparable level to listed in Poland),
   - Gentamicin - 4,7%,
   - Linezolid - 0,1%,

- Ciprofloxacin - 15.0%,
- Vancomycin - 0.1%.

6. *S. pneumoniae*:
   - 15,5% insensitive to penicillin (including 4.2% resistant),
   - 5.9% not susceptible to cephalosporins 3rd generation (including 0.0% ceftriaxone-resistant and 1.5% resistant to cefotaxime),
   - 25.0% resistant to macrolides.
7. *E. faecalis* and *E. faecium* - the resistance is correspondingly:
   - Aminopenicillins 0.5% and 97.6%,
   - Vancomycin 2.5% and 44.0% (from 17,7% in 2015, in 2019 resistance twice higher than the population-weighted average for the Europe),
   - Teicoplanin 2.5% and 38.2%,
   - High grade resistance to gentamicin (HLGR) 40.2% and 46.3%,
   - Linezolid resistance 0.1% and 1.0% [15,19].

APPROACH IN THE CONTEXT OF EUROPE

In the European Union the issue of antibiotic resistance is monitored by the European Antimicrobial Resistance Surveillance Network that is coordinated by the European Centre for Disease Prevention and Control. The bacteria that are monitored are *Staphylococcus aureus, Streptococcus pneumoniae, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa i Acinetobacter baumannii*. The information is collected from 26 European countries.

According to the results:

1. The antimicrobial resistance varies from country to country and is higher in southern and eastern Europe
2. *E. coli* was the most frequently isolated species in Europe
3. Gram-positive cocci resistance to antibiotics is less of an issue than that resistance observed in Gram-negative bacteria.
4. The resistance to *Enterobacteriaceae* is increasing.
5. In comparison to Europe, in Poland all but one resistance level is increased.
6. Only *S. aureus* sensitivity to methicillin is comparable with European average.

   In the case of other microbes' resistance presents as:

- *E. coli*: 3rd generation cephalosporins - 15,1%, carbapenems 0,3%,
- *K. pneumoniae*: fluoroquinolones - 31,2%, carbapenems - 7,9%,
- *Acinetobacter spp*.: MDR (simultaneously to carbapenems, aminoglycosides and fluoroquinolones) 29,7%,
- *S. aureus*: methicillin - 15,5%,
- *S. pneumoniae*: 12,1% insensitive to penicillin,
- *E. faecalis* and *E. faecium*: vancomycin 18,3% [15].

NATIONAL ANTIBIOTICS PROTECTION PROGRAM AND EDUCATIONAL INITIATIVES

Thanks to the cooperation and exchange of information between the European Commission, the European Center for Disease Prevention and Control (ECDC) and the Member States of the European Union, the National Antibiotic Protection Program was established. This program addresses five areas related to antibiotic resistance in bacteria:

1. 1.Determining the level and mechanisms of bacterial resistance (focusing mainly on hospital-grade, multi-drug-resistant bacteria), screening patients on admission to the hospital, controlling the level of sanitary regime and striving to increase it, introducing changes to the standards of empirical therapy, verification of methods of determining drug susceptibility - these activities are carried out by the National Reference Center for Antimicrobial Susceptibility (KORLD).
2. The second institution is the National Reference Center for the Diagnostics of Bacterial Infections of the Central Nervous System (KOROUN). Its tasks include identifying and defining the biological characteristics of the leading bacterial factors of invasive infections, thus estimating the effectiveness of preventive vaccinations and establishing recommendations for empirical therapy.
3. The third area is monitoring the use of antibiotics in primary health care and hospitals.
4. PPS (point prevalence surveys) are point tests in hospitals which register the number of patients with infection at a specific point of time, characterize risk factors for infections, their etiology and drug sensitivity. They also define the number of personnel qualified in the therapy and control of infections, the use of disinfectants, the number of single patient wards with sanitary facilities.

5. Educational programs aimed at doctors, nurses, pharmacists, diagnosticians, microbiologists and the general public using various tools and strategies:
   - Workshops - both in Warsaw and local - to personalize and target activities,
   - Posters and leaflets based on ECDC guidelines for specialists and general public regarding the basics of antibiotic therapy and infection prevention,
   - Thematic exhibitions - e.g., the exhibition "Superbacteria - resistances - the problem of increasing resistance to antibiotics" which was prepared for the occasion of EDWA/WAAW'2021,
   - Displaying information materials in public transport,
   - Creating recommendations regarding therapy, infection control, diagnostics,
   - European Antibiotic Awareness Day - established in 2008 by the European Commission - celebrated on November 18 [2,20].

SUMMARY

Antibiotic resistance is a problem that affects all countries in the world. Both the public and professionals are not sufficiently aware of the risks and size of the problems associated with antibiotic resistance. As a result, antibiotics are often unnecessarily prescribed or not taken as prescribed. It requires multi-sectoral activities - educational campaigns, infection and use of antibiotics control, updating guidelines for rational antibiotic therapy and procedures for maintaining the effectiveness of antibiotics. The current situation forces the search for new solutions such as introducing new drugs, vaccines and therapeutic strategies.

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Is insomnia a growing issue in the modern world?

Aleksandra Kaczmarek, Ewelina Kopczyńska, Olga Ptak, Agata Szlązak

Wroclaw Medical University, Wroclaw, Poland

INTRODUCTION

Insomnia is one of the most common sleep disorders. It is described by The International Classification of Sleep Disorders (Third Edition- ICSD-3) as having difficulty with falling asleep or maintaining sleep. Patients with insomnia can wake up during the night and early in the morning without the ability to return to sleep [1,2,3]. Most adults need seven to nine hours of sleep per day. Lack of sleep can affect their daytime activities and cause fatigue, sleepiness, trouble with concentration, and mood disturbances. Insomnia can occur as a primary disorder or it can be associated with other physical or mental disorders [4].

The ICSD-3 identifies three types of insomnia: short-term insomnia disorder, chronic insomnia disorder, and other insomnia disorders when the patients have symptoms of insomnia but it cannot be classified as the other two types of insomnia [5].

Short-term insomnia disorder (acute) is diagnosed when a patient has symptoms that persist for less than three months and it can be triggered by stress or a change in medication [4]. Acute insomnia can also evolve into chronic insomnia.

The patient with chronic insomnia should have symptoms that occur at least three times per week over a three months period or longer. Both types of insomnia require different treatments.

EPIDEMIOLOGY

The incidence of insomnia varies depending on the age of the study population. It is estimated that 9 to 50% of adults worldwide report insomnia symptoms in some published surveys with higher rates seen among females, divorced or separated individuals, those who have experienced loss of loved ones and elderly people. What is more, prevalence ranges from 4% to 36% in adolescents [6,7,8,9,10]. Among people with insomnia, difficulties in maintaining sleep are the most common (50 to 70%), followed by difficulties in starting sleep (35% to 60%)

and non-regenerative sleep (20% to 25%). In general, it is not clear how many patients with insomnia regularly take hypnotics [8,11].

The COVID-19 pandemic has a strong impact on sleep problems. An international, multicentre study of the general population in 13 countries and on four continents, including Poland, focused on sleep disorders during the first wave of the pandemic. In Poland, clinical insomnia symptoms were reported by 45,2% of respondents and 24,4% met the criteria for a probable insomnia disorder. Risks of sleep disturbance increased with reported having had COVID-19, financial difficulties and living alone [12].

MAIN CAUSES

Insomnia may be the primary problem, which means that the insomnia is independent from any known physical or mental condition or it may be associated with other medical conditions like restless legs syndrome, chronic pain, gastroesophageal reflux disease and respiratory issues. In fact, insomnia is more frequently associated with psychiatric disorders like depression, anxiety and post-traumatic stress disorder than any other medical illness. It is assumed that insomnia is secondary to mental illnesses, however, it is possible that in some cases insomnia precedes the psychiatric disorder.

Chronic insomnia is usually a result of stress, anxiety and bad sleep habits. Stress can provoke a profound reaction in the body and impact sleep quality and duration. People who have difficulty dealing with stressful situations have an elevated propensity to develop chronic insomnia [13,14].

RISK FACTORS

Everyone can suffer from insomnia but there are factors that increase the possibility for developing insomnia such as:

- Female gender
- Older age
- Stress or worrying
- Hormonal shifts (e.g. during pregnancy or menopause) [1]
- Irregular sleep wake schedules
- Genetics predisposition (family history of insomnia) [15]

- Some medications (e.g. blood pressure drugs, corticosteroids, antidepressants) [6]
- Certain medical conditions (e.g. heart failure, cancer, pulmonary disease, chronic pain) [6]
- Obesity [16]
- Lifestyle (caffeine, alcohol, nicotine, daytime napping)

HEALTH IMPACT

Long-term insomnia can affect health. Lack of sleep is a significant risk factor for cardiovascular diseases in particular: arterial hypertension, myocardial infarction, and chronic heart failure. Chronic insomnia can lead to type 2 diabetes and obesity. Persistent sleep deprivation increases cardiometabolic mortality [1,3,4,17,18,19]. Another consequence of problems with maintaining healthy sleep habits is mental disorders. Patients with insomnia have a greater risk of developing depression, suffering from anxiety and committing suicide [17,18]. The usual complaints are fatigue, depressed mood, poor health condition, difficulty concentrating and focusing attention, memory issues. Insomnia can have a negative impact on the nervous system. It may lead to the development of neurodegenerative diseases, especially dementia [18]. People with insomnia are more likely to have respiratory symptoms, urinary problems, chronic pain and gastrointestinal problems [3]. Insufficient amount of sleep is also a risk factor for driving accidents, injuries and falls [1,18].

PATHOPHYSIOLOGY OF INSOMNIA

The pathophysiology of insomnia may be explained on genetic, molecular, cellular levels, by circuit impairment, by physiological and behavioral disorders [20]. This means that some people may be more susceptible to developing this condition than others.

For insomnia to occur the patient has to have predisposing factors, triggers and later circumstances that deepen insomnia which creates a positive feedback loop in the organism. Predisposing factors for insomnia include [5]:

- depression and anxiety disorders
- high stress job f.e. military
- brain injury
- substance abuse

- menopause and aging
- ongoing and past traumatic life events
- post traumatic stress disorder
- low socioeconomic status
- somatic disorders that interfere with the sleep cycle: dyspnea, nycturia, chronic pain

Currently, hyperarousal disorder is the leading model explaining insomnia. Hyperarousal is defined most commonly in literature as heightened brain activity that disturbes daily functioning and causes impairment to the natural process of falling asleep [20]. It is an umbrella term to disorders affecting physiologic, affective, and cognitive activity. The patient is too ‘keyed up’ and too much ‘vibrating with energy’ to sleep.

DIAGNOSTICS

As insomnia is both a symptom and a disorder in itself, it is important to define and differentiate it from other psychiatric disorders and medical conditions are necessary before reaching a clinical diagnosis [21].

The diagnosis of insomnia and the search for its cause may include:

- Sleep history: it requires a general description of the sleep disorder, i.e., its duration, severity and the patient's sleep habits [21].
- Sleep diary or sleep log is a daily record of important sleep-related information which may include information about wake-up time, how long it takes to fall asleep or the number and duration of sleep interruptions [21,22].
- Use of prescription drugs: sleeping problems can be a side effect of many types of medications. Examples include anticonvulsants, blood pressure drugs, antidepressants and non-steroidal anti-inflammatory drugs.
- Sleep and psychological rating scale: the Epworth Sleepiness Scale (ESS) measures the general level of sleepiness during normal everyday situations (sitting, watching TV, sitting in a car, talking to someone).
- Physical exam: a physical examination can be helpful in diagnosing diseases such as chronic obstructive pulmonary diseases (COPD), asthma or restless leg syndrome which may disturb sleep.

- Blood tests: may help to rule out certain medical conditions such as thyroid problems, iron deficiency anemia and vitamin B12 deficiency that can negatively impact sleep quality [21].
- Polysomnography: a polysomnogram is a procedure that utilizes electroencephalogram, electrooculogram, electromyogram, electrocardiogram, pulse oximetry and respiratory effort. It is considered the gold standard for diagnosing sleep-related breathing disorders such as obstructive sleep apnea [21,23].
- Actigraphy: is the process of measuring movement with the use of a small device called an actigraph which looks similar to a wristwatch. Actigraphy can help establish total sleep time and identify how long it takes a person to fall asleep [21,24,25].

Insomnia is listed in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, revised text (DSM-5-TR). The DSM-5 defines insomnia as dissatisfaction with sleep quantity or quality, associated with one (or more) of the following symptoms: difficulty falling asleep, staying asleep, or returning to sleep [26,27].

NONPHARMACOLOGIC THERAPY OF INSOMNIA

Since the mid-1970s when sleep hygiene education was conceived, there are several nonpharmacological options for the treatment of insomnia. These methods can be effectively used to treat insomnia over an extended period of time [5,8,10].

Sleep Hygiene Education

Sleep hygiene includes educating the patients about lifestyle modifications like avoiding daytime naps, maintaining a regular sleep schedule, avoiding going to bed until drowsy and getting out of bed in 15–20 minutes if not asleep. In addition, discussing with patients the importance of avoiding caffeine, nicotine, alcohol and stimulants within 6 hours of the bed remains an important counseling point. The newest aspect of sleep hygiene education is restricting the use of electronic gadgets/smartphones during bedtime. The sleep environment should be quiet, dark, cool and comfortable [5,7,8,10,28].

Relaxation Therapy

Relaxation techniques are becoming more and more popular every year. Regular breathing exercises, meditation, yoga, relaxation and mindfulness training can help improve the

sleeping pattern. These techniques are designed to reduce somatic tension by relaxing the muscles and reducing intrusive thoughts at bedtime [7,10,29].

Sleep Restriction Therapy

It is important to limit the time in bed to the number of hours of actual sleep. Reduced sleep time improves sleep efficiency. Patients are provided with sleep diaries for at least one week from which the actual number of hours of sleep is estimated. The main disadvantage is the risk of increased daytime sleepiness [7,8,10].

Stimulus Control Therapy

This therapy consists of specific behavioral instructions designed to reconnect the idea of bed and bedroom with sleep. Stimulus control therapy includes going to bed only when one feels tired, not using the bed for reading, working or lounging, not napping during the day and maintaining a constant wake-up time each morning [7,8,29].

Cognitive Behavioral Therapy for Insomnia

Cognitive behavioral therapy for Insomnia (CBTI) is the mainstay of the management of insomnia. It consists of 6 to 10 sessions with a trained therapist that focuses on psychoeducational, sleep hygiene, relaxation training, stimulus control therapy, sleep restriction therapy and cognitive therapy. Cognitive treatment of insomnia aims to identify and challenge the negative beliefs, behaviors and myths about sleep. Many clinical trials recommend cognitive behavioral therapy for insomnia as the first-line treatment for chronic insomnia. CBTI has more lasting benefits and fewer adverse effects compared to drug therapy. Additionally, the effectiveness of this therapy has been demonstrated in patients with comorbid mental disorders [5,7,8,18,28,30].

TREATMENT

Pharmacological treatment should be reserved for cases where nonpharmacological methods have been proven to be unsuccessful or unavailable to the patient. There are many types of medicine that have a hypnotic effect and therefore can be used to treat insomnia. The main categories include benzodiazepines, benzodiazepine receptor agonists (so-called Z-

drugs), antidepressants, antipsychotics, antihistamines, melatonin receptor agonists and phytotherapeutics [31].

Patients with light sleep disturbances usually seek help from phytotherapeutics such as valerian root, hop cones and lemon balm. They may be taken separately or be combined in pills, advertised for their sleep inducing abilities and sold as over the counter medication. The effectiveness of sleep inducing phytotherapeutics is poorly proven and documented as the methodology in carried out clinical trials was poor and inconsistent. Nevertheless, in the general population there is a belief that herbs are fully capable of helping with mild insomnia usually caused by short term stress factors. The other advantage of these substances is the lack of severe side effects and the very low risk of developing an addiction to them [31,32].

In recent years there have been an increase of interest in melatonin and its hypnotic and chronobiotic properties. Melatonin is produced naturally in the human pine gland and influences circadian rhythm. High melatonin levels occur during low light settings and correspond with the feeling of sleepiness in sighted persons. Melatonin levels decrease with age, so use of melatonin in insomnia therapy in elderly patients may have a positive outcome. Moreover, melatonin has low toxicity and is well-tolerated in high doses [31,33,34].

Medications for insomnia treatment usually prescribed by GP are Z-drugs and less often benzodiazepines. The therapy should last no longer than 3-4 weeks because of loss of effectiveness during prolonged exposure to these types of medications and their highly addictive potential. Patients administering the drugs long term may also experience unpleasant side effects that include [35]:

- day time drowsiness,
- hangover effect,
- dizziness,
- memory impairment,
- development of tolerance,
- as a result day-time anxiety, tension, and panic.

Long term use leads to withdrawal symptoms and rebound insomnia [35]. These facts cause general wariness amongst patients and physicians regarding the use of benzodiazepines.

For those that do not want to or cannot use benzodiazepines and Z-drugs an optimal option might be antidepressants with sedative effects: agomelatine, amitriptyline, doxepin, mianserin, mirtazapine, trazodone, trimipramine. Additionally, they may be used for insomnia caused by depressive episodes and aid the therapy.

Antipsychotics and antihistamines are not typically used to treat insomnia but may be considered when insomnia occurs with other ailments [34].

CONCLUSIONS

In conclusion, insomnia is a global health issue that affects a growing number of patients and has a great impact on health, especially the cardiovascular system, nervous system, and mental health that is why it is so important to find appropriate treatment. Moreover, there is still a lot to learn and understand about the causes and pathophysiology of the condition. It is also important to ask patient questions about the range of symptoms because insomnia is a patient-reported symptom and not just the test result. Most of the available treatments are either mostly ineffective or have a lot of serious side effects that impair day-to-day life functioning. There are typically two major treatment options for insomnia, including non-pharmacological and pharmacological approaches. Cognitive behavioral therapy for insomnia is recommended as the first-line treatment for chronic insomnia in adults of any age. People going through stressful situations are more likely to experience chronic insomnia. After Covid 19 outbreak the global population suffers from elevated stress levels, socioeconomic fears, and health problems that is why it is important to raise the issue of insomnia among physicians, researchers, and other medical care professionals.

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Women’s health - sex and gender-specific medicine

Szymon Wiśniewski

Collegium Medicum, Jan Kochanowski University of Kielce, Poland

List of abbreviations

EBM - Evidence-based medicine

HCPs - Healthcare Professionals

SGSM - Sex and Gender-Specific Medicine

WHO - World Health Organization

INTRODUCTION

SGSM is defined by WHO as the study of how biological differences and the characteristics that a society or culture delineates as masculine or feminine affect the presentation, therapeutic approach, outcomes, and other clinical features of the patient's illness. The differences relate to both the cellular and molecular levels [1,2]. Primarily, the current state of knowledge is derived from studies done on males considering both humans and animals [3]. Despite the increased amount of research, a personalized approach to the presented scientific evidence is still not widespread enough, and many HCPs are not aware of the problem that gender differences can bring severe consequences for the course of the disease. Clinical examples were presented over the years with various medical specializations afflicted by a culture of nescience and highly inadequate medical approaches. Hence there is a need to concentrate on that neglected dimension of medicine and improve medical approaches in all specialties to provide appropriate healthcare. This paper aims to conclude and emphasize the need to use all possible means to integrate and foster understanding of the concept and introduce adequate health policies for new requirements, particularly for women.

HISTORICAL BACKGROUND

Historically, women have been excluded from clinical trials, and most of the observations have been made on the men population. In addition, there was no subsequent

attention to gender balance in the studies, and the number of the women subjects included was poor. Most of the drugs were tested in unknown gender or male animals, which did not reflect their pharmacokinetics concerning the differences in female representatives, such as hormones. Many papers require evaluation, new dose guidelines, and research to investigate their side effects [4].

The discussion about gender-specific medicine as a subject started in 1991 when Bernadine Healy published an article named „The Yentl Syndrome", which pointed out that women after a heart attack had worse treatment outcomes than men with the same condition. Paper proved that the clinical presentation in women was significantly different, which delayed diagnosis and treatment implementation. Over time, it has become clear that gender differences in the hospitalization of patients have to be included in the guidelines [5].

The impact of the previous approach continuously affects specific health conditions and leads to insufficiently performed treatment of women. Many studies continue not to document male and female subjects analyzed data by sex, and they miss essential variations in diagnostics and treatments. This piece of science shows the need for implementing significant changes in this field of medicine. Not tackled vigorously may lead to catastrophic consequences, delays, and mistakes medicine could avoid.

GENDER MEDICINE

Personalized medicine is known as the model of approach, which focuses on correcting medical decisions by evaluating them with the patient's individual features. Each year clinicians are working to personalize care better. Unfortunately, the inclusion of SGSM remains inadequate. It is important to note that without considering gender as one of the essential factors, personalized medicine cannot be provided. However, women are burdened with a worse prognosis in many areas of medicine due to the historical background, slow changes, and insufficient dissemination of the topic among medical professionals. The opening of many new pieces of research dedicated to gender medicine concerning diseases and drugs used, and the dissemination of knowledge about them, creates an opportunity to improve the treatment of women [6].

Current knowledge about SGSM is unequivocal and has to be recognized as an essential variable in research. Scientific papers prove a large number of disparities in all medical areas. Chronic diseases impact differently on men and women, and prevalence, degree of severity, and symptoms look entirely different. Variations in pharmacokinetics, metabolism, and drug

distribution in males and females have been identified, many medications require different dosages for men and women for optimal effect, and they can also have various toxicity. Cardiovascular diseases were investigated primarily in males and, in the past, more often have led to numerous frequently recorded misdiagnoses. Nowadays, it still has implications for an suitable approach [7].

An inappropriate Women's Health Strategy can have severe consequences. Currently, initiatives are not sufficiently focused on coping with gender inequalities in medicine. Females live longer, but the quality of life is worse because they tend to be sicker than men. There is still a strong need to eliminate inequalities to have access to the highest possible standard of medical care for both genders [8].

THE COURSE OF COVID 19

The COVID-19 pandemic was caused by severe acute respiratory syndrome coronavirus 2, had an outbreak in China in December 2019, and spread worldwide. The range of symptoms of COVID-19 has a large discrepancy and can be undetectable or even cause death. We can distinguish that the main factors affecting presentation are age, gender, and comorbidities.

Statistics showed that the mortality rate was lower for women patients. In the light of the information they received, we noticed a prime example of the importance of SGSM in reality around us. Subsequent research confirmed sex differences in immune responses to SARS-CoV-2 infection, and males are predisposed to have more severe symptoms and worse outcomes than females. Among the features that may affect various responses, we can distinguish that the X chromosome contains the most extensive number of immune-related genes. Due to having boosting copy, a woman's immune systems respond better to infectious diseases. Also, estrogen may play a protective role. Many variables may cause an immense prevalence of symptomatic COVID-19 in men. The pandemic made us again point out that gender takes an important place in medical sciences [9].

DISCUSSION, LIMITATIONS, AND OPPORTUNITIES

Despite many efforts, until today, a suitable policy could not be implemented in the context of the attention to gender differences in most medical areas. The same patterns and approaches are constantly repeated even though it is against EBM.

For these reasons, a data gathering policy must be implemented swiftly to avoid making the most common mistakes in the future. We must stop extrapolating clinical trials done on men and design and conduct research in conjunction with the extended structure of gender medicine to ensure the results are meaningful. There is a need to introduce guidelines tailored to gender needs and discrepancies in pathophysiology. Structured, up-to-date knowledge of female-specific health conditions is essential to maintaining male-female equality in medicine [10].

Training and workshops are also necessary to disseminate this innovative aspect of medicine. We should focus on increasing awareness, broadening knowledge, and acquiring practical skills. We must promote examples of good practices among the health professionals and the equal opportunities principle for both genders' treatment. Medical education starts at university, and information about the potential distinctions between approaches to patients should always be provided to students by responsible lecturers. Understanding how biology and pathophysiology can influence the outcomes is crucial. The Accreditation Committee should review universities from this point of view to improve the quality of higher medical education and ensure adequate access for students to knowledge about SGSM [11].

In light of the information presented above, gender-specific medicine poses numerous questions. We cannot deny that there is a disparity in medical approaches worldwide. The three main pillars of the SGSM are sex and gender research, translation to clinical practice, and, finally, medical education. There is an immense need to focus on the following objectives and fully enforce all algorithms for disease management concluded by the research based on gender profiles. Gender literacy of healthcare professionals is a critical issue in improving females' health.

Future ideas for revolutionizing the world of medicine include emphasizing the sex and gender medicine component training to develop knowledge regarding the topic in all medical areas. Implementation of that idea can generate significant savings for the health care system, providing appropriate guidance on the treatment issue reduces the patient's stay in the hospital and the number of procedures performed. At present, the main limitation is very clearly inadequate foundation and general lack of knowledge, mainly due to misunderstanding of the concept or confusion about the significance of the word.

CONCLUSIONS

Health systems are failing due to a lack of trying and awareness among healthcare professionals and mistakes of the past. Appropriate knowledge about disease entities is essential

and allows for developing strategies and prevention dedicated to the incidence differences for both sexes. Moreover, adequate therapy shortens the patient's treatment time and reduces the costs generated for the National Healthcare System. When visiting a doctor, we should ask if the manifestation of the indicated disease is the same for both sexes or if the therapy dedicated to it is equivalent for both sexes. The indicated approach allows the dissemination of knowledge about gender-dedicated medicine and prevents medical errors. General information about it is necessary to increase people's awareness. Females and males should be encouraged to become equally involved in health matters that affect them. The approach and methods presented in the article can bring overall improvement in patient outcomes. Furthermore, well-designed large sample-sized randomized controlled clinical trials are necessary to help improve our knowledge base.

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Analysis of the effectiveness of hand disinfection based on survivability of microorganisms

Kalina Kreft[1], Natalia Kuderska[1], Paulina Wójcik[1], Katarzyna Jermakow[2]

1. Student Scientific Circle of Clinical Microbiology and Microbiological Diagnostics, Faculty of Medicine, Medical University of Silesian Piasts in Wrocław, Wrocław, Poland
2. Chair and Department of Microbiology, Medical University of Silesian Piasts in Wrocław, Wrocław, Poland

List of abbreviations

CFU- colony forming unit

CNS- coagulaso-negative *Staphylococcus*

INTRODUCTION

Modern medicine is constantly faced with new challenges, such as the emergence of new pathogens, infections, an increasing share of multi-drug resistant bacteria it leads to the need for new methods of fighting microbes, such as new antibiotics, vaccines, and pro-health actions [1]. The most recent global medical challenge has been the COVID-19 pandemic and the fight against the SARS-CoV-2 virus, which relies heavily on preventing the spread of the virus. The introduced preventive measures in the form of contact isolation of patients, maintaining a safe distance, the requirement to wear masks and frequent disinfection, probably applied to every citizen.

Disinfection process, including hand disinfection is particularly important in stopping the spread of bacteria and viruses. So far the basic principles and technique of disinfection with chemical agents were known only to medical services. Due to easy and common access to the information about the spread of resistant strains; information brochures, posters and leaflets appeared in medical facilities, the technique of hand disinfection has been introduced and explained also to the "ordinary" people [2]. Despite the accessibility of information on the principles of effective disinfection in public places, currently in link with the COVID-19

pandemic, the results are still not satisfactory, as noted by the constantly increasing number of infected and the alarming fact of spreading resistant bacteria outside hospitals [3,4]. Raised awareness of the crucial role of hand disinfection obtained by average citizens, is a success in this difficult pandemic time, but does is also mean people know proper technique of this procedure? Have we all learned how to effectively cut the microbial transmission chains?

AIMS

The aim of the study was to test the ability to disinfect hands in the time of the SARS-CoV-2 pandemic, during the obligatory disinfection of hands in every public space in Poland, in a random group of people in Wrocław. By using the direct method of counting the grown bacteria, before and after the disinfection process, the effectiveness of this process was assessed. Additionally, we analyzed which groups of bacteria survived the disinfection process and remained on the hands despite the use of an alcohol-based disinfectant.

METHODS

In 2021 the Student Research Group of Clinical Microbiology, at the Medical University of Wrocław, led a project which aim was to control the quality of hand disinfection carried out by city residents. The project was co-financed by the Wrocław City Hall. With the use of specialized equipment intended for routine hospital inspections, an imprint of the palm surface of people met in public spaces was taken. During the test, material was collected twice for one proband. First, an imprint of the palm surfaces on a plate with a Count-Tact convex meniscus (made by bioMerieux) was taken before the disinfection process, and then after the hand disinfection process with an alcoholic sanitizer with ethanol. All subjects used the same commercial alcohol hand sanitizer. For the study we used a standardized surface control method with the use of Count-Tact plates, which is used to control in medical facilities, including control of the presence of bacteria on various hospital surfaces, including the hands of staff. Then, the impression plates were incubated in order to grow the microorganisms present on the palmar surfaces, with the rules of microbiological diagnostics kept. After 72 hours of colony growth, the contact plates were assessed in terms of efficiency of the process, and the number of each microorganism was determined. We considered a disinfection process effective if a plate (samples) had the number of microorganisms reduced by at least 80%. Each imprinted

plate carried a material that we decided to examine microscopically (light microscope, Gram staining) and in terms of the specific species of the bacteria. Some of the environmental microorganisms have been classified into a group or type of bacteria. Biochemical identification tests (BBL_Crystal, Becton Dickinson) were used to identify the species.

TEST GROUP

The study group consisted of 93 people of different ages, heading to the COVID-19 vaccination point at the Medical University of Piastów Śląskich in Wrocław, which agreed to take part in the study. Each one, in addition to signing the consent, also completed a survey with questions about the disinfection recommendations. The group included employees of nearby clinics, students of the Medical University as well as people completely unrelated to the medical field.

RESULTS

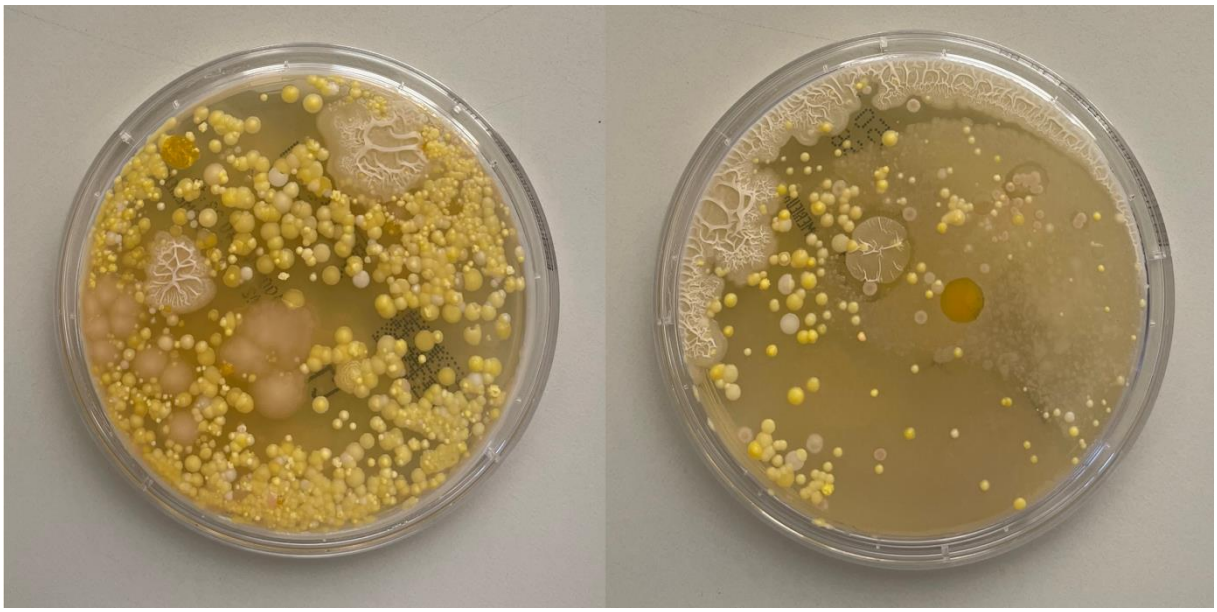
While analysing the data obtained from the study of 186 Count-Tact plates with convex meniscus, obtained before and after disinfection, we paid special attention to those by certain specific bacteria that remained on the hands after the disinfection process. The samples with handprint before disinfection had an average of 93 colonies of bacteria of variable morphology, which is an equivalent of 372 colony forming units (CFU) per square meter of skin (CFU/m^2). However, in the samples collected after the disinfection process, an average of 9 bacterial colonies were identified, which is equivalent to 36 CFU/m^2 of skin. This means an average over 10-fold reduction in the number of microorganisms as a result of hand skin disinfection. In 21 patients, no growth of any bacteria was observed after the disinfection of hands, which is 22% of the study group. Another 57 people correctly performed disinfection procedure, reducing the amount of bacteria on hands by ≥80% CF /m^2 of skin (61% of respondents). Among the research participants, there were 5 people with 50% or more microbes remaining on the skin after the process, compared to the sample before disinfection.

The dominant group of bacteria isolated from the skin of the hands were Gram-positive cocci (97% of samples), among which most frequently isolated were M*icrococcus spp.*, *Staphylococcus spp.* and less frequently, *Streptococcus spp.* and *Enterococcus spp.* Among Staphylococcus genus, all species belonged to the group of coagulase-negative staphylococci,

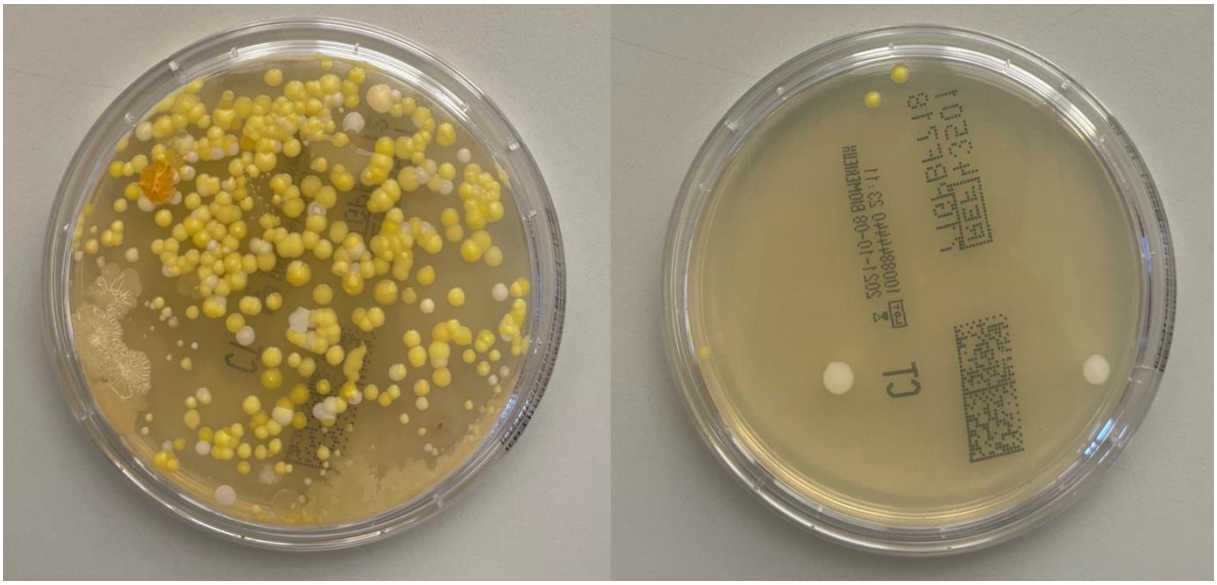
which together with *Micrococcus spp.* form the normal physiological flora of the skin. Observation of bacterial resistance to the disinfection process revealed that coagulase-negative staphylococci (58.1% of people) and *Micrococcus spp.* (40.7% of people) were most often left on the hands of patients. These two groups combined had 47.4% share of bacteria surviving the disinfection process.

Another Gram-positive bacteria, *Brevibacterium spp.* and *Corynebacterium spp.*, Which are typical flora of the dry skin, were found in approx. 17% of people, and their number decreased to 10% after the disinfection process.

On the hands of study participants, before disinfection we identified numerous Gram-negative bacilli, mainly intestinal (*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*), which occurred in 39% of people, and the non-fermenting rod *Acinetobacter baumannii*, identified in 30% of people. Unfortunately, even after the disinfection process, Gram-negative intestinal bacteria remained on the hands in 22.5% of people (mainly *Klebsiella spp*. - almost 12%), and *Acinetobacter spp.* - in 17.2%. Considering the percentage of *Acinetobacter* among bacteria surviving the disinfection process, this dangerous bacterium represented up to 8.2% of the total number of microorganisms remaining on the hands after cleaning the hands.



Photography 1. Test No. 142 - an example of ineffective hand disinfection. On the left, a culture medium with a handprint before disinfection, on the right - after disinfection. Bacteria grown and isolated after disinfection are: *Micrococcus spp., Bacillus spp., Acinetobacter spp.*, Gram-negative intestinal bacilli, *Corynebacterium spp., Brevibacterium spp*



Photography 2. Test No. 149 - an example of effective hand disinfection, before and after. On the left, a culture medium with a handprint before disinfection, on the right - after disinfection. After disinfection, only the species of permanent skin flora remained: *Micrococcus spp.* and Coagulase negative *Staphylococcus*

Incubation of the Count-Tact plates revealed numerous species of environmental *Bacillus spp.* which, due to their low nutritional requirements and vigorous growth, created a challenge in the determination of CFUs. This common environmental microbe appeared on the skin of more than 40% of the people. Its share among the species surviving the disinfection was high and was up to 23.7%.

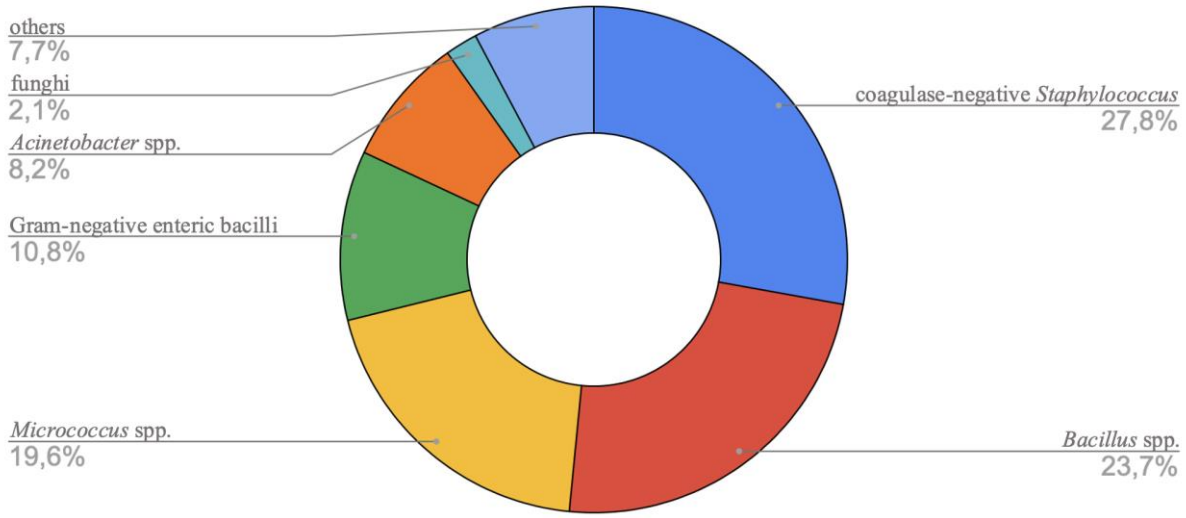


Figure 1. Percentage share of species among microorganisms remaining after the disinfection process

We also identified mold fungi *Aspergillus spp.* and *Penicillium spp.* on the hands of the participants, which appeared in 17% of people. The yeast-like fungi *Candida spp.* were isolated much less frequently, in 3% of people. The disinfection process was ineffective against *Penicillium spp.* identified in 4.3% of the people examined

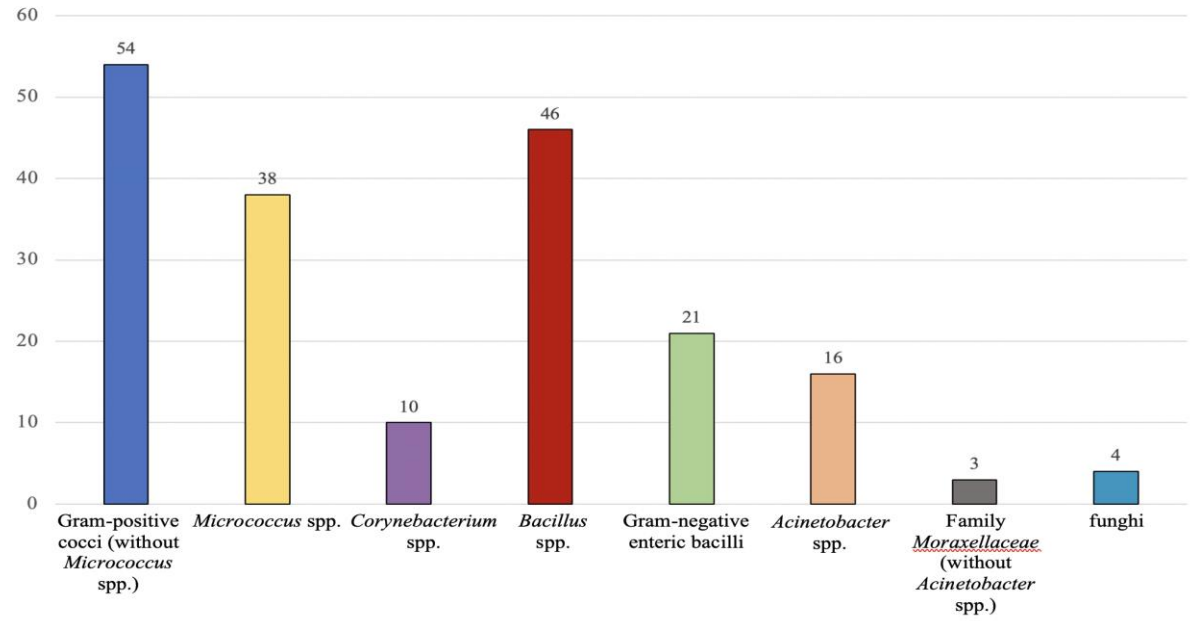


Figure 2. Number of samples (Count-Tact plates) considered positive, plates on which exact microorganisms were found after the hand disinfection procedure (n = 93)

DISCUSSION

Well performed hand disinfection is the basic mechanism in the fight against the spread of microorganisms and should be a part of infection prevention strategy, important in hospitals especially [4].

Sarah L. Edmond-Wilson and her team in a 2015 article [5] showed that there are 8 to 24 families of bacteria on the skin of the hand, mainly *Firmicutes, Actinobacteria, Proteobacteria,* and *Bacteroidetes.* They concluded that bacteria from the families of *Staphylococcaceae, Streptococcaceae, Corynebacteriacea,* and *Moraxellaceae* are common residents, as confirmed by our handprint studies before and after disinfection. In our research, mold and yeast-like fungi appeared, which the group of the above-mentioned scientists did not analyze. In the case of *Aspergillus* and *Penicilium* fungi, they are not permanent skin residents and their presence is only the result of hand contact with the objects in environment. The

isolation of *Penicilium spp.* in 4 people after disinfection can be explained by the resistance of fungal spores to alcohol-based disinfectants [1].

However, it is worth remembering about it and in long-term care medical units, where immunocompromised people susceptible to rare pathogens are hospitalized, wash hands with soap and water before the disinfection process, which will help mechanically remove fungal spores [3]. In the Polish study of microbiological control of hand hygiene, the microorganisms found on the hands of medical personnel were examined. The environmental strain of *Bacillus spp.* was bred in the highest percentage (30.2%), which is consistent with our results. *Bacillus spp.* bacilli were found on the hands before disinfection in 40% of people and were the second most frequent group of bacteria isolated from the skin after disinfection. The examination also showed the presence of numerous coagulase-negative staphylococci on the skin of the hand. In our study, coagulase-negative staphylococci were also the largest group of bacteria isolated, both before and after disinfection, but they were isolated with a much greater frequency (98% of the respondents). This is probably due to the fact that we used a completely different, much more sensitive technique of collecting the material for the examination (direct hand skin imprint) compared to Niecwietajewa's team [6] (hand skin swabs). However, unlike the above-mentioned team, we did not isolate a single strain of *Staphylococcus aureus.*

In the results of the study, the frequent isolation of Gram-negative bacilli, including intestinal (39%) and *Acinetobacter baumannii* (30)% concerned us. These are opportunistic, potentially pathogenic microorganisms that easily acquire antibiotic resistance mechanisms and, as it turns out, easily adhere to the surface of the hand [7]. After the disinfection process, we found the presence of intestinal and *Acinetobacter* bacilli in 22 and 17% of the respondents, respectively. This shows that the disinfection process was carried out incorrectly by the test participants e.g. too little sanitizer, too short duration of the disinfection, the sanitizer applied only to a part of the hand, wet skin, or even an inappropriate chemical composition of the sanitizer formula [4].

It seems that during the COVID-19 pandemic, thanks to the pervasive leaflets and guides, everyone learned the technique of hand disinfection. However, the research revealed imperfections in the procedure, which results in the survival of bacteria that are not the permanent flora of the skin. Changes in the definition of hand hygiene were presented in 2017 by Vandegrift et al. [2] underlining the importance of those actions and practices that reduce the spread or transmission of pathogenic microorganisms, and thus reduce the incidence of disease.

Additionally, it is known that some of the pathogens present on human skin, such as *Staphylococcus aureus* or *Staphylococcus epidermidis*, become drug resistant and forms a problem for the treatment of infections. Quote: “Many of these (e.g., *Staphylococcus aureus* and *Staphylococcus epidermidis*) also have the potential to become multidrug-resistant pathogens)” [7].

Our research has shown that the most common group of microorganisms remaining after the disinfection process are coagulase-negative staphylococci, including *Staphylococcus epidermidis*. However, we want to emphasize the potential danger of presence of intestinal and non-fermenting bacilli on the hands, after disinfection. Those bacteria are characterized by a much higher level of virulence and resistance than the mentioned *Staphylococcus epidermidis.* The hand microbiome is a critical area of research for diverse fields, such as public health. The dynamic microbiota of the hand surface is related to the various hygienic habits of humans and can be transmitted or exchanged upon contact with objects of daily use [7].

Hands represent a critical target for microbiome studies because they have a unique role in transferring microbes. Product use can impact the hand microbiome, with greater pathogen hand carriage on people using frequently hand hygiene products, while other studies have demonstrated reduced pathogen carriage and/or infections with use of these products [5].

Hand disinfection is a key step in cutting the transmission chain of potentially harmful pathogens. Meanwhile, the analysis of the effectiveness of the disinfection in the group of residents of Wrocław showed an insufficient knowledge about the correct technique of this process. This thesis is based on results saying that up to 17% citizens performed disinfection that reduced number of bacteria less than 50%. It seems that in the time of the COVID-19 pandemic, despite the availability and transparency of the disinfection procedure, we still observe the lack of effective reception of recommendations, the low level of the so-called "Compliance" and the lack of understanding the significance of preventing infectious diseases.

CONCLUDING REMARKS; LIMITATIONS OF THE METHODS USED

1. Identifying some of the bacterial species was difficult because biochemical identification tests (BBL_Crystal, Becton Dickinson) are used for microbiological diagnostics of infectious pathogens and do not include environmental species.
2. The study included only aerobic and micro-aerophilic microorganisms present on the skin.

CONCLUSIONS

1. The effectiveness of the disinfection process was insufficient.
2. Skin microbiome bacteria (*Staphylococcus* coagulase-negative, *Micrococcus*) have disturbingly high ability to survive the disinfection process. Fortunately, these bacteria have a low virulence potential and with maintained integrity of the skin, they do not threaten with serious infections.
3. Survival rate of potentially pathogenic microorganisms, such as Gram-negative bacilli *Klebsiella pneumoniae*, *Escherichia coli* or *Acinetobacter baumannii*, enables the transmission of these dangerous bacteria and can be a serious problem, e.g. in hospitals.
4. *Bacillus spp.* bacteria and *Penicillium spp.* fungi that remained on hands after disinfection have a higher resistance to alcoholic sanitizers due to the ability to produce spores.
5. Although in more than 80% of cases, the number of microbes has been significantly reduced after hand disinfection, this is not enough to effectively limit the transmission of pathogens.

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Loss of herd immunity - a current problem in the field of infectious diseases

Olga Ptak[1], Agata Magierska[1], Milena Sitkiewicz[2], Zuzanna Szczepaniak[1] and Krzysztof Gomułka[3]

1. Student Scientific Group of Adult Allergology, Wroclaw Medical University, Wroclaw, Poland
2. Student Scientific Group of Hematology, Wroclaw Medical University, Wroclaw, Poland
3. Department of Internal Medicine, Pneumology and Allergology, Wroclaw Medical University, Wroclaw, Poland

INTRODUCTION

Herd immunity refers to a concept from epidemiology, which is based on preventic impact of individual immunity to pathogen transmission among a group. Herd immunity occurs when enough members of the community have resistance against some pathogen.

In this case an agent, which occurred in one person, has a minimal chance to cause an epidemic because it comes in contact with people with immunity and the path of spreading the infection is interrupted [1,2].

The more resistant individuals, the less probability of pathogens to contact with susceptible organisms [1,2].

Using vaccinations gives humanity a chance to create herd immunity without consequences of suffering from diseases, which is very important, especially in cases of diseases with high mortality or with serious complications [1,2].

Herd immunity can also cause less damage in the population when pathogens appear inside, through minimizing the number of infected people and decreasing speed of transmission. It gives time necessary to react and start prevention in another way [1,2].

In this process some pathogens can be even eradicated, which happened with smallpox [1,2].

VACCINATIONS IN THE WORLD

Among countries in the world health problems are generated by different diseases. Data about immunization goals in global medical efforts is published on the website of Centers for Disease Control and Prevention (CDC) and is divided into four groups.

1. Advance the development of new and/or improved vaccines for diseases that are high burden or have epidemic potential.
2. Control diseases to reduce morbidity and mortality to locally acceptable levels:
    - Influenza,
    - Japanese encephalitis,
    - Tuberculosis,
    - Yellow fever,
    - Diphtheria,
    - Pertussis,
    - *H. influenzae* type b disease,
    - Pneumococcal disease,
    - *Rotavirus gastroenteritis*,
    - Tetanus,
    - COVID-19,
    - Dengue,
    - Ebola virus disease,
    - Hepatitis A,
    - Hepatitis E,
    - Mumps,
    - Typhoid,
    - Varicella.
3. Eliminate transmission of diseases in defined geographic areas and eliminate diseases as a public health problem:
    - Measles,
    - Rubella,
    - Bacterial meningitis,
    - Cervical cancer,
    - Hepatitis B,

- Cholera,
- Rabies,
- Tetanus.

4. Eradicate diseases by stopping all transmission worldwide:

- Polio [3].

VACCINATIONS IN POLAND

Vaccination programs in Poland are updated every year, so vaccination schedules are different for people from individual years of birth.

The Protective Vaccination Program for 2022 includes obligatory vaccinations and recommended vaccinations. Obligatory vaccinations consist of three groups: for children and teenagers according to age, for people at particular risk of infection due to clinical or epidemiological reasons and post-exposure vaccinations. In terms of herd resistance, the first two of this group are the most important.

Obligatory vaccinations for children and teenagers according to age:

- Tuberculosis,
- Hepatitis B,
- Rotaviruses,
- Diphtheria,
- Tetanus,
- Pertussis,
- *Hemophilus influenzae*,
- *Streptococcus pneumoniae*,
- Poliomielitis,
- Measles,
- Mumps,
- Rubella.

Obligatory for people at particular risk of infection due to clinical or epidemiological reasons:

- Hepatitis B,
- Chicken pox.

Recommended vaccination depended on circumstances includes:

- Influenza,
- Chicken pox,
- *Neisseria meningitidis*,
- *Streptococcus pneumoniae*,
- *Haemophilus influenzae*,
- Tick-borne encephalitis,
- Hepatitis B,
- Hepatitis A,
- Measles,
- Mumps,
- Rubella,
- Diphtheria,
- Tetanus,
- Pertussis,
- HPV,
- Tuberculosis,
- Cholera,
- Typhoid,
- Poliomyelitis,
- Rabies,
- Yellow fever [4,5].

In connection with the SARS-CoV-2 pandemic, Poland also introduced anti-COVID-19 vaccinations, which, according to the ordinance, constitute a method of preventing the disease [6].

HERD IMMUNITY AND VACCINATION COVERAGE IN RELATION TO CHOSEN DISEASES

In 2012, the World Health Organization (WHO) established the Global Vaccine Action Plan. Main goal was to achieve at least 90% vaccination coverage for all routine vaccines by 2020. In 2019, the mean percentages of vaccination coverage were lower than 90% for ten routine vaccines. The mean percentages of vaccination coverage decreased from 2015 to 2019 for six routine vaccines [7]. In 2020, 23 million children under the age of 1 year did not receive

basic vaccines. It is the highest number since 2009 [8]. The European Vaccine Action Plan (EVAP) 2015–2020 is a regional interpretation of the Global Vaccine Action Plan. Its three main goals were to sustain polio-free status, eliminate measles and rubella and control hepatitis B infection [9].

Poliomyelitis is eradicated in most countries, thanks to the resolution of the World Health Assembly from 1988 which started the Global Polio Eradication Initiative (GPEI). The premise of GPEI was to eradicate poliomyelitis by the year 2000 [10]. Since 1988 there has been a decrease in the number of cases by 99.9%. Worldwide the eradication of wild type 2 polio virus (WPV2) was announced in 2015 and Wild Type 3 Polio Virus (WPV3) in 2019 [11]. Poliomyelitis caused by wild type 1 polio virus (WPV1) is still present in two countries: Afghanistan and Pakistan, which cause risk of importation of the disease to polio-free regions [8,11,12].

In Poland vaccination against poliomyelitis was introduced in the late 1950s, the last case caused by wild-type viruses took place in 1984 [11].

In recent years, the emergence of polio outbreaks caused by circulating vaccine-derived poliovirus (cVDPV), mainly type 2, in several countries has become an issue of concern for the new GPEI 2022-2026 polio eradication strategy [13].

In 2020, 83% of infants around the world received 3 doses of polio vaccine [8].

Measles immunization's coverage decreased in recent years due to lowering the number of vaccinations of children. The vaccine for measles was introduced in the 1960s. Before that about 130 million people became infected each year. As a result of mass vaccination campaigns in 2000-2010, the global number of deaths from measles has decreased by 78%. In 2006-2009 isolated cases of the disease were reported. Since 2010, there has been a marked increase in the number of cases. It was related to the incorrect suspicions that measles, rubella and mumps vaccines may cause autism. The United States obtained measles elimination status in 2000 and in 2019 recorded the highest number of cases in 25 years [14].

In 2019 the global prevalence of individuals with vaccine-induced measles immunity in the target measles' vaccination population was 88.1%, meanwhile herd immunity against measles provides vaccination status above 95%. Herd immunity against measles was established in 63 countries [7]. By the end of 2020, 84% of children had received 1 dose of measles-containing vaccine by their second birthday and 70% of children received 2 doses [8].

Since mid-2018, after a long period in which the disease was very well controlled and close to elimination, we have been observing an epidemic increase in the incidence of measles in Poland [14].

Rubella is another disease found all over the world against which international efforts are made to reduce its incidence. By the end of 2020 global coverage was estimated at 70% [15]. In countries where vaccination began in the 1970s, the incidence of rubella was reduced by up to 99% compared to the pre-vaccination period. Even though around 100 000 babies worldwide are still born with congenital rubella syndrome each year. In the WHO European Region, 60% of the population received their first dose of the rubella vaccine in 2000. In 2019 31 of 53 countries reached ≥95% of the population vaccinated with the first dose. Second dose vaccination coverage in the WHO European Region reached 96% in 2019.

In Poland, in 2019, the vaccination rate was 92.6% for the first dose of measles, mumps, and rubella (MMR) vaccine and 91.1% for the second dose. Between 2013 and 2019, the number of reported rubella cases decreased significantly [15].

Global coverage with 3 doses of hepatitis B vaccine is estimated at 83% by the end of 2020 [8]. In 2016 around 3.9% of the global population lived with chronic HBV infection. More than 800 000 people die each year from chronic hepatitis B and its late sequel. The death rate due to hepatitis in the world increased by 22% in the 2000-2015 period.

In Poland the number of new cases is 4-9 per 100.000 inhabitants. There were no cases of disease in the group of people under 25 years of age - the group covered by the general vaccination [16].

86% of children worldwide are currently vaccinated with the DTP vaccine (against diphtheria, tetanus and pertussis). In Poland, no case of diphtheria has been reported since 2001. Compulsory vaccinations have virtually eliminated the incidence of tetanus in children and adolescents in Poland, however this disease is one of the most important health issues in Africa, Asia and South America. For several years in Poland and also in many countries, even those with high levels of vaccination, there has been an increase in pertussis incidence [16,17,18].

CAUSES OF LOSING HERD IMMUNITY

The main causes of losing herd immunity are: human migration, change of contact patterns, pathogen mutation, population turnover and waning of immune response.

Massive migration may cause an influx of people susceptible to disease or the loss of a large number of vaccinated people leaving the population vulnerable against pathogens.

In the last few years, the significant change in contact patterns between people has been observed. Social campaigns to reduce direct contact, people undergoing self-quarantine and efforts to lower population density in public spaces in hopes to stop the spread of the COVID-

19 contributed to lowering the spread of the epidemic and allowing it to stop transmission patterns .

The pathogen evolution is different depending on its kind and species. Most viruses are known for their ability to change their genetic material and great capability to cause epidemics. We see this every year with influenza virus and now with COVID-19. Bacteria evolution is slower but still causes many treatment problems especially when the evolution involves antibiotic resistance.

There are also factors that are inevitable but the changes overall are slower. The main processes here are: population turnover and waning of immune response.

The waning of immune response over time is natural and expected and mostly applies to elderly people. For that reason in an aging population the herd immunity may fall below the threshold that protects from endemic outbreaks.

Population turnover results in fewer people that have achieved the correct immune response over their lifetime and more children that have never come in contact with pathogens and never had a chance to immunize. This explains the repedality of epidemic cycles [19].

WHY ARE PARENTS CONCERNED ABOUT VACCINATING THEIR KIDS?

In recent years the public has been flooded with a multitude of news regarding the anti-vax movement, its postulations and the legal debate that has taken place over compulsory vaccinations and the extent of parental rights and responsibilities for their children and to society.

Nowadays, the parents are constantly inundated with various claims that mostly come down to whether it is safe to vaccinate their child or not. Most of the doubts seem to arise from reading about possible side effects of vaccinations and claims about their alleged toxicity. One of the main sources of that information are social media and internet forums where parents share their own experiences and spread misinformation about the possibility of vaccines causing autism and/or mercury poisoning. Most of the more popular claims have been repeatedly proven to be unfounded but still exist in the minds of parents causing increasing doubts and hesitations.

Nevertheless, in many unrelated studies that took place over the years, in Poland the majority of parents (over 90%) still vaccinate their children according to the vaccination program [20,21]. Most of them describe their knowledge on that topic as ‘average’ or ‘great’. Although they also express uncertainty about the security and possible unwanted post-vaccine reaction, they also acknowledge the benefits of immunization and accept the compulsory

vaccination program. Doctors and nurses are still considered as main sources of information about vaccines.

Still, more and more parents decide not to vaccinate their children. This alarming trend seems to be becoming a worldwide problem. In Poland, in 2020 the number of unvaccinated children reached 50 000 [22].

The vaccine hesitancy is mostly caused by: fear of unknown mechanism of vaccine, risk of the post vaccine reaction and other side effects, misinformation about the etiology of autism in children. There is also a belief that vaccines are a big conspiracy by pharmaceutical concerns whose main goals include: monetary gain, decreasing population numbers and control of society [23].

CONTRAINDICATIONS TO VACCINATION

Vaccinations are mainly administered to healthy people. There are many advantages of vaccines for society as a whole but when it comes to an individual patient, it is sometimes necessary to consider what is better and more safe. Contraindications to vaccination are conditions and clinical situations such as ongoing or chronic diseases and drug therapies in which carrying out preventive vaccination would be associated with an increased risk of serious adverse effects or less effective vaccination. Contraindications depend on the type of vaccine and the clinical situation [24].

Contraindications:

1. Severe allergic (anaphylactic) reaction to vaccine or vaccine's components.
2. Serious adverse events, complications requiring invasive or long-term treatment, without *restitutio ad integrum,* following a prior dose when the risk due to infectious disease and its complications is low or moderate.
3. Live attenuated vaccines are contraindicated in patients with agammaglobulinemic syndrome, complete T-cell deficiency, HIV immunodeficiency (with less than 15% CD4+ lymphocyte count of total lymphocyte count), transplant within six months and solid or hematologic neoplasia during treatment.
4. Current therapies such as chemotherapy and radiotherapy (up to six months from suspension), high-dose steroids (up to 2-4 weeks from suspension) and high-dose immunosuppressive drugs [25].

Some conditions must be taken under special consideration:

1. Pregnancy - live attenuated vaccines (such as Varicella, Measles-mumps-rubella and Calmette-Guerin Bacillus tuberculosis BCG) are contraindicated.
2. Preterm infants with weight less than 2000g - first dose of hepatitis B vaccine administered in hospital after birth does not count to the sequency, which started at one month of age.
3. Immediate allergy reaction to milk and egg proteins which are components of some vaccines.
4. Immunocompromised state:
   - Mild to moderate immune deficiency;
   - Genetic diseases which can be associated with immune deficiency (e.g. DiGeorge syndrome);
   - Hemato-oncological diseases;
   - Human immunodeficiency virus infection;
5. Severe illness such as chronic disease (concerning lungs, heart and liver), end-stage renal disease, diabetes, asplenia etc.
6. Health care personnel.
7. Men who have sex with men [26,27].

Lower efficacy of vaccines may be caused by interactions with some drug therapies - for example treatment with immunoglobulins can cause that effect on Measles-mumps-rubella, Varicella and Rotavirus vaccine. Combination of Varicella vaccine and salicylates increase risk for Reye's syndrome. Influenza vaccines can interact with carbamazepine, phenytoin, theophylline and warfarin. Efficacy of oral typhoid vaccine can be decreased by amoxicillin, ciprofloxacin, chloramphenicol, doxycycline, sulfonamides and proguanil treatment. In patients using ethambutol, isoniazid and rifampicin, BCG vaccination is contraindicated [25].

VACCINATION AGAINST COVID-19 DISEASE

People can acquire immunity in two ways - if they become infected or by vaccination. Herd immunity can be achieved if 86% of the population is vaccinated [26]. Efficacy of every vaccine consists of common acceptance and the fact that the majority of the population use it [27]. Vaccination against COVID-19 disease is widely treated with mistrust. People are concerned about its efficacy and adverse effects that it can cause [28]. That indicates the importance of building trust and providing commonly available and transparent sources of true

information. This can be achieved by launching advertising campaigns, unifying the message and dispelling doubts because knowledge is the best way to promote vaccines [29,30].

In Poland, the amount of people vaccinated with at least one dose of the coronavirus vaccine is about 59%, while fully vaccinated people account for less than 52% of the population (as of July 2022). This statistic means that there is no herd immunity to this disease in Poland [31].

WHAT HAS TO CHANGE?

The actions have to be taken on many levels including the government, education system and the GPs offices. The main objective should be to improve and maintain confidence in the validity, safety and essentiality of vaccines. Physicians should be knowledgeable about the vaccine program, the possible post-vaccine reactions, side effects but also about the vast health benefits. The parents' concerns should be answered with facts, empathy and be understandable for all parties involved in the conversation [32].

SUMMARY

Herd immunity has become a very relevant topic in recent years. It's a term constantly used by mass media on television, the internet and in medical settings. Over time, the meaning has been lost and also its significance. Herd immunity protects the population from epidemic outbreaks and has a real scientific backing. Many epidemiologists work to ensure that the medical field has enough data to protect the population from infectious diseases. And we, as a society, should spread the facts and combat misleading information that arises regarding the topic. Everyday parents have to make a decision to vaccinate their children so they should have access to relevant, updated information and to receive support from their family medicine doctor, nurses and regional midwives to make a well-thought-out decision regarding their offspring's health.

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