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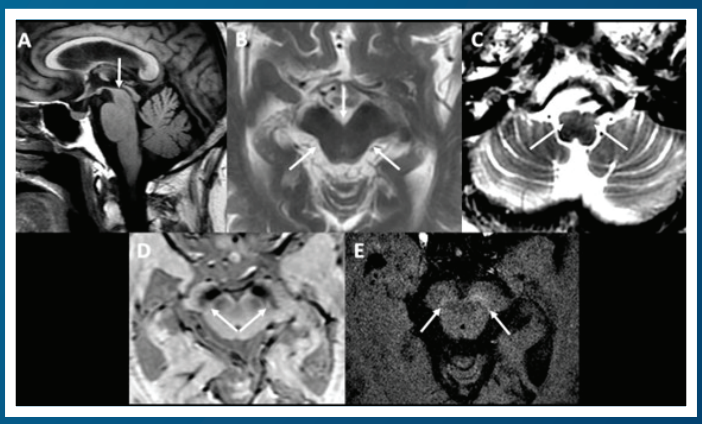

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Arquivos de Neuro-psiquiatria

Volume 80, Number 6, June 2022, São Paulo, SP, Brazil

EDITORIAL

547 **Measuring optic nerve sheath diameter using ultrasonography for the detection of non invasive intracranial pressure: what it is and what it is not**
Medição do diâmetro da bainha do nervo óptico por ultrassonografia para aferição não invasiva da pressão intracraniana: o que é e o que não é
Chiara ROBBA

ARTICLES

550 **Stroke in the state of Alagoas, Brazil: a descriptive analysis of a northeastern scenario**
Acidente vascular cerebral no estado de Alagoas, Brasil: análise descritiva de um cenário do nordeste brasileiro
Letícia Januzi de Almeida ROCHA, Kauan Araújo da SILVA, Arthur de Lima CHAGAS, Arthur de Oliveira VERAS, Vitor Gustavo Leão SOUTO, Maria Clara Motta Barbosa VALENTE, Jussara Almeida de Oliveira BAGGIO

557 **Passive smoking may be associated with bleeding of cerebral arteriovenous malformation in non-smoking women:a retrospective analysis**
O tabagismo passivo pode estar associado com o sangramento de malformação arteriovenosa cerebral em mulheres não fumantes: uma análise retrospectiva
Jiao WANG, Shuai ZHANG

563 **Effect of the COVID-19 pandemic on patients with inherited neuromuscular disorders**
Efeito da pandemia do COVID-19 em pacientes com doenças neuromusculares hereditárias
Cristiane Araujo Martins MORENO, Clara Gontijo CAMELO, Pedro Henrique Marte de Arruda SAMPAIO, Alulin Tácio Quadros Santos Monteiro FONSECA, Eduardo de Paula ESTEPHAN, André Macedo Serafim SILVA, Renann Nunes PIROLA, Luiz Henrique Libardi SILVA, Karlla Danielle Ferreira LIMA, Marco Antônio Veloso de ALBUQUERQUE, Antonio Edvan CAMELO FILHO, Marcos Vinícius Oliveira MARQUES, Mario Teruo YANAGIURA, Wagner Cid Palmeira CAVALCANTE, Ciro MATSUI JUNIOR, Lucas Michielon de Augusto ISIHI, Rodrigo Holanda MENDONÇA, Ana Flávia Pincerno POUZA, Mary Souza de CARVALHO, Umbertina Conti REED, Edmar ZANOTELI

570 **Diagnostic accuracy of CompCog: reaction time as a screening measure for mild cognitive impairment**
Acurácia diagnóstica do CompCog: tempo de reação como uma medida de rastreio para comprometimento cognitivo leve
Larissa HARTLE, Marina MARTORELLI, Giulia BALBONI, Raquel SOUZA, Helenice CHARCHAT-FICHMAN

580 **Measuring optic nerve sheath diameter using ultrasonography in patients with idiopathic intracranial hypertension**
Medição do diâmetro da bainha do nervo óptico por ultrassonografia em pacientes com hipertensão intracraniana idiopática
Kenan DAĞDELEN, Merve EKICI

586 **A study on the correlation between pain frequency and severity and vitamin B12 levels in episodic and chronic migraine**
Estudo da correlação entre frequência e gravidade da dor e níveis de vitamina B12 em enxaqueca episódica e crônica
Sibel ÜSTÜN ÖZEK

593 **Does length of time since diagnosis in Parkinson's disease influence heart rate variability? A cross-sectional study**
O tempo de diagnóstico na doença de Parkinson influencia a variabilidade da frequência cardíaca? Um estudo transversal
Mileide Cristina STOCO-OLIVEIRA, Heloisa Balotari VALENTE, Laís Manata VANZELLA,Larissa Borba ANDRÉ, Mariana Viana RODRIGUES, Franciele Marques VANDERLEI,Augusto Cesinando de CARVALHO, Luiz Carlos Marques VANDERLEI

601 **Diagnosis of Guillain-Barré syndrome and use of Brighton criteria in Peruvian hospitals**
Diagnóstico del Síndrome de Guillain-Barré y uso de los criterios de Brighton en hospitales Peruanos
Marco *MALAGA*, Aaron *RODRIGUEZ-CALIENES*, Victor *VELASQUEZ-RIMACHI*, Carlos *ALVA-DIAZ*

607 **HIV-associated painful neuropathy: where are we?**
Neuropatia dolorosa associada ao HIV: onde estamos?
Karina Lebeis PIRES, Marcelle Seraphim de Menezes BARANDA, Talita Mota Almeida BRUM, Bruno PESSÔA, Camila Castelo Branco PUPE, Osvaldo José Moreira do NASCIMENTO

616 **Translation and adaptation of the sleep apnea quality of life index (SAQLI) to Brazilian Portuguese**
Tradução e adaptação cultural do questionário de qualidade de vida (SAQLI) parao português brasileiro
Amélia Paula Fávero PERRONE, Vanessa Ruotolo FERREIRA, Lucila Fernandes do PRADO, Gilmar Fernandes do PRADO, Marco Antonio MACHADO, Luciane Bizari Coin de CARVALHO

VIEW AND REVIEW

620 **Autism and Down syndrome:early identification and diagnosis**
Autismo e síndrome de Down: identificação precoce e diagnóstico
Natália Lisce Fioravante DINIZ, Erika PARLATO-OLIVEIRA, Priscila Gonçalves Ayres PIMENTA,Liubiana Arantes de ARAÚJO, Eugênia Ribeiro VALADARES

631 **My journey after a mild infection with COVID-19: I want my old brain back**
Minha jornada após uma infecção leve por COVID-19: eu quero meu cérebroantigo de volta
Clarissa Lin YASUDA

BRAZILIAN ACADEMY OF NEUROLOGY

634 **Brazilian Academy of Neurology practice guidelines for stroke rehabilitation: part I**
Diretrizes da Academia Brasileira de Neurologia para reabilitação do acidente vascular cerebral: parte I
Cesar MINELLI, Rodrigo BAZAN, Marco Túlio Araújo PEDATELLA, Luciana de Oliveira NEVES, Roberta de Oliveira CACHO, Sheila Cristina Sayuri Abe MAGALHÃES, Gustavo José LUVIZUTTO,Carla Heloísa Cabral MORO, Marcos Christiano LANGE, Gabriel Pinheiro MODOLO, Bruna Correia LOPES, Elisandra Leites PINHEIRO, Juli Thomaz de SOUZA, Guilherme Riccioppo RODRIGUES, Soraia Ramos Cabette FABIO, Gilmar Fernandes do PRADO, Karla CARLOS, Juliana Junqueira Marques TEIXEIRA, Clara Monteiro Antunes BARREIRA, Rodrigo de Souza CASTRO, Thalita Dayrell Leite QUINAN, Eduardo DAMASCENO, Kelson James ALMEIDA, Octávio Marques PONTES-NETO, Marina Teixeira Ramalho Pereira DALIO, Millene Rodrigues CAMILO, Michelle Hyczy de Siqueira TOSIN, Bianca Campos OLIVEIRA, Beatriz Guitton Renaud Baptista de OLIVEIRA, João José Freitas de CARVALHO, Sheila Cristina Ouriques MARTINS

HISTORICAL NOTES

653 **Ivan Petrovich Pavlov and Santiago Ramón y Cajal, scientists and Nobel laureates of a new century**
Iván Petrovich Pavlov y Santiago Ramón y Cajal, científicos y premios Nobel de un nuevo siglo
Jairo Alonso ROZO, Leonardo PALACIOS-SÁNCHEZ, Andrés Manuel PÉREZ-ACOSTA

IMAGES IN NEUROLOGY

656 **Simultaneous mixed phenotype and neuroimaging of progressive supranuclear palsy, progressive ataxia and palatal tremor: two different faces of tauopathies**
Fenótipo misto simultâneo e neuroimagem de paralisia supranuclear progressiva, ataxia progressiva e tremor palatal: duas faces diferentes das tauopatias
Leonardo Furtado FREITAS, Victor Moreira de CARVALHO, José Luiz PEDROSO, Márcio Luís DUARTE, Rodrigo Meirelles MASSAUD

658 **Rucksack palsy after military boot camp**
Paralisia do mochileiro após treinamento militar
Pedro Henrique Almeida FRAIMAN, Igor Matheus Diniz PAPA, Bruno de Medeiros FERNANDES, Fernanda Thaysa Avelino dos SANTOS, Clecio GODEIRO-JUNIOR

IN MEMORIAM

659 **Professor Paulo Norberto Discher de Sá(1939-2022)**
Professor Paulo Norberto Discher de Sá (1939-2022)
Ylmar CORREA NETO, Hélio Afonso Ghizoni TEIVE

ERRATUM

660 **Erratum**

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Measuring optic nerve sheath diameter using ultrasonography for the detection of non invasive intracranial pressure: what it is and what it is not

Medição do diâmetro da bainha do nervo óptico por ultrassonografia para aferição não invasiva da pressão intracraniana: o que é e o que não é

Chiara ROBBA[1,2]

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Over the last decade, the study of optic nerve sheath diameter (ONSD) using ultrasonography has gained particular interest for the assessment of non-invasive intracranial pressure (nICP)[1].

ONSD ultrasonography is an elegant technique, which has the advantage of being easily available, repeatable at bedside, low cost and cheap, avoiding the risks of infection or hemorrhage related to intracranial catheters. The pathophysiology behind this technique is simple: the optic nerve is surrounded by the meninges and the subarachnoid space, and has elastic properties; therefore, when intracranial pressure (ICP) rises, the optic nerve sheath is distended and the ONSD increases.

ONSD has been evaluated on Magnetic Resonance imaging and Computed Tomography studies[2,3], demonstrating a good accuracy for the real time estimation of ICP. The possibility to evaluate ONSD as a surrogate of ICP using a safe method, which does not require the transfer of patients to the radiological suite and does not expose them to ionizing radiation has led to a high number of studies and publications on the Ultrasound based estimation of this tool.

In general, observational studies and meta-analysis suggest promising results regarding the correlation between ONSD and nICP, showing moderate to high sensitivity for the detection of elevated ICP (86% to 97%)[4-6].

However, some striking points and issues have been described for this tool, especially regarding the lack of a universal methodology used in different studies. A vast heterogeneity is present in the literature regarding the transducers and frequencies adopted[4,5] by researchers, the measurements planes[4,5], the number of measures from one or two ONSDs, the patient´s positioning[4,5]; in addition, a non-universal definition of the quality of the images obtained and of the US visualization of ONSD exists, thus resulting in the measure in some cases of the ONS instead of the entire ONSD[4,5].

Open questions also remain, such as the ability of ONSD to return to its initial size after treatment or resolution of increased ICP, or in case of intracranial hypotension.

In patients after subarachnoid hemorrhage (SAH), for instance, dramatic increases of ICP consequent to aneurysm rupture can lead to a disruption of the elastic properties of the ONS membrane, thus resulting in enlarged ONSD even without the presence of intracranial hypertension[7].

In addition, a major issue remains the large variations in ONSD cutoffs evaluated to estimate the critical threshold of ICP> 20 mmHg, ranging from 4.2 to 6.5 mm with wide confidence intervals according to literature[8,9].

Systematic reviews and meta-analysis[5,9], suggest the best cut-off value of ONSD of 5.1 and 5.8 mm, with the area under the hierarchical summary receiver-operating characteristic curve of ONSD for predicting increased ICP of 0.938[9].

Studies on healthy volunteers show also heterogeneity on the normal values of ONSD according to ex, age and race[10].

In a study conducted in China, the mean ONSD value was 4.33 ± 0.38 mm in normal individuals and 6.61 ± 0.39 mm in patients with increased ICP[10].

In healthy volunteers in Europe[11], ONSD was significantly different between males and females [4.2 (3.9-4.6) mm vs. 4.1 (3.6-4.2) mm, $p = 0.01$)] and it was correlated with age, with increasing values in the elderly population ($R = 0.50$, $p < 0.0001$). However, in traumatic brain injured patients, no differences in ONSD were found according to sex and age, thus suggesting that different ONSD cut-off values do not need to be age- or sex-adjusted in brain injured patients patients.

Finally, a possible inter-intraobserver variability has been reported, which is an intrinsic limitation of US technique[12].

Potentially, well-defined criteria for training and the definition of educational projects aimed to standardize the methodology of ONSD measurement can importantly minimize these limitations; however, at present, the use of ONSD is limited to the settings of specialized Neurocritical Care Units.

In a recent consensus of experts of the European Society of Intensive Care, ONSD was not considered as a basic skill for general intensivists[13]; this was related to the idea of nICP estimation as an advanced skill with no consideration of this tool in the general intensive care unit training and certifications programs.

However, a consensus of experts considering only the neurocritical care settings defined ONSD as a "basic-plus skill", which requires training and an appropriate learning curve, but which should be considered fundamental for the management of these patients[14]. This suggests the need of implementing brain ultrasonography in a process of formal certification processes, consensus statements, and documents also outside the neurocritical care settings to ensure the widespread use of this technique.

All these limitations have led to the concept that ONSD cannot provide a value of ICP "as a number", thus making it unfeasible and not accurate enough to be used to substitute invasive ICP measurement, especially in brain injured patients.

However, ONSD has still to be considered a valuable technique in other clinical contexts.

In a recent study, ONSD was measured in patients with Idiopathic intracranial hypertension (IIH) and compared to normal healthy individuals[15].

Ninety-seven participants aged 18-80 years were divided into two groups as patients with IIH (n=47) and the control group (n=50). The mean ONSD was statistically significantly larger in the IIH group compared to the control group (6.4 vs 4.90 mm). The cut-off value of ONSD in patients with IIH was measured as 5.70 mm. Also, a positive correlation between body mass index and ONSD ($r = 0.437$, $p<0.001$) was found.

This study clearly represents one of the most useful applications of ONSD[16]. Although the cut-off is not completely determined in literature, the difference of median ONSD found between the two groups suggests that these patients, taking in consideration age, sex, and BMI, ONSD can reliably help in the qualitative discrimination of high vs low ICP values, and posing the question in borderline situations of the need for additional evaluations, minimizing the risk related to invasive measurements.

In conclusion, a number of limitations have been demonstrated for the evaluation of ONSD as a surrogate of ICP; despite these limitations have to be taken in consideration, ONSD can be a useful qualitative method to assess the risk of increased ICP, and in particular the changes of ICP within time. This can pave the way on the utilization of this tool in all these situations when invasive tools are not available or contraindicated, but where ICP estimation would be helpful for patient management. This includes a number of neurological conditions (such as meningitis, IIH), or in the general ICU population with no primarily brain injury but with high risk for increased ICP (cardiac arrest, sepsis, pregnancy-related complications etc.).

In the next years educational projects and research should focus in the standardization of ONSD measurement and training and in the implementation of this method at bedside in the context of a "head to toes" Ultrasound evaluation of patients.

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ARTICLE

Stroke in the state of Alagoas, Brazil: a descriptive analysis of a northeastern scenario

Acidente vascular cerebral no estado de Alagoas, Brasil: análise descritiva de um cenário do nordeste brasileiro

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ABSTRACT

Background: There is little information available on stroke epidemiology in the northeast of Brazil. **Objective:** Our objective was to investigate the prevalence of the stroke subtypes, prevalence of cerebrovascular risk factors and patterns of management in a public neurovascular outpatient referral service, in Alagoas. **Methods**: Data were prospectively collected from consecutive patients with stroke who were treated in a specialized neurovascular clinic between November 2016 and June 2018. Recurrence was evaluated by telephone 12 months after patients had been included in the study. **Results**: We evaluated 190 patients (mean age, 60.22 ± 13.29 years; 60.5% males). Ischemic stroke was the most frequent subtype (85.2%). Sedentary lifestyle was the most common risk factor (71.6%), followed by hypertension (62.6%) and stroke family history (41.1%). Only 21.5% of the patients were transported by ambulance to the hospital, and 42.6% received medical support in hospital units or emergency units with no imaging support. The median NIHSS was 2.5 (IQR, 1-5) and mRS was 2 (IQR, 1-3). We found a high rate of undetermined stroke (35.8%), and few patients completed the etiological investigation. One year after inclusion in the study, 12 patients (6.3%) had died and 14 (7.3%) had had another stroke. **Conclusions**: The prevalence of cerebrovascular risk factors and clinical presentation were similar to what had been seen in previous series. A notable number of patients received medical support in institutions with no imaging equipment. The high number of cases of undetermined stroke etiology shows the difficulty in accessing healthcare services in Alagoas.

Keywords: Stroke; Epidemiology; Risk Factors; Functional Status.

RESUMO

Antecedentes: Até o momento existe pouca informação disponível na literatura sobre a epidemiologia do acidente vascular verebral (AVC) no nordeste brasileiro. **Objetivo:** Investigar a prevalência dos subtipos de AVC, dos fatores de risco para doenças cerebrovasculares e o manejo do AVC em um serviço público especializado em Alagoas. **Método:** Os dados foram coletados de forma prospectiva e consecutiva de pacientes com diagnóstico de AVC em um ambulatório especializado em neurovascular, de novembro de 2016 a junho de 2018. Recorrência do AVC foi avaliada por telefone 12 meses após a inclusão no estudo. **Resultados:** Foram avaliados 190 pacientes, idade média de 60,22±13,29 anos, 60,5% homens. AVC isquêmico foi o subtipo mais comum (85,2%). Sedentarismo foi o fator de risco mais prevalente (71,6%), seguido de hipertensão (62,6%) e história familial de AVC (41,1%). Somente 21,5% dos pacientes foram transportados por ambulância até o hospital e 42,6% receberam o primeiro atendimento em serviço médico sem suporte de exame de imagem. A mediana do NIHSS foi 2,5 (IQR, 1-3). Encontramos alta prevalência de AVC indeterminado (35,8%) e poucos pacientes completaram a investigação etiológica. Após um ano da inclusão no estudo, 12 pacientes (6,3%) morreram e 14 (7,3%) tiveram outro AVC. **Conclusão:** A prevalência dos fatores de risco para doenças cerebrovasculares e a apresentação clínica foram similares a séries prévias. Um número expressivo de pacientes recebeu atendimento médico em locais sem exames de imagem. Houve alto número de pacientes com AVC indeterminado, o que mostra a dificuldade de acesso ao sistema de saúde em Alagoas.

Palavras-chave: Acidente Vascular Cerebral; Epidemiologia; Fatores de Risco; Estado Funcional.

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INTRODUCTION

Cerebrovascular diseases, including stroke, are one of the leading causes of mortality in most Latin American countries[1]. In Brazil, the incidence of stroke is 139.91/100,000 inhabitants. Stroke has a huge social impact, with an estimated loss of 1437.74 years of healthy life, and its treatment is costly for the Brazilian healthcare system[2–4].

Several studies have been developed to characterize the prevalence, incidence and clinical characteristics of stroke patients in Brazil[5–8]. However, regional differences are significant. In the northeastern region, the stroke age-standardized mortality rate is high. In comparison with other state capitals in the northeastern region, Maceió had the highest mortality rate and the lowest human development index (HDI)[9]. A cohort study conducted in Fortaleza, also located in the northeastern region, demonstrated that investigation of stroke etiology was less common and that the frequency of post-stroke disability was higher than in other national and international studies[5]. Hence, regional studies are helpful for understanding the clinical characteristics of stroke patients and for improving the management of this disease.

The objective of this study was to investigate the prevalence of the stroke subtypes, the prevalence of cerebrovascular risk factors and the patterns of management in a public neurovascular outpatient referral service, in Alagoas.

METHODS

Study population

We evaluated patients with cerebrovascular disease, confirmed by means of neuroimaging, who were consecutively treated in a public specialized neurovascular clinic in Alagoas, Brazil, between November 2016 and June 2018. All the patients were over 18 years old. Patients were excluded if they had another neurological condition or any severe concomitant systemic illness.

The ethics committee of the Federal University of Alagoas approved this study and written informed consent was obtained from all of the participants.

Study protocol

The protocol consisted of assessment of demographic and clinical data, including use of the Bamford classification, which classifies stroke as lacunar syndrome (LACS), partial anterior circulation syndrome (PACS), total anterior circulation syndrome (TACS) and posterior circular syndrome (POCS)[10]; and use of the National Institutes of Health Stroke Scale (NIHSS)[11] and the modified Rankin Scale (mRS)[12].

Risk factors, including hypertension, diabetes mellitus, smoking, alcoholism, dyslipidemia, atrial fibrillation, coronary artery disease, prior stroke or TIA, were registered upon inclusion of patients in the study. Hypertension, diabetes mellitus and dyslipidemia were defined as histories of prior or current use of appropriate medications for these conditions. Smoking and alcohol habits were defined as current use in the year of the stroke or one year before the ictus. Coronary artery disease was defined as a history of angina, acute myocardial infarction or coronary revascularization. Atrial fibrillation was defined from known previous diagnoses or through new evidence from Holter monitoring or electrocardiogram.

We also registered any complementary examinations that the patients had undergone, in order to enable TOAST (*Trial of Org 10172 in Acute Stroke Treatment)* classification[13]. Recurrence was evaluated by means of telephone calls 12 months after patients had been included in the study.

Statistical analysis

The analyses were performed using the SPSS software (version 20.0; Chicago, IL, United States) at a significance level of 5%. Continuous variables were summarized as means and standard deviations or as medians and interquartile ranges (IQR). Categorical variables were presented as percentages. We also compared groups of ischemic versus hemorrhagic stroke and of female versus male patients, using the Mann-Whitney test and χ^2 test.

RESULTS

We included 190 patients with a mean age of 60.22 ± 13.29 years, and 115 (60.5%) were males. The mean length of time from stroke to inclusion in the study was 27.2 ± 33.1 months. Table 1 describes the demographic characteristics and risk factors of all the patients and according to gender.

The majority of the patients (78.8%) had access to medical assistance on the first day of the event. However, only 21.5% were transported by ambulance to the hospital, 42.6% received medical support in hospital units or emergency units with no imaging support and only 2.6% received acute reperfusion treatment.

Among these 190 patients, 131 (68.9%) were seen at the time of their first-ever stroke. Ischemic strokes occurred most frequently, in 162 (85.2%) of the patients, while 20 (10.5%) had intraparenchymal hematoma, 3 (1.6%) transitory ischemic attack, 1 (0.5%) subarachnoid hemorrhage, 3 (1.6%) cerebral venous thrombosis and 1 (0.5%) ischemic and hemorrhagic stroke. The pathological subtype distribution of the ischemic strokes is shown in Table 2.

The median NIHSS score was 2.5 (IQR, 1-5) and the mRS was 2 (IQR, 1-3). In the Bamford classification, we found that 84 cases (44.2%) were LACS, 77 (40.5%) were PACS, 11 (5.8%) were TACS, 15 (7.9%) were POCS and 3 (1.6%) were undetermined.

With regard to neuroimaging, all the patients underwent parenchymal imaging, 138 (72.6%) brain computed tomography and 139 (73.2%) brain magnetic resonance imaging. Regarding vascular imaging, 132 (69.5%) underwent carotid and vertebral doppler ultrasound, 66 (34.7%) transcranial doppler ultrasound, 93 (48.9%) angioresonance of intracranial vessels,

Table 1. Demographic characteristics and risk factors of all patients according to sex.

Characteristics		Total n = 190 (100%)	Males n = 115 (60.5%)	Females n = 75 (39.5%)	p-value
Age, mean (± SD)		60.22 (13.29)	60.33 (1.10)	60.02 (1.76)	0.93
Ethnicity (%)[1]	White	29 (15.3)	21 (18.2)	8 (10.6)	0.34
	Brown	115 (60.5)	68 (59.1)	47 (62.6)	
	Black	39 (20.5)	23(20)	16 (21.3)	
	Indigenous	2 (1.1)	1(0.8)	1 (1.3)	
	Not declared	5 (2.63)	2 (1.7)	2 (2.6)	
Marital status (%)	Married	118 (62.1)	89 (77.3)	29 (38.6)	0.0001#
	Single	30 (15.8)	10 (8.6)	20 (26.6)	
	Widower	27 (14.2)	8 (6.9)	19 (25.3)	
	Divorced	15 (7.9)	8 (6.9)	7 (9.3)	
Years of schooling (%)	Illiterate	38 (20)	19 (16.5)	18 (24)	0.57
	1-4 years	48 (25.3)	30 (26.08)	19 (25.3)	
	5-9 years	59 (31.1)	36 (31.3)	23 (30.6)	
	10-12 years	27 (14.2)	16 (13.9)	11 (14.6)	
	13 years or more	16 (8.4)	12 (10.4)	4 (5.3)	
	Not declared	2 (1.1)	2 (1.7)	0	
Occupation (%)[2]	Employed	18 (9.5)	14 (12.1)	4 (5.3)	0.001#
	Unemployed	25 (13.2)	15 (13.04)	10 (13.3)	
	Government beneficiary	36 (18.9)	25 (21.7)	11 (14.6)	
	Pensioner	4 (2.1)	0	4 (5.3)	
	Retired	95 (50)	60 (52.1)	35 (46.6)	
	Student	3 (1.6)	1 (0.8)	2 (2.6)	
	Housewife	9 (4.7)	0	9 (12)	
Income (%)[3] (in minimum monthly wages)	Up to 1	73 (38.4)	38 (33)	35 (46.6)	0.001#
	2 to 3	93 (48.9)	57 (49.5)	36 (48)	
	> 3	17 (8.9)	16 (13.9)	1 (1.3)	
	Not declared	7 (3.6)	4 (3.4)	3 (4)	
Risk factors (%)	Sedentary lifestyle (yes)	136 (71.6)	81 (70.4)	55 (73.3)	0.63
	Hypertension (yes)	119 (62.6)	71 (61.7)	48 (64)	0.93
	Stroke familiar history (yes)	78 (41.1)	48 (41.7)	30 (40)	0.77
	Prior stroke or TIA (yes)	59 (31.1)	32 (27.8)	21 (28)	0.98
	Diabetes (yes)	56 (29.5)	38 (33)	18 (24)	0.40
	Smoker (yes)	40 (21.1)	25 (21.7)	15 (20)	0.72
	Alcoholism (yes)	37 (19.5)	33 (28.6)	4 (5.3)	0.0001#
	Cardiomyopathy (yes)	23 (12.1)	12 (10.4)	11 (14.6)	0.29
	Atrial fibrillation (yes)	16 (8.4)	5 (4.3)	11 (14.6)	0.009#
	Chagas disease (yes)	12 (6.3)	7 (6.08)	5 (6.6)	0.77

SD: standard deviation; TIA: transient ischemic attack; [1]: for the χ^2 test, the participants were classified as white, brown or others; [2]: for the χ^2 test, the participants were classified as employed, unemployed, beneficiaries or without income (students and housewives); [3]: for the χ^2 test, the participants were classified as up to 1 minimum monthly wage, 2 to 3 wages or > 3 wages; #χ^2 test: significance level < 0.05.

52 (27.4%) angioresonance of cervical vessels, 20 (10.5%) angiography and 7 (3.7%) angiotomography. The most common abnormality was involvement of the middle cerebral artery region in 74 (54%), followed by multiple regions in 11 (15.3%). Patients also underwent other complementary examinations: 127 (66.8%) had an electrocardiogram, 85 (44.7%) Holter, 160 (84.2%) transthoracic echocardiogram and 15 (7.9%) transesophageal echocardiogram.

One year after inclusion in the study, 12 patients (6.3%) had died and 14 (7.3%) had had another stroke. Table 3 describes the frequencies of non-pharmacological and pharmacological treatments.

Table 2. Distribution of etiological subtypes of ischemic stroke according to the TOAST classification (N = 162).

Subtype	N	%
Large-artery atherosclerosis	36	22.2%
Small vessel disease	40	24.6%
Cardioembolism	15	9.2%
Other etiology	13	8.02%
Undetermined etiology	58	35.8 %
Incomplete	38	23.4%

Table 3. Frequencies of non-pharmacological and pharmacological treatments.

	All patients (n = 190)	Ischemic stroke (n = 162)	Hemorrhagic stroke* (n = 21)	p-value
Speech therapy	27 (14.2%)	25 (15.4%)	2 (9.5%)	0.27
Physical therapy	70 (36.8%)	62 (38.2%)	7 (33.3%)	0.46
Occupational therapy	16 (8.4%)	16 (9.8%)	0 (0%)	-
Antihypertensive use	142 (74.7%)	118 (72.8%)	18 (85.7%)	0.02
Statin use	142 (74.7%)	125 (77.1%)	12 (57.1%)	-
Antiplatelet use	150 (78.9%)	138 (85.1%)	7 (33.3%)	-
ASA	112 (58.9%)	101 (62.3%)	7 (33.3%)	-
Clopidogrel	7 (3.6%)	7 (4.3%)	0 (0%)	-
ASA + clopidogrel	24 (12.6%)	23 (14.1%)	0 (0%)	-
Cilostazol	2 (1.05%)	2 (1.2%)	0 (0%)	-
Others	5 (2.6%)	5 (3.08%)	0 (0%)	-
Anticoagulant use	14 (15.5%)	12 (7.4%)	0 (0%)	-
Warfarin	10 (5.2%)	8 (4.9%)	0 (0%)	-
Dabigatran	2 (1.05%)	2 (1.2%)	0 (0%)	-
Rivaroxaban	2 (1.05%)	2 (1.2%)	0 (0%)	-

*For hemorrhagic strokes, only the cases of intraparenchymal hematoma and subarachnoid hemorrhage were considered; ASA: acetylsalicylic acid; #χ^2 test: significance level < 0.05.

DISCUSSION

This was, to the best of our knowledge, the first study to characterize stroke outpatients in Alagoas. Most of them were male and brown-skinned, and had a maximum income of three minimum monthly wages; 45% had low educational levels (maximum of four years). The most prevalent risk factors were sedentary lifestyle, hypertension and family history of stroke.

An association between stroke and socioeconomic indicators had previously been described in the literature. Low socioeconomic status was correlated with a 67% increased risk of stroke[14] and low educational levels were found to be an important predictor of functional dependence[15,16]. In the city of São Paulo, stroke mortality was found to differ among its districts according to their HDI, such that it was almost three times higher in the lowest HDI stratum of the city[17]. Alagoas has the lowest HDI of Brazil[18] and the highest mortality rate among all northeastern state capitals[9]. Low socioeconomic status can be correlated with poor risk factor control[19,20] and greater difficulty in accessing healthcare services, adequate acute treatment and post-acute care[21]. These factors directly affect patients' prognoses and long-term survival[22].

In Alagoas, the mortality rate has shown an increasing trend over recent decades[23]. Deaths caused by cerebrovascular diseases are concentrated in the eastern region of the state, probably caused by greater centralization of specialized healthcare services in the state capital, Maceió[24]. In 2018, only one stroke unit was available in the state, and this was located in the capital. In addition, also in the state capital, some private hospitals had stroke protocols. This scenario is insufficient for the whole population, and especially for people who do not live in the metropolitan region of Maceió, for whom no specialized stroke service is available. This situation can partially explain our reperfusion rate. Moreover, there is no defined flow of referrals from the stroke unit to specialized outpatient clinics after discharge, which therefore leads to delays in accessing investigative examination.

Other alarming findings were the low number of patients transported by ambulance to hospitals and the high number who sought a healthcare service with no imaging support. These results suggest that the population has poor knowledge about stroke. Pontes-Neto et al, 2008, showed that there was a lack of vital information in Brazilian population about stroke recognition and activation of the emergency medical services

(EMS)[25]. In Alagoas, EMS are present throughout the state and there are 14 ambulances in the state capital. However, among our sample, the service was poorly activated. In Spain, being transported by an EMS vehicle was correlated with earlier arrival at the hospital and shorter door-to-imaging time, which is crucial for acute stroke management[26]. So far, few studies about prehospital care for stroke cases have been conducted in Brazil[27]. Such studies are necessary in order to understand people's reasons for not requesting the EMS and the influence of this decision on the patient's prognosis.

Low-complexity emergency care units (ECUs) are an intermediate level healthcare service that form part of the national emergency care program in Brazil. They connect primary care, the EMS and tertiary-level care[28]. However, ECUs do not have imaging support and are not adequate for initial stroke treatment. In Fortaleza, Ceará, ECUs are the type of institution that is second most sought by patients with stroke symptoms. Age, educational level, sex and headache at onset, no speech deficits and prehospital transportation were previously found to be predictors of ECU utilization[29]. That study also indicated the importance of adequate training for ECU healthcare staff, to be able to rapidly recognize stroke symptoms and thus call out the EMS for referral of the case to hospital. Another matter is the importance of education for the population, so that stroke symptoms can be recognized and the EMS is then activated.

In our sample, some patients were doing some kind of rehabilitation therapy, among which physiotherapy was undertaken most frequently (36.8%). In a previous study about functional outcomes among stroke patients in Alagoas, a functional dependence rate of 34.8% was found approximately two years after the ictus[30]. This was a high rate in comparison with other national studies[15,31]. Functional dependence may be related to greater stroke severity, the degree of access to adequate treatment during the acute phase and the availability of rehabilitation during the acute and post-acute phases[32–34]. Seventeen specialized rehabilitation services are currently available in Alagoas to attend to the 6% of this population that are declared to be disabled[35,36]. In addition to the insufficient number of rehabilitation services, the organization and quality of rehabilitation need to be considered.

No study has yet been conducted in Alagoas regarding the specialized stroke rehabilitation services in this state. However, certain factors contribute towards improving the quality of rehabilitation services, including systematic triage involving use of the International Classification of Functioning, Disability and Health (ICF); implementation of an individual therapeutic plan; frequent and systematic monitoring of functioning; and continuous education for the multidisciplinary team[37]. All of these aspects of the rehabilitation services need to be investigated in order to improve the rehabilitation process for stroke patients.

Regarding etiology, we observed that the rate of undetermined strokes was 35.8%, and that for 23.4% this was because of incomplete investigation. A previous study conducted in Joinville, southern Brazil, found that the rate of undetermined etiology was 28.4%. In that study, all the patients underwent electrocardiography, extracranial and intracranial Doppler ultrasound, transthoracic echocardiography and at least one brain computed tomography. The high rate of undetermined strokes can be explained by the cryptogenic stroke included in this group[6].

Our stroke protocol for investigation of the event mechanism consists of laboratory tests, parenchymal imaging, study of intra and extracranial vessels and investigation of the cardiac routine (electrocardiogram and/or 24-hour Holter monitoring). However, in our state, the population has difficulty in accessing examinations within our public healthcare system and the low income of the study population does not allow these examinations to be performed within the private healthcare system. Similar results were found in Fortaleza, thus demonstrating the differences in access to healthcare services in Brazil[5]. These cases may be receiving inappropriate secondary prophylaxis and, consequently, there may be a higher chance of recurrence of cerebrovascular events.

Our study had some limitations. Our sample was restricted to patients attended in a specialized neurovascular clinic and our conclusion does not represent the reality of the entire state of Alagoas. The rates relating to examinations performed to investigate the stroke etiology, access to rehabilitation and recurrence may be worse overall because, in our scenario, patients are seen by a trained vascular neurologist and have easier access to examinations and treatments in the tertiary hospital. The majority of the patients included were chronic and we did not have access to all the data about the acute phase. As there is no referral flow of patients from acute-phase care services to outpatient clinics, we postulate that many more severely ill patients are unable to access outpatient care. Thus, further studies are necessary in order to understand the real situation of stroke treatment in Alagoas.

In conclusion, our study was the first in Alagoas to characterize the clinical profile of a stroke sample, which is important, given the inequalities in Brazil. Our sample showed risk factors similar to those previously described in the literature, i.e. low educational level and low income. We also found that only a low number of patients were transported by ambulance to the hospital and that a high number of patients sought assistance at healthcare services with no imaging support, which suggested that the population has poor knowledge about stroke. The high number of cases of undetermined stroke etiology shows the difficulty in accessing healthcare services in our state and the urgent need for effective healthcare policies to improve the stroke care system.

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ARTICLE

Passive smoking may be associated with bleeding of cerebral arteriovenous malformation in non-smoking women: a retrospective analysis

O tabagismo passivo pode estar associado com o sangramento de malformação arteriovenosa cerebral em mulheres não fumantes: uma análise retrospectiva

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ABSTRACT

Background: Smoking has been considered to be a risk factor for cardiovascular disease, cancer, depression and other diseases in previous reports, and active smoking is considered to be a risk factor for hemorrhagic stroke. In addition, a retrospective study showed that male smokers were at increased risk of bleeding from arteriovenous malformation (AVM), compared with non-smokers. However, the effect of passive smoking on rupturing of cerebral AVM in non-smoking women has not been addressed. **Objective:** This study aimed to assess the impact of tobacco exposure on AVM bleeding risk in non-smoking women. **Methods:** A total of 393 non-smoking women diagnosed with AVM were included. They were divided into a bleeding group (205 women) and a non-bleeding group (188 women). We conducted univariate and multivariate analysis on these two groups. In univariate analysis, risk factors that might be related to AVM bleeding were analyzed. In multivariate analysis, the relationship between passive smoking and AVM rupture was analyzed by correcting confounding factors. **Results:** Multivariate analysis showed that the proportion of passive smoking was statistically different between the bleeding group and the non-bleeding group (OR = 1.609; CI = 1.031-2.509; p = 0.036). **Conclusion:** Passive smoking may increase the risk of AVM bleeding in non-smoking women. This increased risk may be related to the inflammatory response, vascular wall damage, hemodynamic disorders, changes in atherosclerosis and changes in gene expression caused by passive smoking.

Keywords: Tobacco Smoke Pollution; Hemorrhage; Intracranial Arteriovenous Malformations; Risk.

RESUMO

Antecedentes: O tabagismo tem sido considerado fator de risco para doenças cardiovasculares, câncer, depressão e outras doenças em relatos anteriores, e o tabagismo ativo é considerado fator de risco para acidente vascular cerebral hemorrágico. Além disso, um estudo retrospectivo mostrou que os fumantes do sexo masculino apresentavam risco aumentado de sangramento por malformação arteriovenosa (MAV), em comparação com os não fumantes. No entanto, o efeito do tabagismo passivo na ruptura da MAV cerebral em mulheres não fumantes não foi abordado. Objetivo: Este estudo teve como objetivo avaliar o impacto da exposição ao tabaco no risco de sangramento de MAV em mulheres não fumantes. **Métodos**: Foram incluídas 393 mulheres não fumantes diagnosticadas com MAV. Elas foram divididas em um grupo com sangramento (205 mulheres) e um grupo sem sangramento (188 mulheres). Realizamos análise univariada e multivariada nesses dois grupos. Na análise univariada, foram analisados os fatores de risco que podem estar relacionados ao sangramento de MAV. Na análise multivariada, a relação entre tabagismo passivo e ruptura de MAV foi analisada por meio da correção de fatores de confusão. **Resultados:** A análise multivariada mostrou que a proporção de tabagismo passivo foi estatisticamente diferente entre o grupo com sangramento e o grupo sem sangramento (OR = 1,609; IC = 1,031-2,509; p = 0,036). **Conclusão**: O tabagismo passivo pode aumentar o risco de sangramento de MAV em mulheres não fumantes. Esse risco aumentado pode estar relacionado à resposta inflamatória, danos na parede vascular, distúrbios hemodinâmicos, alterações na aterosclerose e alterações na expressão gênica causadas pelo tabagismo passivo.

Palavras-chave: Poluição por Fumaça de Tabaco; Hemorragia; Malformações Arteriovenosas Intracranianas; Risco.

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INTRODUCTION

Tobacco exposure is a healthcare challenge around the world. A survey of adults conducted in 2010 showed that the smoking rates among Chinese men and women were 52.9% and 2.4%, respectively[1]. This means that a large number of non-smoking women may be affected by secondhand smoke. In a 2012 study, the proportion of women who experienced passive smoking was as high as 60.6%[2].

The high incidence of passive smoking has always been a social issue that many people are concerned about. It may bring various adverse health problems, which will increase the national medical burden and economic pressure.

Smoking has been considered to be a risk factor for cardiovascular disease, cancer, depression and other diseases in previous reports[3-7], and active smoking is considered to be a risk factor for hemorrhagic stroke[8]. In addition, a retrospective study showed that male smokers were at increased risk of bleeding from arteriovenous malformation (AVM), compared with non-smokers[9]. However, the effect of passive smoking on rupturing of cerebral AVM in non-smoking women has not been addressed. Hence, we designed this study with the aim of assessing the impact of tobacco exposure on AVM bleeding risk in non-smoking women.

METHODS

Patient selection

This retrospective analysis study was approved by the Ethics Committee of Beijing Tiantan Hospital and Beijing Jingmei Group General Hospital. Data on patients diagnosed with AVM who were admitted to the Beijing Tiantan Hospital and Beijing Jingmei Group General Hospital between August 2015 and April 2018 were collected. Most of the patients were admitted to the hospital because of symptoms such as headache, nausea, vomiting or epilepsy. A small number of people were also admitted to the hospital because of the presence of AVM, observed during the physical examination. All the cases of AVM were confirmed by means of cerebral angiography.

The inclusion criteria were as follows: non-smoking women, diagnosed with AVM during hospitalization. The exclusion criteria included the following: (1) the patient's medical records were incomplete or we could not obtain follow-up information, such as lack of digital subtraction angiography (DSA) and computed tomography (CT) data; (2) interventional embolization, surgical resection or radiation treatment were performed before admission; and (3) the patient had one of the following types of malformation: Galen's venous malformation, dural arteriovenous fistula, hereditary hemorrhagic capillary dilatation, cavernous hemangioma, carotid cavernous sinus fistula or pial arteriovenous fistulas. Whether there was bleeding or not was judged through the results from CT/MRI or lumbar puncture, and these examinations were usually completed after admission.

Data collection and definition of some indicators

In line with reports in the literature, the following indicators were included in our statistical table: passive smoking, age, diabetes, hypertension, ischemic heart disease, family history of stroke, size of AVM, location of AVM, association with blood flow-related intracranial aneurysms (IAs), number of drainage veins, number of feeding arteries, direction of venous drainage, stenoses of drainage veins and dilation of drainage veins.

In this study, non-smoking was defined as having smoked no more than 100 cigarettes in a lifetime. Passive smoking was defined as being exposed to tobacco for at least one hour a day for at least six months before admission. The size of the AVM was divided into three types: small (≤ 3 cm), medium (3-6 cm) or large (≥ 6 cm). With regard to AVM location, cortical referred to the gray matter of the parietal lobe, occipital lobe, frontal lobe and temporal lobe; deep referred to the deep part of the cerebral hemisphere; and infratentorial referred to the cerebellum and brainstem. There were three types of blood flow-related intracranial aneurysms (IAs): proximal aneurysm, distal aneurysm and intra-nest aneurysm. Stenosis and dilation of drainage veins were judged based on whether the diameter of the drainage vein had significantly increased or decreased, compared with normal drainage veins.

The above demographic information was obtained by reviewing medical cases. The vascular architecture characteristics of the AVM were evaluated by two neurointerventional physicians. If there was any dispute about the assessment of the vascular architecture, the evaluation task would be assigned to a third neurointerventional physician. Occurrences of passive smoking were ascertained through a telephone questionnaire survey, using questions such as: "Were there smokers around you every day?" and "How long was each exposure to tobacco?"

Statistical analysis

We performed univariate and multivariate analyses on the data that had been collected. In univariate analyses, independent-sample t tests were used for continuous variables, and categorical variables were tested using chi-square tests. Variables that were statistically different in univariate analyses were included in the multivariate analysis model. In multivariate analysis, logistic binary regression analysis (LR) was used. For both univariate and multivariate analyses, P-values < 0.05 were considered statistically significant.

RESULTS

General characteristics of patients in this study

A total of 393 patients were included in this study. Respectively, 205 were in the bleeding group and 188 were in the non-bleeding group (Table 1). The mean ages of the two groups were 28.6 ± 11.9 and 28.5 ± 12.5 years. The proportions of passive smoking in the two groups were 39.0% and 26.6%.

Table 1. Basic characteristics of 393 non-smoking women with cerebral arteriovenous malformations.

Characteristics		Total (393 patients)	Bleeding (205 patients)	Non-bleeding (188 patients)
Age, mean (SD)		28.5 (12.2)	28.6 (11.9)	28.5 (12.5)
Diabetes		16 (4.1%)	9 (4.4%)	7 (3.7%)
Hypertension		50 (12.7%)	25 (12.2%)	25 (13.3%)
Ischemic heart disease		13 (3.3%)	7 (3.4%)	6 (3.2%)
Family history of stroke		34 (8.7%)	17 (8.3%)	17 (9.0%)
Size	Small	160 (40.7%)	100 (48.8%)	60 (31.9%)
	Medium	172 (43.8%)	78 (38.2%)	94 (50.0%)
	Large	61 (15.5%)	27 (13.2%)	34 (18.1%)
Location	Cortical	300 (76.3%)	145 (70.7%)	155 (82.4%)
	Deep	55 (14.0%)	33 (16.1%)	22 (11.7%)
	Infratentorial	38 (9.7%)	27 (13.2%)	11 (5.9%)
Association with blood flow-related IAs		85 (21.6%)	56 (27.3%)	29 (15.4%)
Number of drainage veins (≤ 2)		254 (64.6%)	135 (65.9%)	119 (63.3%)
Number of feeding arteries (≤ 2)		303 (77.1%)	163 (79.5%)	140 (74.5%)
Venous drainage	Superficial	213 (54.2%)	104 (50.7%)	109 (58.0%)
	Deep	96 (24.4%)	47 (22.9%)	49 (26.1%)
	Deep and superficial	84 (21.4%)	54 (26.3%)	30 (16.0%)
Stenoses of drainage veins		27 (6.9%)	10 (4.9%)	17 (9.0%)
Dilation of drainage veins		120 (30.5%)	54 (26.3%)	66 (35.1%)
Passive smoking		130 (33.1%)	80 (39.0%)	50 (26.6%)

IAs: intracranial aneurysms; SD: standard deviation.

Univariate and multivariate analysis results

Univariate analysis revealed that the risk of AVM bleeding was associated with passive smoking (p = 0.009), size (p = 0.003), location (p = 0.014), IAs (p = 0.004) and direction of venous drainage (p = 0.043). Multivariate analysis showed that the proportion of passive smoking was statistically different between the bleeding group and the non-bleeding group (OR = 1.609; CI = 1.031-2.509; p = 0.036). In addition, multivariate analysis results showed that size (medium vs small: p = 0.001; large vs small: p = 0.023), location (infratentorial vs cortical: p = 0.009) and association with IAs (p = 0.006) were statistically different between the two groups (Table 2).

DISCUSSION

Passive smoking may increase the risk of AVM bleeding in non-smoking women

Exposure to secondhand smoke for various reasons is called passive smoking. The smoke generated from smoking cigarettes contains harmful substances, such as nicotine. Passive smoking mainly takes place at home or at work. In China, the majority of passive smokers are women. A study conducted by Yao et al. showed that Chinese women's medical expenses due to the effects of secondhand smoke were as high as $900 million[10]. Passive smoking increases not only the cost of healthcare but also the risk of several other diseases, such as lung cancer, coronary heart disease, adult chronic respiratory disease and childhood asthma[11]. Smoking has also been demonstrated to be a risk factor for some subtypes of hemorrhagic stroke[12]. A retrospective analysis conducted by Ming Lv also showed that male smokers were at increased risk of AVM rupture[9].

In our study, the rate of passive smoking in the bleeding group was about 39.0%, and in the non-bleeding group it was 26.6%. Univariate analysis showed that there was a statistical difference in the proportions of passive smoking between the two groups (P = 0.009). After excluding the influence of confounding factors, the results from multivariate analysis also showed that there was a statistical difference in the proportions of passive smoking between the two groups (P = 0.036). The proportion of passive smoking in the bleeding group was higher than that in the non-bleeding group. This suggests that passive smoking may be a risk factor for bleeding in women with AVM.

In addition, the multivariate analysis result showed that the following factors may also be related to the risk of AVM bleeding in the non-smoking female population: size, location and association with IAs. These factors were not the focus of this study and will not be discussed here. In our previous studies, it was found that there may be a correlation between smoking and AVM bleeding risk among males[9].

The uniqueness of the present study is that, for the first time, the relationship between the exposure factors for passive smoking and the risk of AVM bleeding in non-smoking females was analyzed. As is well known, the proportion of Chinese women who smoke is relatively small, but they face the threat

W. Univariate and multivariate regression analysis results relating to passive smoking and AVM bleeding among non-smoking women with AVM.

Characteristics		Univariate	Multivariate	
		p-value	OR (95% CI)	p-value
Age		0.936		
Diabetes		0.738		
Hypertension		0.743		
Ischemic heart disease		0.902		
Family history of stroke		0.792		
Size	Small	0.003	Reference	
	Medium		0.470 (0.298-0.741)	0.001
	Large		0.490 (0.265-0.906)	0.023
Location	Cortical	0.014	Reference	
	Deep		1.609 (0.880-2.942)	0.122
	Infratentorial		2.795 (1.299-6.014)	0.009
Associated with blood flow-related IAs		0.004	2.072 (1.232-3.487)	0.006
Number of drainage veins (≥ 2)		0.597		
Number of feeding arteries (≥ 2)		0.235		
Venous drainage	Superficial	0.043		
	Deep			
	Deep and superficial			
Stenoses of drainage veins		0.103		
Dilation of drainage vein		0.059		
Passive smoking		0.009	1.609 (1.031-2.509)	0.036

IAs: intracranial aneurysms; CI: confidence interval.

of smoke exposure brought by men when they smoke. In this study, a quantitative method was adopted for the factor of passive smoking, and the method of multivariate analysis was used to minimize the occurrence of bias.

Possible mechanism

This study mainly focused on the association between passive smoking and AVM bleeding in non-smoking women. Therefore, we will address the possible mechanisms through which passive smoking may increase the risk of AVM bleeding. These may include the following aspects (Figure 1):

(1) Inflammation: Tobacco-burning smoke can recruit inflammatory cells via increased fibrinogen[13]. Inflammatory cells in AVM can produce substances that cause inflammation or instability of blood vessel walls, such as signal transduction molecules or molecules related to enzyme activity. Among these molecules, metalloproteinase 9 and peroxidase can break down collagen, fibrin, laminin and other substances on the basement membrane of blood vessel[14-18].

(2) Damage to the blood vessel wall: Tobacco smoke can cause damage to blood vessel walls. The endothelial cells of the blood vessel wall can be affected by aromatic compounds, and the functioning of these cells is weakened. Accordingly, the production of nitric oxide will be reduced, and endothelium-related diastolic functioning will gradually decrease[19]. Vascular remodeling will occur after vascular wall injury and this can lead to bleeding events.

(3) Hemodynamic abnormalities: Epidemiological studies of the normal population have suggested that smoking could cause vasospasm[20]. Simultaneously, carbon monoxide in smoke can inhibit combination of hemoglobin and oxygen molecules, such that red blood cells are compensated and blood viscosity is increased[21]. Furthermore, compared with non-smokers, the average blood pressure of smokers also increases[22].

(4) Atherosclerosis: During the smoking process, exposure of the matrix components of the vascular wall may occur, in which collagen activates adhesion and aggregation of platelets on the endothelium. The aggregated platelets further secrete platelet-derived growth factor (PDGF). Mononuclear cells gradually migrate to the intimal layer and differentiate into macrophages, which accelerates the process of atherosclerosis[19]. This makes the vessel wall more brittle and increases the risk of bleeding.

(5) Changes to gene expression: Gene chip technology was used by Miao et al. and they found that smoking can induce multiple gene expressions, such as ZFP36, PTGS2, NFKBIZ and TNFAIP3[23]. Among these genes, PTGS2 may increase the risk of AVM bleeding through the NF-**κB** signaling pathway and the inflammatory response pathway. NFKBIZ can also mediate inflammatory responses through interaction between ankyrin and NF-**κB** protein[24].

Limitations

Firstly, this study was a retrospective study with limited statistical power, rather than a prospective cohort study. In addition, the number of patients enrolled in this study was not enough, and statistical bias was inevitable. Furthermore, the AVM patients included were inpatients and no outpatients were included. There may have been some selection bias. Moreover, the survey of passive smoking was conducted through telephone interviews. There was also a lack of investigation of the relationship between dose and response. Lastly, the population of this study was from China. In contrast, among populations in Europe, the United States and other countries, women's exposure to passive smoking is not the same as in China. Therefore, whether the results from this study are universal remains uncertain.

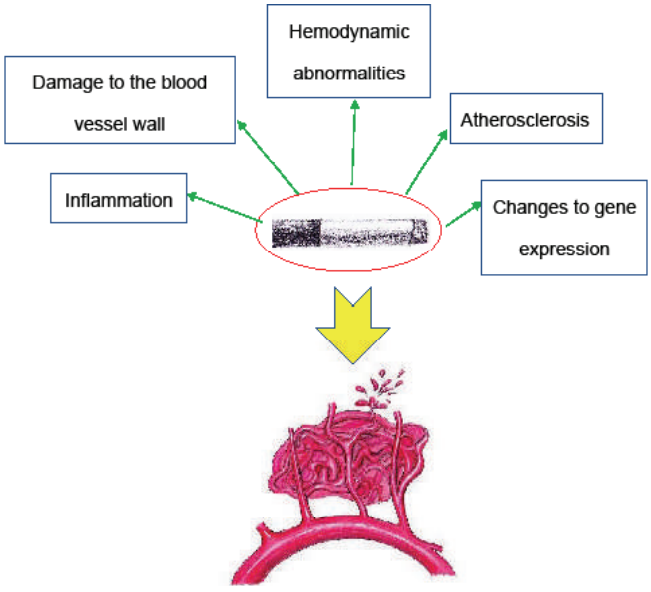

Figure 1. Possible mechanisms for AVM bleeding caused by passive smoking among non-smoking women.

In conclusion, passive smoking may increase the risk of AVM bleeding in non-smoking women. This increased risk may be related to the inflammatory response, vascular wall damage, hemodynamic disorders, changes to atherosclerosis and changes to gene expression caused by passive smoking.

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ARTICLE

Effect of the COVID-19 pandemic on patients with inherited neuromuscular disorders

Efeito da pandemia do COVID-19 em pacientes com doenças neuromusculares hereditárias

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ABSTRACT

Background: The COVID-19 pandemic has brought substantial challenges for current practices in treating hereditary neuromuscular disorders (hNMDs). However, this infection has not been the only concern for these patients. Social distancing has compromised multidisciplinary assistance and physical activity, and has brought about several mental health issues. We presented a follow-up on 363 patients with hNMDs at a Brazilian tertiary center during the peak of the COVID-19 pandemic. **Objective:** We aimed to show the frequency and severity of SARS-CoV-2 infection among hNMD patients and to demonstrate the effects of the pandemic on life habits, disease progression and multidisciplinary supportive care status. **Methods:** Three hundred and sixty-three patients (58% male and 42% female) were followed for three months through three teleconsultations during the peak of the COVID-19 pandemic in Brazil. **Results:** There were decreases in the numbers of patients who underwent physical, respiratory and speech therapies. For several patients, their appetite (33%) and sleep habits (25%) changed. Physical exercises and therapies were interrupted for most of the patients. They reported new onset/worsening of fatigue (17%), pain (17%), contractions (14%) and scoliosis (7%). Irritability and sleep, weight and appetite changes, and especially diminished appetite and weight loss, were more frequent in the group that reported disease worsening. There was a low COVID-19 contamination rate (0.8%), and all infected patients had a mild presentation. **Conclusion:** The isolation by itself was protective from a COVID-19 infection perspective. However, this isolation might also trigger a complex scenario with life habit changes that are associated with an unfavorable course for the NMD.

Keywords: Neuromuscular Diseases; COVID-19; Social Isolation; Consequence Analysis.

RESUMO

Antecedentes: A Pandemia por COVID-19 tem trazido desafios subtanciais para a prática clínica no tratamento das doenças neuromusculares hereditárias (DNMh). A infecção não tem sido a única preocupação para os pacientes. O distanciamento social tem comprometido a assistência multidisciplinar, atividade física e tem trazido problemas mentais em decorrência do próprio isolamento. Nós apresentamos aqui um seguimento de 363 pacientes com DNMh de um centro terciário Brasileiro durante o pico da Pandemia de Covid-19. Objetivos: Mostrar a frequência e gravidade da infecção por Sars-Cov-2 em pacientes com DNMh e demonstrar os efeitos da pandemia nos hábitos de vida, na progressão da doença e no cuidado multidisciplinary. **Métodos:** Trezentos e sessenta e três pacientes (58% homens and 42% mulheres) foram acompanhados por 3 meses através de 3 teleconsultas durante o pico da Pandemia de Covid-19 no Brasil. **Resultados:** Houve um decréscimo no número de pacientes que faziam terapia física, respiratória e fonoaudiológica. Em muitos pacientes, o apetite (33%) e hábitos do sono (25%) se alteraram. Exercícios físicos e terapias foram interrompidas pela maioria dos pacientes. Physical exercises and therapies were interrupted for most of the patients. Eles relataram piora ou aparecimento de fadiga (17%), dor (17%), retrações (14%), e escoliose

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(7%). Irritabilidade, mudanças no sono, peso e apetite, sendo principalmente diminuição do apetite e peso foram mais frequentemente encontrados em pacientes que apresentaram piora clinica da doença. Houve uma baixa taxa de contaminação por Covid-19 (0.8%), e todos os pacientes infectado apresentaram quadro clinico leve. **Conclusão:** O isolamento por si só se mostrou protetor na perspectiva de infecção por Covid-19, mas pode desencadear um cenário complexo com mudanças nos hábitos de vida e curso desfavorável da doença de base.

Palavras-chave: Doenças Neuromusculares; COVID-19; Isolamento Social; Análise de Consequências.

INTRODUCTION

The COVID-19 pandemic has been significantly changing current practices for treating neurological disorders and has brought substantial challenges among the different subgroups of disorders[1-6]. Inherited neuromuscular diseases (hNMDs) constitute a group of heterogeneous conditions affecting both children and adults to a degree that varies widely from one patient to another. They include diseases affecting muscles, neuromuscular junctions, peripheral nerves, metabolic systems and motor neurons. A significant number of these patients display great disability, and many of them present cardiac, respiratory and/or bulbar involvement in addition to muscle weakness[7,8].

COVID-19 has brought up several issues for the field of neuromuscular disorders. Many specialists in this field have adopted a state of vigilance due to the potential neuromuscular complications of SARS-CoV-2 infection[9,10]. However, there has not been much discussion about how to assess the risk of severe COVID-19 presentations among neuromuscular patients. It has been speculated that heightened risk would be attributable to the presence of comorbidities, older age and use of immunotherapies that patients might be receiving. Moreover, patients without swallowing and breathing difficulties would not be considered to be in the high-risk category[1].

In this pandemic scenario, the infection itself is not the only concern for neuromuscular patients. Although social distancing was established as the only effective measure for diminishing the risk of contamination, the isolation by itself has compromised medical assistance and multidisciplinary supportive therapies and limited physical activity. These support measures are directly involved in enabling a better long-term prognosis for hNMDs.

In Brazil, the epidemic phase of COVID-19 began in March 2020 and resulted in the implementation of emergency measures and cancelation of routine neurological appointments at our reference center. The neuromuscular clinic promptly switched its in-person appointments to teleconsultations. The main goals were to protect the patients from contamination and to ensure continuity of their treatment. The follow-up allowed us to collect the patients' perceptions of their disease progression and any comorbidities that they may have presented during this time.

In this study, we present the follow-up of 363 patients with hNMDs who were being attended through a Brazilian tertiary center during the peak of the COVID-19 pandemic. We aimed to show the frequency and severity of SARS-CoV-2 infection in this group of patients and to demonstrate the effects of the pandemic and the consequent restrictive measures regarding psychological factors, disease progression and multidisciplinary supportive care status for the patients.

METHODS

We reviewed the clinical database of the neuromuscular clinic of HC/FMUSP and we were able to select 468 eligible patients with clinically, histologically and/or genetically confirmed hNMD whose last appointment at the neuromuscular disorders section of Hospital das Clínicas, São Paulo, Brazil, was more recent than 2016. Phone calls were made by the authors every 30 days up to a total of three calls per patient between April and July 2020. Adult patients were required to answer for themselves, while for patients below the age of 18, parents or a legal guardian were required to respond.

All information was collected using a questionnaire that was designed for the NMD teleconsultations during the pandemic period. The first part of the questionnaire asked for pre-pandemic data regarding the following: on maximum motor skill; need for/use of respiratory support and feeding devices; presence of tracheostomy; use of medications for treatment of the NMD condition; regular practice of physical (PT), respiratory (RT) and speech therapy (ST); presence of comorbidities (cardiopathy, obesity, diabetes and asthma); and whether the patient was in a home care regime. The second part covered the pandemic period and asked about (1) access to therapies; (2) psychological factors, socioeconomic factors aspects and life habits (irritability, fear, appetite changes [yes, more or less], sleep changes [yes, more or less], weight changes [yes, gain or loss] and the patient's family income [stable, more or less]); (3) COVID-19 infection (whether the patient or a close family member had presented signs and symptoms of confirmed/suspected COVID-19 infection); and (4) the patient's and/or family member's perception of disease progression and new onset or worsening of preexisting symptoms related to the hNMD during the pandemic period (fatigue, pain, independence in daily life activities, duration of respiratory support use, swallowing difficulty, cardiopathy, contractures and scoliosis).

The study protocol was approved by the local IRB. Statistical analysis was carried out by means of the R software. A chi-square test for categorical variables was performed using the Yates correction, and Fisher's exact test was used to check

differences between the group of patients (both bed-restricted and walking patients) who reported disease worsening and the group that said that their own condition was stable.

RESULTS

Data were collected from the medical records of 468 patients. These patients were followed for three months through three teleconsultations. Subjects who did not undergo all three phone-call assessments were excluded from the final analysis. This resulted in retention of 363 patients in this analysis (78%); of these, 58% were male and 42% female.

The patients had the following diagnoses: congenital myopathy (CM), congenital muscle dystrophy (CMD), congenital myasthenic syndrome (CMS), spinal muscle atrophy (SMA), facioscapulohumeral dystrophy (FSH), limb girdle muscle dystrophy (LGMD), hereditary neuropathy (Charcot-Marie-Tooth [CMT]), Duchenne and Becker muscular dystrophies (DMD/BMD), mitochondrial disease (MitoD), Pompe disease (PD) and myotonic dystrophy type 1 (DM1). The findings were divided according to the disease group between pre-pandemic findings (Table 1) and post-pandemic findings (Table 2).

Baseline clinical characteristics of the patients

Baseline information was collected from the patients' charts and was confirmed in the first teleconsultation, which focused on the pre-pandemic period. The patients' average age was 26 (± 20) years; 42% were male, 66% were able to walk, 38% were wheelchair-bound and 5% were bed-restricted. Most of the patients (93%) were orally fed; 74% did not need ventilatory support (VS), 17% needed it only during the night and 9% needed it intermittently or continuously. Tracheostomy was present in 4% of the patients. Cardiopathy was referred to by 13% of the patients, asthma by 7%, diabetes by 4% and obesity by 13%.

Rehabilitation during the pandemic period

There were decreases in the numbers of patients who underwent in-person PT ($p < 0.001$), RT ($p < 0.001$) and ST ($p < 0.001$) during the pandemic period. However, some of the patients looked for alternatives such as doing exercises with family members or online with their therapists.

COVID-19 infection

COVID-19 infection was suspected in 38 patients. Among these, three were admitted to a hospital, stayed for fewer than seven days and tested negative for SARS-CoV-2, whereas 35 had only mild symptoms that did not require hospitalization. Tests were performed only on nine patients, among which three were positive. Symptomatic close family members were reported in the cases of 72 patients, including 22 who tested positive for COVID-19, but the patients had no symptoms within 30 days after the contact.

Patients' reports during the pandemic period

Sleep pattern changes were reported by 25% of the patients, appetite changes by 33% and weight changes by 39%. Concerning new onset or worsening of the preexisting symptoms related to the hNMD, 17% of the patients reported fatigue, 17% reported pain, 15% complained that they were more dependent for daily activities, 14.5% noticed that their contractures were worse and 7.3% considered that their scoliosis was aggravated. In addition, 2% of the patients indicated that they needed more time on VS, 1.3% experienced more swallowing issues and 0.8% reported cardiopathy worsening.

At the last evaluation, disease worsening was noticed by 6% of the bed-restricted patients, 27% of the wheelchair-bound patients and 27% of the patients who were able to walk. Among the disease groups, patients with LGMD were the ones who complained most of disease worsening. In total, 44% of them reported worsening, followed by patients with DM1 (40%), DMD (40%), FSH (40%) and CMD (30%). However, there was no statistical difference between them. A comparison was made between the group of patients (both bed-restricted and walking patients) who reported disease worsening ($n = 84$) and the group who reported that they were stable ($n = 240$). There was no statistical difference in average age with regard to motor, respiratory and bulbar baseline status between the two groups. Patients who complained about worsening of their disease also reported more irritability ($p = 0.003$; OR = 2), sleep changes ($p < 0.001$; OR = 2.78), weight changes ($p < 0.001$; OR = 2.77), weight loss ($p = 0.002$; OR = 3.47), appetite changes ($p < 0.001$; OR = 2.48) and low appetite ($p < 0.001$; OR = 4.16).

DISCUSSION

Social isolation and cancelations of in-person consultations were shown to decrease contamination rates but brought about several issues for this population, which continuously requires physical exercise, PT, RT and ST, as well as multidisciplinary medical appointments.

There were not enough data to conclusively determine the severity of COVID-19 among the hNMD patients in this cohort. However, all the suspected patients had mild symptoms. Only three suspected patients (1 SMA_I, 1 SMA_II and 1 LAMA2) tested positive. In spite of their severe hNMD disease, all of them had mild COVID-19 symptoms. An additional 20% of the patients had close contact with a suspected COVID-19 patient, but they had no related symptoms either prior to or after the contact. We speculate that our low infection rates and low severity of cases were due to the low rates of comorbidities such as obesity and diabetes, as well as the low average age. Previous data had shown that pediatric COVID-19 cases tended to be less severe than adult cases and that children were less likely to become positive when exposed[11]. Patients receiving immunosuppressive treatment were expected to have worse outcomes[1,10]. In our cohort, only the DMD patients were using

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Table 1. Self-report findings from 363 patients with hNMD during the COVID-19 pandemic, over a three-month follow-up period: pre-pandemic data.

		CM/CMS	CMD	ColVI	MD1	BMD	DMD	FSH	LGMD	MitoD	CMT	Pompe	SMA_I	SMA_II/III	Total
Demographics	Patients (count)	63	36	8	34	19	31	10	34	42	26	8	11	41	363
	Age (years)	21 (± 12)	10 (± 5)	14 (± 3)	44 (± 15)	33 (± 14)	17 (± 15)	51 (± 15)	38 (± 26)	41 (± 21)	19 (± 9)	46 (± 6)	5 (± 3)	11 (± 6)	26 (± 20)
	Sex (male/female)	32/31	16/20	6/2	22/12	17/2	31/0	7/3	16/18	19/23	13/13	4/4	4/7	25/16	212/151
Baseline	Cardiopathy	1	–	–	11	7	14	2	4	7	2	–	–	–	48 (13.2%)
	Asthma	4	5	2	1	–	–	–	3	–	7	–	–	1	23 (6.3%)
	Diabetes	1	–	–	4	1	–	3	1	5	–	–	–	–	15 (4.1%)
	Overweight	7	1	–	8	5	4	2	12	2	1	2	–	4	48 (13.2%)
	Flu vaccine	51	27	7	28	16	23	7	25	36	17	6	8	31	282 (77.7%)
	Continuous med. intake	19	12	5	19	6	15	4	13	18	10	4	6	17	148 (40.8%)
Disease burden	Bed-restricted	1	–	–	–	–	–	–	–	–	2	–	7	–	10 (2.8%)
	Few movements	1	–	–	–	–	–	–	1	–	–	–	2	4	8 (2.2%)
	Roll over	2	–	–	–	–	–	–	1	–	2	–	9	4	18 (5.0%)
	Wheelchair-bound	–	4	–	–	–	–	–	3	1	1	–	–	11	20 (5.5%)
	Sit with support	6	22	2	2	1	12	–	5	1	2	–	–	16	69 (19.0%)
	Sit without support	5	5	–	–	–	–	–	2	1	1	–	2	1	17 (4.7%)
	Stand with support	5	5	–	–	–	–	–	2	1	1	–	2	1	17 (4.7%)
	Stand with support	16	36	2	2	1	12	–	12	4	5	–	4	29	123 (33.9%)
	Walk	50	5	6	32	18	19	10	23	39	20	8	–	9	239 (65.8%)
	A few steps	1	–	1	–	2	–	–	1	–	1	–	–	2	8 (2.2%)
	Bilateral support	3	–	–	3	–	2	–	–	–	1	1	–	–	10 (2.8%)
	Unilateral support	3	–	–	7	1	–	3	8	3	3	2	–	1	31 (8.5%)
	Short distances	5	1	2	9	6	5	3	6	1	1	–	–	1	40 (11.0%)
	Medium/long distance	38	4	3	13	9	12	4	8	35	14	5	–	5	150 (41.3%)
	TQ	5	–	–	–	–	–	–	–	1	1	–	8	3	18 (5.0%)
	VS continuous	3	–	–	–	–	–	–	–	1	1	–	8	4	17 (4.7%)
	VS intermittent	5	2	–	3	–	–	–	1	1	–	1	1	4	18 (5.0%)
	VS nighttime	14	15	1	10	1	–	1	3	1	–	1	1	17	65 (17.9%)
	No VS	41	19	7	21	18	31	9	30	39	25	6	1	16	272 (74.9%)
	GTT only	4	1	–	–	1	–	–	–	1	2	–	8	3	20 (5.5%)
	GTT/mouth tasting	3	1	–	–	–	–	–	–	1	–	–	1	–	6 (1.7%)
	GTT/mouth	1	1	–	–	–	–	–	–	–	–	–	–	3	5 (1.4%)
	Mouth mashed food	5	21	1	7	–	1	1	2	9	1	1	–	7	59 (16.3%)
	Mouth only	50	12	7	27	18	30	9	32	31	23	7	2	28	282 (77.7%)

CM: congenital myopathy; ADG: alpha-dystroglycanopathy; ColVI: collagen VI myopathy; CMS: congenital myasthenic syndrome; MD1: myotonic dystrophy type 1; BMD: Becker muscle dystrophy; DMD: Duchenne muscle dystrophy; FSH: facioscapulohumeral dystrophy; LGMD: limb girdle muscle dystrophy; MitoD: mitochondrial disorders; CMT: Charcot-Marie-Tooth; Pompe: Pompe disease; SMA: spinal muscular atrophy; M: male; F: female; Med: medication; TQ: tracheostomy; VS ventilatory support equipment (bipap); GTT: gastrostomy tube.

Table 2. Data collected after four months of isolation due to COVID-19 pandemic: pandemic data.

		CM/CMS	CMD	ColVI	DM1	DMB	DMD	FSH	LGMD	MitoD	CMT	Pompe	SMA_I	SMA_II/III	Total
During pandemic	Difficulty in obtaining medication	7	4	1	3	1	6	1	–	3	3	1	–	5	35 (9.6%)
	Fear (n = 314)*	19	15	1	17	4	11	3	17	15	13	4	–	14	135 (43.3%)
	Irritability (n = 314)*	22	8	1	13	5	15	2	15	8	11	3	–	15	118 (37.6%)
	Sleeping more	10	8	–	6	4	6	–	8	–	3	–	1	3	49 (13.5%)
	Sleeping less	6	7	–	7	1	5	–	4	3	2	1	1	4	41 (11.3%)
	Eating more	14	12	3	10	2	9	2	14	8	8	2	3	10	97 (26.7%)
	Eating less	3	5	–	3	1	5	1	5	2	1	–	–	2	28 (7.7%)
	Gained weight	22	18	2	13	2	11	2	16	11	7	1	2	7	114 (31.4%)
	Lost weight	3	2	–	2	3	5	1	5	4	2	–	–	3	30 (8.3%)
Therapies	PT_PrePandemic	31	31	7	10	12	26	7	19	21	17	6	11	39	237 (65.3%)
	PT_Pandemic	9	6	4	17	4	8	2	11	11	7	1	1	5	86 (23.7%)
	PT_Pandemic_alternative	18	9	–	5	1	8	1	6	7	4	1	3	10	73 (20.1%)
	RT_PrePandemic	16	21	4	3	1	9	1	8	10	2	3	11	30	116 (32.0%)
	RT_Pandemic	5	7	3	10	3	6	–	8	7	2	–	–	1	48 (13.2%)
	RT_Pandemic_alternative	6	7	–	2	–	6	–	1	1	1	–	1	3	23 (6.3%)
	ST_PrePandemic	11	22	1	–	–	–	1	3	10	1	2	9	22	78 (21.5%)
	ST_Pandemic	4	11	2	5	–	2	–	4	6	2	–	–	3	32 (8.8%)
	ST_Pandemic_alternative	3	8	–	1	1	–	–	–	–	–	–	1	–	6 (1.7%)
COVID-19 infection	Close_contact_suspected	11	7	4	8	2	4	–	7	6	5	–	3	15	72 (19.8%)
	Not_tested	8	4	4	6	1	3	–	6	2	3	–	1	5	43 (11.8%)
	Tested (-)	0	1	–	1	–	–	–	1	3	1	–	–	–	7 (1.9%)
	Tested (+)	3	2	–	1	1	1	–	–	1	1	–	2	10	22 (6.1%)
	Patient_suspected	7	5	–	8	2	–	1	3	4	1	1	3	3	38 (10.5%)
	Not_tested	6	4	–	6	–	–	1	1	4	–	–	2	2	26 (7.2%)
	Tested (-)	1	–	–	2	2	–	–	2	–	1	1	–	–	9 (2.5%)
	Tested (+)	0	1	–	–	–	–	–	–	–	–	–	1	1	3 (0.8%)
Self-perception of disease progression after four months of the pandemic	Fatigue	6	5	–	12	2	7	–	10	6	5	–	–	8	61 (17%)
	Pain	7	5	1	7	2	4	–	11	11	4	–	1	6	62 (17%)
	More dependent (DLA)	9	5	–	9	–	9	2	5	4	2	–	1	6	55 (15%)
	Respiratory dysfunction	1	–	–	1	–	1	–	1	–	–	–	–	2	7 (2%)
	Swallowing dysfunction	1	–	–	1	1	1	–	1	–	–	–	–	–	5 (1.3%)
	Cardiopathy	0	–	–	–	–	–	–	1	1	–	–	–	–	3 (0.8%)
	Contractures	3	8	–	7	–	6	2	11	4	5	–	1	5	54 (14.5%)
	Scoliosis	1	1	–	4	–	2	–	6	4	5	–	1	–	27 (7.3%)
	General	10	12	1	14	3	11	4	15	6	6	–	2	8	97 (26.1%)

*Data referring to fear and irritability were included only for patients older than 7 years of age.
CM: congenital myopathy; ADG: alpha-dystroglycanopathy; ColVI: collagen VI myopathy; CMS: congenital myasthenic syndrome; MD1: myotonic dystrophy type 1; BMD: Becker muscle dystrophy; DMD: Duchenne muscle dystrophy; FSH: facioscapulohumeral dystrophy; LGMD: limb girdle muscle dystrophy; MitoD: mitochondrial disorders; CMT: Charcot-Marie-Tooth; Pompe: Pompe disease; SMA: spinal muscular atrophy; PT: physical therapy; RT: respiratory therapy; ST: speech therapy; DLA: daily life activities.

corticosteroids, but none of them were suspected or confirmed to have COVID-19. There was no information about asymptomatic carriers because we were unable to perform extensive COVID-19 testing.

Di Stefano et al. (2020) demonstrated that there was decreased physical activity among hNMD patients during the pandemic period and showed that less exercise correlated directly with diminished quality of life[12]. Handberg et al. (2021) also reported that health and physical functioning decreased and changes to access to physiotherapy or healthcare occurred due to the pandemic, thus demonstrating that the pandemic had had a negative effect on the biopsychosocial health and quality of life of patients with neuromuscular diseases[13]. Our data agree with this finding. We found that an impressive number of patients had reduced their in-person PT, RT, and ST, going from 65%, 31% and 21% prior to the pandemic period, down to 23%, 13% and 9%, respectively. This information indicates that more than half of the patients who regularly underwent rehabilitation therapies before the pandemic period interrupted them for at least four months.

We found that 27% of the patients complained of disease worsening after four months of social isolation. These patients were distributed within all the diagnostic groups except PD, CMS and MitoD. As expected, worsening of symptoms occurred less frequently among bed-restricted patients, among whom only 6% had any complaint, versus 27% of the wheelchair-bound patients and 27% of the patients who were able to walk. Most of the bed-restricted patients were in a home care regime and were less affected by the pandemic restrictions. We speculate that self-assessment would not be able to capture small changes in such severely affected patients.

The main complaints relating to disease progression were worsening of the contractures, fatigue and pain. Patients reported that they were becoming more dependent for daily life activities. There was no statistically significant difference between patients who continued their therapies and those who discontinued. We compared the group of patients (both bed-restricted and walking patients) who reported disease worsening with the group that reported that their condition was stable. We noticed that average age, comorbidities and severity of the disease at the baseline assessment were not correlated with the perception of disease worsening. However, irritability and sleep, weight and appetite changes, and especially diminished appetite and weight loss, occurred more frequently in the group that reported disease worsening. It is not possible to infer whether these symptoms might be the cause of the worsening or whether they are only red flags for a complex pandemic scenario involving mental health issues. The psychosocial effects of the pandemic are a significant concern, and patients considered to be at heightened risk of severe COVID-19 presentations, such as hNMD patients, are more vulnerable to such effects[14].

This study had several limitations. The data were collected using phone calls and were dependent on the patients' and/or parents' perceptions of their disease. An in-person follow-up would have been ideal for evaluating how the patients were really affected by the pandemic, in addition to enabling a detailed psychological evaluation.

In conclusion, the isolation might have been protective from the perspective of COVID-19 infection, but for hNMD patients, it brought on new symptoms and/or aggravated previous ones such as pain, joint retraction and fatigue. Reduction of physical exercises and therapies may have had a catastrophic impact on daily life activities and disease progression during the pandemic period. However, sleep, weight and appetite changes may also have played an important role in the disease and these need to be routinely evaluated for hNMD patients. We emphasize the importance of keeping social distancing and maintaining all healthcare measures in order to avoid contamination. However, it is also important to encourage hNMD patients to keep doing physical exercises and to keep track of their eating and sleeping habits, so as to avoid disease complications and an unfavorable course for their condition.

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ARTICLE

Diagnostic accuracy of CompCog: reaction time as a screening measure for mild cognitive impairment

Acurácia diagnóstica do CompCog: tempo de reação como uma medida de rastreio para comprometimento cognitivo leve

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ABSTRACT

Background: Reaction time is affected under different neurological conditions but has not been much investigated considering all types of mild cognitive impairment (MCI). **Objective:** This study investigated the diagnostic accuracy of CompCog, a computerized cognitive screening battery focusing on reaction time measurements. **Methods:** A sample of 52 older adults underwent neuropsychological assessments, including CompCog, and medical appointments, to be classified as a control group or be diagnosed with MCI. The accuracy of CompCog for distinguishing between the two groups was calculated. **Results**: The results from diagnostic accuracy analyses showed that the AUCs of ROC curves were as high as 0.915 (CI 0.837-0.993). The subtest with the highest sensitivity and specificity (choice reaction time subtest) had 91.7% sensitivity and 89.3% specificity. The logistic regression final model correctly classified 92.3% of individuals, with 92.9% specificity and 91.7% sensitivity, and included only four variables from different subtests. **Conclusions:** In summary, the study showed that reaction time assessed through CompCog is a good screening measure to differentiate between normal aging and MCI. Reaction time measurements in milliseconds were more accurate than correct answers. This test can form part of routine clinical tests to achieve the objectives of screening for MCI, indicating further procedures for investigation and diagnosis and planning interventions.

Keywords: Cognitive Dysfunction; Reaction Time; Diagnosis; Dementia; Cognitive Aging.

RESUMO

Antecedentes: O tempo de reação é afetado em diferentes condições neurológicas, mas não foi muito investigado considerando todos os tipos de comprometimento cognitivo leve (CCL). **Objetivo:** Este estudo investigou a acurácia diagnóstica do CompCog, uma bateria computadorizada de rastreio cognitivo focada em medidas de tempo de reação. **Métodos:** Uma amostra de 52 idosos passou por uma avaliação neuropsicológica, incluindo o CompCog, e uma consulta médica para serem classificados como grupo controle ou serem diagnósticos com CCL. A acurácia do teste para distinguir entre os dois grupos foi calculada. **Resultados**: Os resultados das análises de acurácia diagnóstica mostraram AUC das curvas ROC tão altas quanto 0,915 (CI 0,837-0,993). O subteste com maior sensibilidade e especificidade – subteste de tempo de reação de escolha – apresentou sensibilidade de 91,7% e especificidade de 89,3%. O modelo final de regressão logística classificou corretamente 92,3% dos indivíduos, com especificidade de 92,9% e sensibilidade de 91,7%, e incluiu apenas 4 variáveis de diferentes subtestes. **Conclusões:** Em resumo, o estudo mostrou que o tempo de reação avaliado pelo CompCog é uma boa medida de rastreio para diferenciar entre envelhecimento normal e CCL. Medidas de tempo de reação em milissegundos se mostraram melhores que o número de respostas corretas. O teste pode fazer parte de testes clínicos de rotina para atingir o objetivo de rastrear o CCL, indicar outros procedimentos para investigação e diagnóstico e planejar intervenções.

Palavras-chave: Disfunção Cognitiva; Tempo de Reação; Diagnóstico; Demência; Envelhecimento Cognitivo.

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INTRODUCTION

The American Academy of Neurology has acknowledged the utility of diagnosing mild cognitive impairment (MCI) as proposed by Petersen[1]. Its utility is related to the higher rate of conversion of individuals diagnosed with MCI to dementia than among those not diagnosed[2], and to the possibility of implementing early interventions to improve quality of life[3,4].

The diagnosis of MCI has evolved over the years. Today, it includes subtypes with different etiologies and prognostics[5]. Thus, it is a heterogeneous construct that can involve subtle cognitive impairment of several functions that are not consistently detectable through commonly used screening tests[6]. It is a challenge to detect MCI in its early years, before it has progressed to severer forms of cognitive decline like dementia. Although research is making progress, it is usually more focused on (1) forms of MCI related to Alzheimer's disease[7,8] and (2) techniques using technologies that are not always accessible or used in screening processes, like neuroimaging and biomarkers[9,10].

Evidence suggests that assessment of some cognitive variables may constitute a noninvasive and affordable first step regarding screening for cognitive decline[11,12]. One cognitive variable that might be affected more homogenously through MCI heterogeneity is processing speed. This can be assessed through several different variables[13]. Response speed and reaction time are the ones most used and can be understood as the time taken by an individual to issue a response after a stimulus[14]. This can be measured as a mean or median from several trials or also by considering intraindividual variability[14]. Although the findings have not been consistent, variability and reaction time are not necessarily impaired or affected simultaneously or with the same severity[14]. Nevertheless, concerning MCI, both measurements are of interest, given that studies have shown that both of them may be impaired[15,16].

For a long time, processing speed has been seen as a fundamental aspect of cognition and an essential aspect of healthy aging[17]. Studies have shown that it declines through many neurodegenerative conditions[13,15,16,18–20]. One metanalysis found slower reaction time among MCI patients than among healthily aging individuals[21]. Although the majority of such studies only considered amnestic patients, the same results were found in two studies that also considered non-amnestic MCI patients[22,23].

Studies have shown that reaction time can decrease before errors start to be committed. Sometimes, a task can be completed, but in more time than usual[24,25]. However, this variable is not commonly measured, considering that (1) precision is required for detecting changes at the beginning of pathological aging processes[19,23] and (2) paper-and-pencil neuropsychological assessment predominates[26]. Paper-and-pencil neuropsychological tests rarely involve precise reaction time measurements that can detect the subtle changes in the first stages of pathological aging[27,28]. However, one option for addressing this matter is to use computerized tests. These can be successful in this task because they provide precise reaction time measurements[29].

Use of computerized tests also brings other benefits, such as greater control over the administration and scoring of tests, reduction of errors in scoring and reduction of examiner's bias[26]. This is especially true for low and middle-income countries, where resources are limited and there is a need for fast and cheap methods that are amenable to large-scale administration[10].

In the present study, we investigated whether the reaction time measurements of the CompCog computerized battery are helpful for discriminating between MCI and healthy individuals. This battery uses an iPad interface, and all responses are issued using a touchscreen. During each test, the type of response and reaction time in milliseconds are recorded. A previous version of the same test is already known to distinguish between healthy individuals and individuals with Alzheimer's disease[30]. Thus, CompCog was expected to form a valuable tool for detecting MCI.

METHODS

Setting and procedures

Participants were invited after involvement in a larger study conducted in partnership with a social program offered by Rio de Janeiro's government[31]. This program provides daily activities for older adults during the day, such as physical exercises, stretching, yoga, dance, cognitive stimulation, crafts, theater, etc. The first study evaluated older adults through a brief neuropsychological assessment done by researchers and senior neuropsychologists. All psychologists attended weekly supervision with the coordinator of the Applied Psychology Service of the Pontifical Catholic University of Rio de Janeiro. The evaluation lasted one hour and was held in a quiet room in the houses where the social program commonly took place. During the assessment, cognitive tests and scales were used to assess cognition, depressive symptoms and functionality. These are all described in the corresponding section below.

Participants in the larger study were randomly invited to join the present study. The ones who accepted this underwent another neuropsychological testing session and a medical appointment with a doctor, at which diagnoses were given. The neuropsychological assessment consisted of (1) a new anamnesis to confirm the clinical and sociodemographic characteristics of the individuals, and the inclusion and exclusion criteria for recruitment; and (2) administration of CompCog. The average session duration was 1h15, and the sessions were carried out at the Applied Psychology Service of the Pontifical Catholic University of Rio de Janeiro. Medical appointments aimed at making diagnoses were conducted at the same place or in the outpatient clinics of the Department of Medicine of the same university.

Geriatricians evaluated the cases and made the diagnoses during medical appointments. The diagnoses were based on clinical history, neuroimaging when available and the initial neuropsychological protocol. This protocol included the following tests and scales: 1) Mini-Mental State Examination

(MMSE)[32]; 2) Brief Cognitive Screening Battery[31,33] consisting of the following tests: Figure Memory Test (MFT), Categorical Verbal Fluency Test (VF) and Clock Drawing Test (CDT); 3) Geriatric Depression Scale (GDS-15)[34]; 4) Functional Activities Questionnaire (FAQ)[35] and 5) Lawton Instrumental Activities of Daily Living Scale[36]. Although the FAQ formed part of the evaluation, it was not used in the analysis because of a high rate of missing data. The maximum interval between the first evaluation and the medical appointment was six months.

Participants

Seventy older adults (above 60 years old) were recruited for this study. Among them, 40 were classified as healthy older adults, i.e. individuals with no changes in cognitive performance tests and without functional impairment. The other 30 were diagnosed as older adults with MCI. Exclusion criteria eliminated six individuals from the MCI group and two individuals from the control group (CG). The exclusion criteria were the following: (1) presentation of conditions other than MCI that affect cognition (e.g. stroke); (2) recent history of alcohol or other drug dependence; (3) high levels of depressive symptoms, assessed from the score on the depression scale; (4) presence of visual or hearing disorders without correction; (5) illiteracy; and/or (6) use of medications that could affect reaction time (e.g. benzodiazepines). In the CG, 10 cases were randomly excluded until the variables of number of years of education, sex, age, number of health issues, depressive symptoms and number of medications in use had become matched with those of individuals in the MCI group. The resulting sample consisted of 24 participants with MCI and 28 individuals in the CG. The mean age of the MCI group was 73.9 years (6.9); the mean number of years of education was 11.6 (5.3); and 70.8% were women. The mean age of the CG was 71.4 years (5.7); the mean number of years of education was 14.1 (3.3); and 82.1% were women.

Although the diagnosis did not include the MCI type, it was possible to propose a classification into amnestic or non-amnestic based on the paper-and-pencil tests used, i.e. the tests in the Brief Cognitive Screening Battery. Out of the 24 MCI participants, 13 had at least one Z score below -1 in the memory test, and therefore these individuals could be classified as presenting an amnestic MCI type. The other 11 participants did not have Z scores below -1 in the memory test, and therefore could be classified as presenting a non-amnestic MCI type. We consider that these data were insufficient to classify the amnestic or non-amnestic types as multi-domain or single-domain, because more extensive assessments might have shown more deficits[37]. Nevertheless, the differences between the control group and the MCI group are described in the results.

Instrument

CompCog is a computerized cognitive screening battery with eight subtests that evaluate different cognitive domains: Simple Reaction Time (SRT), Choice Reaction Time (CRT), Implicit Learning Test (ILT), Visual and Spatial Short-Term Memory (STM), Face Recognition and Memory (FRM), Inhibitory Control Test (ICT), Stroop Test (StT) and Survey Test (ST). The subtests are usually presented in this order but can also be randomized. In our study, we used the standard test order. Each subtest is explained in Table 1 with the respective variables evaluated (52 in total). All responses are issued using a touch screen and recorded. All tests generate reaction time measurements registered in milliseconds for each touch and are presented as the total time and median time, in order to eliminate possible discrepant data from each test.

Furthermore, correct response percentages, errors and differences in reaction time between errors and correct responses are also registered. All the stimulus tests are visuospatial, except for one test: the Stroop Test, which contains written words to maintain the original paradigm[38]. With two exceptions, all reaction time medians are calculated after more than 50 trials, with a maximum of 100 trials. The FRM test has a total of 40 trials total, and STM test trials depend on correct responses, with a maximum of 105 trials.

A previous version of the same test is already known to distinguish between healthy individuals and individuals with Alzheimer's disease[30]. Previous analyses regarding the current version showed (1) good construct validity in a principal component analysis, in which variables clustered in agreement with the subtest divisions; and (2) good concurrent validity, with moderate and strong correlations between the CompCog tasks and their equivalents in paper-and-pencil tests[39].

Ethics

The National Commission for Research Ethics approved this study (opinion no. 965.264; CAAE: 39381514.3.0000.5285) through the UNIRIO Research Ethics Committee. Individuals participated in the study through signing a free and informed consent statement that had been drawn up in accordance with resolution 196/96 of Brazil's National Health Council, which deals with guidelines and standards for research involving human individuals. Participation in this survey was voluntary and the participants did not receive any payment. The study did not bring any risk to the participants' health and they could refuse and/or withdraw consent to participate in the study at any time.

Statistical analysis

All analyses were conducted using the Statistical Package for the Social Sciences (SPSS, version 22). After verifying through Shapiro-Wilk tests whether the data were normally distributed, differences between groups were tested using t tests for normal distributions or Mann-Whitney tests for non-normal distributions. A chi-square test was used in the case of sex. Receiver operating characteristic (ROC) analysis was performed for each CompCog variable. ROC curves were plotted in order to determine the degree to which subtests discriminated between controls and MCI. As proposed in a recent meta-analysis[6], sensitivity was prioritized instead of specificity since we were offering a screening measure. Therefore, false positives would be better than false negatives, with regard to continuing the

Table 1. CompCog tests and variables.

Test	Cognitive functions involved and how they are evaluated	Variables
Simple Reaction Time (SRT)	Processing speed. As soon as a white square appears in the middle of the screen, the person should touch the rectangle at the bottom of the screen.	Median reaction time
Choice Reaction Time (CRT)	Processing speed. As a white or orange square appears in the middle of the screen, the person should touch the rectangle of the same color at the bottom of the screen.	Median reaction time; Correct responses; Revised median reaction time (choice reaction time – simple reaction time).
Implicit Learning Test (ILT)	Implicit learning. As one of ten gray squares distributed in the screen turns white, the person should press it. There is a fixed sequence of 25 squares that is repeated four times and one last random sequence.	Median reaction time in each of five tasks; Implicit learning (median reaction time in sequence 4/median reaction time in sequence 1).
Visual and Spatial Short-Term Memory (STM)	Working memory. There are ten gray squares distributed on the screen. One will become white at a time, making a sequence that should be reproduced.	Correct responses; Direct order SPAN; Median reaction time in direct order; Inverse order SPAN; Median reaction time in inverse order.
Face Recognition and Memory (FRM)	Episodic memory. Ten drawings of unknown faces are presented for 30 seconds. The participant should then choose from among ten pairs of faces, the one that was among those initially shown for memorization, in four attempts.	Correct responses and median reaction time for each of the four tasks and for all tasks together.
Inhibitory Control Test (ICT)	Attention and inhibitory control. Squares of different colors will appear in the middle of the screen for one second each: the white ones should be avoided.	Median reaction time; Correct responses; Median reaction time for correct responses; Median reaction time for errors; Errors.
Stroop Test (StT)	Attention and inhibitory control. All tasks have four colored rectangles located at the bottom of the screen. The person should touch the one matching the stimulus that appears in the middle of the screen considering its color without distracters (task 1) and with distracters (tasks 2 and 3).	Interference; Median reaction time and errors for each of the three tasks.
Survey Test (ST)	Attention. Squares of different colors will appear in the middle of the screen for one second each. Participants should press the white ones in the first task, whites and blues in the second and also yellow ones in the third.	Median reaction time, correct responses, reaction time for correct responses, errors and reaction time for errors, for each of the three tasks.

clinical investigation. This prioritization was done by choosing the highest sensitivity that still allowed specificity of at least 70%. This method could not be followed regarding five variables for which specificity of at least 70% would cause sensitivity lower than 70%. In those cases, the cutoff point with sensitivity higher than 70% for which the specificity was closest to 70% was chosen.

The variables with higher sensitivity and specificity in ROC analyses were then used in a logistic regression model with the stepwise forward method, to create a model for predicting MCI with the least number of variables. All variables with specificity and sensitivity above 70% were included (24 variables in total). Age and the number of years of education were also included in order to ascertain whether they influenced the model.

RESULTS

Sample characteristics

The participants' performance in neuropsychological assessments and their demographic and clinical characteristics are described in Table 2. There was a tendency towards no significant difference between the groups regarding educational level in years ($t(37.486) = 2.008$; $p = 0.052$), and there were no

Table 2. Clinical characteristics of the sample.

Variable	CG (n = 28) Mean (SD), min-max	MCI (n = 24) Mean (SD), min-max	p-value
Sex*	23/5	17/7	0.335
Age	71.4 (5.7), 62-83	73.9 (6.9), 61-85	0.164
Number of years of education	14.1 (3.3), 6-17	11.6 (5.3), 3-18	0.052
Health problems	1.5 (1.0), 0–3	1.7 (1.4), 0–4	0.403
Medications in use	2.0 (1.9), 0-6	1.9 (2.0), 0-6	0.840
Depressive symptoms	2.8 (1.9), 0–6	3.6 (2.6), 0-9	0.224
Naming	10.0 (0.0), 10-10	9.8 (4.4), 8–10	0.123
Incidental memory	5.9 (1.2), 4–8	5.2 (1.5), 3–8	0.084
Immediate memory**	8.5 (1.1), 6–10	7.2 (1.4), 5–10	0.001
Learning**	9.3 (0.8), 8–10	8.3 (1.1), 6–10	0.001
Delayed recall**	8.6 (1.5), 4–10	7.2 (1.6), 4-10	0.005
Recognition	9.7 (0.4), 9–10	9.5 (0.9), 7–10	0.930
Clock drawing test	6.2 (2.2), 4–10	5.5 (2.5), 1–10	0.259
Verbal fluency**	20.7 (4.3), 13–30	16.6 (4.6), 8-26	0.002
MMSE30	27.0 (2.1), 22–30	25.7 (2.7), 21-29	0.067
Functionality**	20.9 (0.2), 20–21	19.6 (1.6), 15–21	< 0.001

* # female/male; ** significant differences between groups.

significant differences regarding age ($t(50) = -1.414$; $p = 0.164$), number of health problems ($t(40.60) = -0.0846$; $p = 0.403$), number of medications in use ($t(50) = 0.203$; $p = 0.840$), number of depressive symptoms ($t(50) = -1.234$; $p = 0.224$) and sex ($x^2(1) = 0.931$; $p = 0.335$).

There were differences in cognition with regard to immediate memory ($t(50) = 3.562$; $p = 0.001$), learning ($t(50) = 3.572$; $p = 0.001$), delayed recall ($t(50) = 2.914$; $p = 0.005$) and verbal fluency ($t(50) = 0.732$; $p = 0.002$). Functionality also differed between the groups ($U = 1440$; $Z = -4.257$; $p < 0.001$). The tests did not show differences regarding naming ($U = 308$; $Z = -1,542$; $p = 0.123$), incidental memory ($t(50) = -1.764$; $p = 0.084$), recognition ($U = 332.5$; $Z = -0.087$; $p = 0.930$), clock drawing test ($t(50) = 1.141$; $p = 0.259$), and MMSE ($t(50) = 1.873$; $p = 0.067$).

ROC curve

The area under the ROC curve (AUC) for all variables can be seen in Table 3. For significant variables, the same table shows sensitivity, specificity and cutoff points.

In general, reaction time measurements in cognitive tasks of lower complexity (e.g. choosing between colors) and memory tasks were the variables that best discriminated between the CG and MCI group. Simple reaction time, reaction time relating to the Stroop effect, reaction time regarding errors, number of errors and number of correct responses did not differentiate between the CG and MCI group.

Regression models

The final model correctly classified 92.3% of the individuals, with 92.9% specificity and 91.7% sensitivity, and included four variables. All of these variables concerned reaction time, but in four different tasks: the first task of the Stroop test (odds ratio = 0.979; 95% CI = 0.963-0.996; $p = 0.015$); the inhibitory control test (odds ratio = 1.027; 95% CI = 1.007-1.048; $p = 0.008$); the second task of the memory test (odds ratio = 1.009; 95% CI = 1.001-1.017; $p = 0.021$); and the second sequence of the implicit learning test (odds ratio = 1.018; 95% CI = 1.001-1.036; $p = 0.033$). Age and the number of years of education did not influence the model. The final model had a chi-square value of 46.183 (4); $p < 0.001$. The -2 log likelihood was 25.597, with Cox & Snell R-square of 0.589 and Nagelkerke R of 0.786.

DISCUSSION

Differences between paper-and-pencil and computerized tests

The first thing to notice is the neuropsychological profile of the sample. Significant differences were found between the groups in paper-and-pencil tests evaluating episodic memory and semantic verbal fluency. The latter has been reported to be highly dependent on semantic memory[40]. Episodic and semantic memory impairments are characteristics of the amnestic subtype of MCI[41]. On the other hand, the reaction times in CompCog tasks involving memory, attention and executive functions showed good accuracy in distinguishing between participants with MCI and the CG.

These results suggest that there is a potential benefit from using computerized tests. These can track a more significant number of impairments than those typically measured through traditional paper-and-pencil assessments. Moreover, with regard specifically to memory performance in CompCog, the

Table 3. AUC for all variables; cutoff points, sensitivity and specificity for significant variables.

Test	AUC, 95% confidence interval range	Cutoff point (milliseconds)	Sensitivity/specificity
Simple Reaction Time Test			
MRT	0.506, 0.339-0.673		
Choice Reaction Time Test			
MRT†	0.915, 0.837-0.993*	689.813	91.7%/89.3%
Correct responses	0.650, 0.498-0.801		
Revised MRT	0.705, 0.559-0.852		
Implicit Learning Test			
MRT 1	0.839, 0.721-0.957*	688.125	83.3%/75%
MRT 2	0.836, 0.720-0.953*	651.531	75%/75%
MRT 3	0.823, 0.703-0.943*	616.159	79.2%/67.9%
MRT 4	0.829, 0.710-0.948*	618.139	75%/71.4%
MRT 5	0.804, 0.674-0.933*	664.784	75%/75%
Implicit learning	0.521, 0.361-0.681		
Visual and Spatial Short-Term Memory Test			
Correct responses	0.718, 0.577-0.859		
Direct order SPAN	0.725, 0.588-0.861		
MRT in direct order	0.774, 0.642-0.906*	643.635	75%/71.4%
Inverse order SPAN	0.868, 0.774-0.962*	3.5	95.8%/64.3%
MRT in inverse order	0.781, 0.648-0.915*	668.615	75%/67.9%
Face Recognition and Memory			
MRT†	0.896, 0.799-0.993*	1580.791	83.3%/85.7%
MRT 1	0.823, 0.703-0.943*	1905.385	75%/71.4%
MRT 2	0.881, 0.781-0.981*	1506.316	91.7%/75%
MRT 3	0.872, 0.767-0.977*	1430.946	87.5%/75%
MRT 4	0.813, 0.693-0.932*	1486.333	79.2%/71.4%
Correct responses	0.811, 0.685-0.937*	98.750	79.2%/57.1%
Correct responses 1	0.763, 0.628-0.899		
Correct responses 2	0.673, 0.537-0.838		
Correct responses 3	0.688, 0.537-0.838		
Correct responses 4	0.757, 0.619-0.894		
Inhibitory Control Test			
MRT	0.884, 0.782-0.976*	664.447	87.5%/78.6%
CAMRT	0.871, 0.774-967*	663.279	83.3%/78.6%
EMRT	0.753, 0.615-0.891		
Correct responses	0.794, 0.664-0.924*	96.5	75%/75%
Errors	0.794, 0.664-0.924*	3.5	75%/75%
Stroop Test			
MRT 1	0.847, 0.732-0.962*	814.839	87.5%/75%
MRT 2	0.799, 0.672-0.926*	911.100	83.3%/67.9%
MRT 3	0.743, 0.604-0.881		
Errors 1	0.587, 0.430-0.744		
Errors 2	0.541, 0.378-0.704		
Errors 3	0.525, 0.336-0.684		
Interference	0.506, 0.343-0.669		
Survey Test			
MRT 1	0.818, 0.703-0.934*	637.844	79.2%/71.4%
Correct responses 1	0.648, 0.497-0.799		

Table 3. Cont.

Test	AUC, 95% confidence interval range	Cutoff point (milliseconds)	Sensitivity/specificity
CAMRT 1	0.818, 0.703-0.934*	637.844	79.2%/71.4%
Errors 1	0.648, 0.497-0.799		
EMRT 1	0.465, 0.307-0.623		
MRT 2	0.829, 0.714-0.944*	663.004	79.2%/75%
Correct responses 2	0.798, 0.676-0.919*	97	79.2%/71.4%
CAMRT 2	0.835, 0.721-0.949*	663.004	79.2%/75%
Errors 2	0.798, 0.676-0.919*	3	79.2%/71.4%
EMRT 2	0.573, 0.415-0.731		
MRT 3	0.823, 0.707-0.939*	653.629	83.3%/71.4%
Correct responses 3	0.802, 0.678-0.926*	93	75%/75%
CAMRT 3	0.826, 0.711-0.941*	664.223	83.3%/75%
Errors 3	0.802, 0.678-0.926*	7	75%/75%
EMRT 3	0.507, 0.346-0.669		

MRT: median reaction time; AUC: area under the ROC curve; CAMRT: median reaction time for correct response; EMRT: median reaction time for error; †best accuracy; *$p < 0.001$.

accuracy of the number of correct responses was not as high as that of the reaction time.

There are differences between the CompCog memory task and the paper-and-pencil memory test. The CompCog task uses recognition and not recall, as the paper-and-pencil test does. This difference suggests that the CompCog task is easier.

Two benefits can be extracted from this information. The first is the possibility of evaluation without generating performance anxiety and frustration[42], since the numbers of correct responses are similar between the groups. The second is the ability to distinguish between groups before errors start to be committed.

One hypothesis in this regard is that a slower reaction time is one of the first cues of cognitive impairment. Other studies have already shown that the time required for completing tasks increases[25], even before errors hinder their completion[24]. There is also evidence of a correlation between reductions in processing speed and general cognitive performance.[18] It is interesting to note that a reduction in processing speed is also related to subjective memory complaints[43]. Although this kind of complaint usually does not involve an objective deficit in standard tests, it is possible that patients somehow already perceive their slower reaction time. A meta-analysis has suggested that people with subjective memory complaints have twice as high a risk of developing MCI and dementia as do older adults who have no complaints[44]. However, their condition is difficult to measure through traditional memory tasks because individual performances are similar to those of controls[45].

ROC curve: reaction time is useful as a screening measure for MCI

In general, the ROC curve results showed that reaction time measurements on different cognitive processes were good at distinguishing between healthy individuals and participants with MCI. In comparing these measurements with the numbers of errors and correct responses in the same subtest, the sensitivity and specificity of the reaction time were usually higher, considering reaction times. Normal aging is known to correlate with slower reaction time[13,18]. However, the results showed signs that the decline might be even more considerable under certain circumstances of pathological conditions, such as in relation to cognitive processes of low and moderate complexity. This conclusion can be drawn from numerous results, but a comparison between the first two subtests might be the clearest: (1) simple reaction time, which was not good at distinguishing the groups; and (2) choice reaction time, which showed the best accuracy, with AUC as high as 0.9.

The results in the literature regarding the topic are mixed. Some studies investigated reaction time in simple tasks and found that this showed good accuracy for distinguishing between participants with MCI and controls[46–48]. In one study[49], the effect of increasing complexity stimulus was investigated and a division of reaction time into a movement component and a cognitive component was proposed. Activities that solely involved motor reactions, without decision making, could be used to differentiate between patients with Alzheimer's disease and cognitively healthy old adults, but not between the latter and MCI patients. Only the cognitive component was sensitive to MCI, which suggests that although lower complexity tasks may be useful in this regard, at least some cognitive processing must be involved. This may explain why the Simple Reaction Time test (motor component only) could not distinguish between the groups, but the Choice Reaction Time could, which is a low-complexity cognitive component.

Nevertheless, the same study[49] and others[19,50] found that more complex variables were better at distinguishing between groups, i.e. a contrary finding. One hypothesis for these contrasting results is that these studies used only the amnestic subtype of MCI. Using just one subtype creates a more homogeneous sample concerning cognitive impairment. So, perhaps, using more subtypes would produce different results. For example,

cognitive impairment in complex cognitive processes would be more heterogeneous, and reaction time in simple cognitive tasks would still be homogenously impaired in the sample.

Another common problem in research that may cause divergence is how reaction time is measured and reported. Some studies have suggested that intraindividual variability is higher in individuals going through cognitive decline and, therefore, in patients with MCI[49,51]. Although measurement of intraindividual variability itself can be worth investigating, it can create noise when the goal is to compare reaction time. Mean results from one or a few trials might not provide a good comparison measurement. CompCog does not have this problem since it uses the median reaction time derived from multiple trials. This would eliminate the variability problem that affects the MCI sample and does not affect the control sample. Even so, studying the intraindividual variability itself is another option for future studies with CompCog.

In addition to the abovementioned benefits of some computerized tests, two more can be added in the same context. First, simple choice reaction time can be evaluated longitudinally and without a learning effect. This enables longitudinal follow-up in which individuals will be compared with themselves in order to detect any decline right from its beginning, with the consequent possibility of early interventions.

Lastly, comparison between the reaction times for errors and correct responses in the two subtests that measure it (Survey test and Inhibitory Control test) showed that only the reaction times for correct responses could differentiate between the groups. Separated variables showing reaction times for errors and correct responses are not common in tests. The majority of computerized tests still use the same measurements used in paper-and-pencil tests, i.e. errors and total scores. The tests that investigate reaction time mainly focus on attention processes[52,53], probably because the cognitive process construct is highly relatable to processing speed[23]. However, the results show that reaction times are not the same between situations of getting answers right or wrong. These differences might be worth considering as variables if new tests are created and might be worth investigating in future studies.

Regression models

The final model that best predicted MCI with the least number of variables included three reaction time measurements regarding attention and one regarding memory, which correctly classified 92.3% of the individuals. The direction of the reaction times in the inhibitory control test, the second task of the memory test and the second sequence of the implicit learning test differed from the direction of the fourth variable selected, i.e. the reaction time in the first task of the Stroop test. Upon closer inspection, we hypothesized that the MCI group committed more errors, while the healthy group took more time in order to avoid mistakes.

We propose that these results should be seen as an exploratory analysis. It could be difficult to use only the selected variables in a test, because variables inside tests from unrelated tasks were selected for the model. Even so, the model suggests that a reaction time score composed of performance levels in different tasks could have even higher accuracy than reaction time measured separately. This proposal has to go through further testing in future studies with a specific hypothesis and larger samples.

In conclusion, we can infer from the results that reaction time measurements through CompCog are an efficient and accurate way to screen for MCI. Although the initial cost of the equipment might be high, there is no maintenance cost for its administration thereafter. There is also the possibility of expanding the technology to other devices in future studies, such as to cellphones. Thus, this method could form a low-cost option for screening for MCI on a large scale. Low-cost options are especially necessary in low and middle-income countries[54]. It is not our proposal to use the test as a diagnostic tool but to bring in technology that allows doctors or caregivers to perform simple screening on individuals who are at the threshold of old age. Additional tests and investigations should be done to reach a diagnosis and indicate treatments, depending on the results.

In order to achieve the above objective, more evidence needs to be produced. To assess cognitive decline, it is important to compare individuals with themselves at different times[9], which is a matter that our study could not cover. The best way to screen for MCI would be to compare individuals' results year by year. Studies with follow-up could provide more evidence of the utility of CompCog for MCI screening.

Furthermore, two other variables that could have been controlled for were the individuals' subjective cognitive decline and the time that elapsed between the first evaluation and the diagnosis. Controlling for the latter could have ensured that the length of time between the diagnosis and the neuropsychological assessment did not influence results. Controlling for subjective cognitive decline could have shown how and whether reaction time relates to cognitive complaints.

Lastly, the sample size can also be seen as a limitation of the present study. Although there is a need for larger samples to achieve more reliable results, there is a lack of studies exploring all MCI subtypes together. Most studies have explored Alzheimer's disease and amnestic MCI. Other MCI subtypes have been less investigated and, therefore, our findings remain relevant. Our results show that CompCog is a useful tool for screening for cognitive impairment regardless of the etiology, with reaction time measurements that are easy to obtain. CompCog can be a practical and advantageous instrument for selecting patients for a more comprehensive neuropsychological assessment and, therefore, enabling early diagnosis of MCI.

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ARTICLE

Measuring optic nerve sheath diameter using ultrasonography in patients with idiopathic intracranial hypertension

Medição do diâmetro da bainha do nervo óptico por ultrassonografia em pacientes com hipertensão intracraniana idiopática

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ABSTRACT

Background: Idiopathic intracranial hypertension (IIH) is primarily a disorder of obese young women characterized by symptoms associated with raised intracranial pressure in the absence of a space-occupying lesion. **Objective:** To compare the mean optic nerve sheath diameter (ONSD) measured using ultrasonography (USG) in patients with idiopathic intracranial hypertension (IIH) and normal healthy individuals. **Methods:** A prospective study. Ninety-seven participants aged 18-80 years were divided into two groups as patients with IIH (n=47) and the control group (n=50). The ONSD was measured using ultrasound with a 10-MHz probe. ONSD was measured 3 mm behind the optic disc. Receiver operating characteristic (ROC) curve analysis was performed to determine patients with IIH using ONSD. **Results:** Body mass index was higher in the IIH group compared with the control group (p=0.001). The mean ONSD was statistically significantly thicker in the IIH group (6.4 mm) than in the control group (4.90 mm). The cut-off value of ONSD in patients with IIH was measured as 5.70 mm. There was a significant negative correlation between ONSD and age (r:-0.416 and p<0.001). There was a positive correlation between BMI and ONSD (r: 0.437 and p<0.001). **Conclusions:** Ultrasound can be a reliable, non-invasive and rapid tool to measure ONSD in monitoring patients with IIH. After the first diagnosis of IIH, based on neuroimaging and measuring intracranial pressure using invasive methods, ONSD can be used in treatment and follow-up.

Keywords: Pseudotumor Cerebri; Ultrasonography; Optic Nerve.

RESUMO

Antecedentes: A hipertensão intracraniana idiopática (HII) é primariamente um distúrbio de mulheres jovens obesas caracterizado por sintomas e sinais associados à pressão intracraniana elevada na ausência de uma lesão ocupante de espaço. **Objetivo:** Comparar o diâmetro médio da bainha do nervo óptico (ONSD) medido por ultrassonografia (USG) em pacientes com hipertensão intracraniana idiopática (HII) e indivíduos normais e saudáveis. **Métodos:** Estudo prospectivo. Noventa e sete participantes com idade entre 18-80 anos foram divididos em dois grupos: pacientes com HII (n=47) e o grupo controle (n=50). O ONSD foi medido por ultrassonografia com uma sonda de 10 MHz. O ONSD foi medido 3 mm atrás do disco óptico. A análise da curva ROC foi realizada para determinar pacientes com HII usando-se o ONSD. **Resultados:** O índice de massa corporal foi maior no grupo HII comparado ao grupo controle (p=0,001). O ONSD médio foi estatística e significativamente mais espesso no grupo HII (6,4 mm) do que no grupo controle (4,90 mm). O valor de corte do ONSD em pacientes com HII foi medido em 5,70 mm. Houve correlação negativa significativa entre ONSD e idade (r:-0,416 ep<0,001). Houve correlação positiva entre IMC e ONSD (r:0,437 ep<0,001). **Conclusões:** A ultrassonografia pode ser uma ferramenta confiável, não invasiva e rápida para medir o ONSD no monitoramento de pacientes com HII. Após o primeiro diagnóstico de HII, com base em neuroimagem e na medida da pressão intracraniana por métodos invasivos, o ONSD pode ser utilizado no tratamento e acompanhamento.

Palavras-chave: Pseudotumor Cerebral; Ultrassonografia; Nervo Óptico.

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INTRODUCTION

Idiopathic intracranial hypertension (IIH) is quite common in routine neuro-ophthalmology clinics. The diagnostic criteria for IIH were first introduced by Walter Dandy in 1985[1]. Clinically, it progresses with headaches and loss of vision-visual field in young-middle-aged women[2].

In evaluating patients with IIH, lumbar puncture is generally preferred invasively, and magnetic resonance (MRI) and computed tomography (CT) noninvasively. Although invasive techniques are accurate and highly sensitive, they can cause adverse effects such as hemorrhage and infection that need to be managed[3]. However, CT and MRI are time-consuming, costly, and require patient transport. Therefore, evaluation of optic nerve sheath diameter (ONSD) using ultrasonography (USG), which provides low-cost and fast bedside examination, is a better option, especially in cases where patient transport is difficult, such as in the intensive care unit (ICU)[4–7]. The technique is cheap and effective, and examinations take approximately 5 minutes at the bedside[8]. ONSD has been measured as retrobulbar at a distance of 3 mm in most studies[9,10]. The optic nerve is surrounded by a dural sheath as part of the central nervous system. There is a small subarachnoid space of 0.1-0.2 mm between the dural sheath and white matter and communicating with the subarachnoid space surrounding the brain. When intracranial pressure (ICP) increases, the dural sheath expands and changes in the diameter of the sheath can be demonstrated using transocular USG[5].

This study was conducted to review the effectiveness of USG in the evaluation of patients with IIH and to compare the findings with other studies in the literature.

METHODS

This study was conducted as a case-control study in Ankara Provincial Health Directorate Beytepe Murat Erdi Eker State Hospital department of ophthalmology and neurology, Ankara, Turkey in the first quarter of 2021. The study protocol was approved by the ethics committee (registration number is E1/1541/2021). Fifty healthy volunteers and 47 patients with IIH were included in the study. The inclusion criteria for the study were as follows: age 18-80 years, diagnosed with IIH for a maximum period of 12 months, no additional disease, no drug history, no active or previous intraocular and orbital infections, no ophthalmologic disease other than refractive error, no history of eye-orbital-cranial surgery, less than -5.00 D (Diopter) and +3.00 D refractive error, no history of eye or head injury, no history of radiotherapy to the head and orbital region. Informed consent was obtained from all participants. The diagnosis of IIH was made by a neurologist according to the Dandy criteria. The patients underwent detailed neurologic examinations, ICP measurements, and lumbar puncture by a neurologist. Patients in the IIH group were also subjected to examinations by an ophthalmologist to exclude other causes of optic disc edema and diagnose papilledema. Participants were divided into two groups as patients with IIH and healthy volunteers. Measurements were taken in the supine position using a 10-MHz probe speed real-time ultrasound device (ultrasound scanner model E-Z Scan 5500+ by Sonomed Inc. NY) from the participants in both groups, with the probe placed in the superolateral of the globe with the upper eyelid closed. Only one eye of all participants was evaluated. The optic nerve head was visualized as a linear hypoechoic structure. ONSD was measured three times by the same investigator and the mean value was calculated. ONSD was measured 3 mm behind the optic nerve head (optic disk) as the transverse length of the optic nerve sheath (Figure 1).

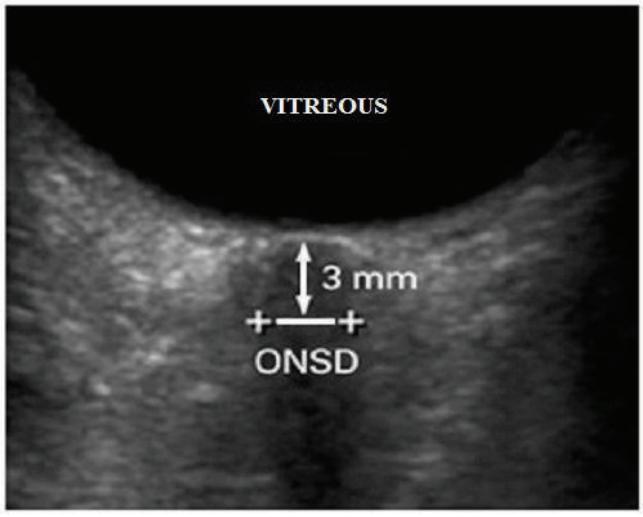

Figure 1. Transverse length of the optic nerve sheath, starting 3 mm behind the optic nerve head.

Statistical analysis

The data were recorded on a spreadsheet and analyses were performed after transfer to the SPSS version 25 software. Frequency and percentage values were used to describe categorical data, and Chi-square tests were used for comparison. The compatibility of continuous data to normal distribution was tested using the Shapiro-Wilk test. The continuous data did not conform to normal distribution and parametric assumptions were not met; thus these variables were described with median and 25-75% interquartile range (IQR) values. The Mann–Whitney U test was used to compare quantitative variables. Spearman's correlation coefficient was used for the comparison of continuous variables. Receiver operating characteristic (ROC) curve analysis was performed to determine patients with IIH using ONSD. Any p-value of <0.05 was accepted as demonstrating significance.

Power Analysis was performed through the PASS 11 program. Using the ONSD values of the patient and control groups in the study by Rehman et al.[2], it was concluded that each group should consist of at least 35 people with an 80% power level and 0.05 alpha errors.

RESULTS

The mean disease duration of patients with IIH was 3.85 ± 2.67 months. Ninety-seven eyes of 97 patients included in the study were examined. There was no significant difference between the two groups in terms of right and left eye distributions (p=0.917). In the IIH group, 36 (76.6%) people were female and 11 (23.4%) were male, and in the control group, 34 (68.0%) were female and 16 (32.0%) were male (Table 1).

Table 1. Distribution of the two groups by sex and eye care included.

		Group		P value
		IIH n (%)	Control n (%)	
Eyes	Right	23 (48.9%)	25 (50.0%)	0.917
	Left	24 (51.1%)	25 (50.0%)	
Sex	Male	11 (23.4%)	16 (32.0%)	0.345
	Female	36 (76.6%)	34 (68.0%)	

IIH: idiopathic intracranial hypertension.

The mean age was 28 (range, 26-32) years in the IIH group, and 38 (range, 32-45) years in the control group; the IIH group was significantly younger (p=0.001). Body mass index (BMI) and blood pressure (diastolic) were higher in the IIH group compared with the control group (p=0.001 and p=0.039, respectively). The mean ONSD was statistically significantly thicker in the IIH group (6.4 mm) compared with the control group (4.90 mm) (p=0.001). There was no significant difference between the groups in terms of spherical equivalent (diopter), glycated hemoglobin (HbA1C) (mMol0/L), and blood pressure (systolic) values. The demographic data and examination findings of the two groups are given in Table 2. In the IHH group, 57.4% of the cases were receiving acetazolamide treatment.

Table 3 shows the correlation of the ONSD and demographic data. A high level of negative correlation was observed between ONSD and age (r: -0.416 and p<0.001). A high level of positive correlation was observed between BMI and ONSD (r: 0.437 and p<0.001). Moderate positive correlation was observed between HbA1C (mMol/L) and ONSD (r: 0.227 and p=0.025). There was no significant correlation between ONSD and disease duration, blood pressure, and spherical equivalent. The mean cerebrospinal fluid (CSF) pressure was 269.72 ± 66.29 mmH_2O in the IHH group. A high level of positive correlation was determined between CSF pressure and ONSD (r: 0.740 and p<0.001).

According to the ROC analysis, the cut-off points of 5.70 mm, showed 100% sensitivity and 98% specificity (AUC: 0.999 [0.996-1.000]) (Figure 2).

DISCUSSION

In our study, the efficiency of USG in the evaluation of patients with IIH and the measured mean ONSD value and cut-off value was compared with other studies in the literature. IIH is seen in young women. ONSD was highly correlated with age (r: -0.416, p<0.001) and BMI (r: 0.437, p<0.001). The cut-off value of ONSD in patients with IIH was determined as 5.70 mm.

ONSD measurement using USG is a simple, fast, non-invasive, and reliable method. Although lumbar puncture is the gold standard for measuring ICP, studies have reported that ONSD has a positive correlation with ICP[11–13]. ONSD values are measured at a fixed distance, and measurements taken as retrobulbar at a distance of 3 mm are considered reliable in the literature[2,9,14,15]. In our study, the average ONSD values were calculated using B-mode USG from a retrobulbar 3 mm distance. However, as with all USG evaluations, it requires training. It has intra and interobserver variance, but these variations are small. In recent studies, the mean intraobserver variance was found as ± 0.1-0.2 mm, and the mean interobserver variance was ± 0.2-0.3 mm[9,10]. ONSD can also be measured using MRI, but the patient must be transported for MRI. Bedside evaluation of patients provides a great advantage, especially in ICPs and emergency departments. Studies comparing USG and MRI on this subject are also available in the literature. In a study comparing ONSD values measured using USG and MRI, it was concluded that ONSD values taken from a retrobulbar 3 mm distance showed a high level of correlation between the two methods[16]. Chen et al. showed ultrasonographic measurements

Table 2. Demographics and optic nerve sheath diameter values in controls and patients with Idiopathic intracranial hypertension.

	Group		P-value
	IIH n (%)	Control n (%)	
	IIH n (%)	Control n (%)	
Age	28 (26-32)	38 (32-45)	0.001*
Spherical equivalent (diopter)	-1.00 (-2.00-1.00)	-1.00 (-2.00-1.00)	0.663
Body mass index	34.81±5.33	28.58±3.91	0.001*
Blood pressure (systolic)	120 (110-130)	117.5 (105-120)	0.097
Blood pressure (diastolic)	80 (70-85)	72.5 (70-80)	0.039
HbA1C (mMol/L)	4 (3.5-4)	3.5 (3.5-4)	0.279
Optic nerve sheath diameter	6.4 (6-6.7)	4.9 (4.6-5.2)	0.001*

*: statistically significant, p-value <0.05; IIH: idiopathic intracranial hypertension.

Table 3. Correlation of optic nerve sheath diameter and demographics.

		Optic Nerve Sheath Diameter (mm)		
		Total	IIH	Controls
Age	r	-0.416*	0.039	0.118
	p	<0.001*	0.793	0.416
Disease duration (months)	r	-0.160	-0.160	–
	p	0.282	0.282	–
Spherical equivalent (Diopter)	r	-0.006	-0.179	0.272
	p	0.953	0.228	0.056
Body mass index	r	0.437*	0.051	-0.263
	p	<0.001*	0.733	0.065
Blood pressure (systolic)	r	0.120	0.020	-0.121
	p	0.241	0.896	0.404
Blood pressure (diastolic)	r	0.095	-0.203	-0.144
	p	0.356	0.171	0.318
HbA1C (mMol/L)	r	0.227*	0.353	0.178
	p	0.025*	0.015	0.217

*: statistically significant p-value of <0.05; HbA1C: Hemoglobin A1c.

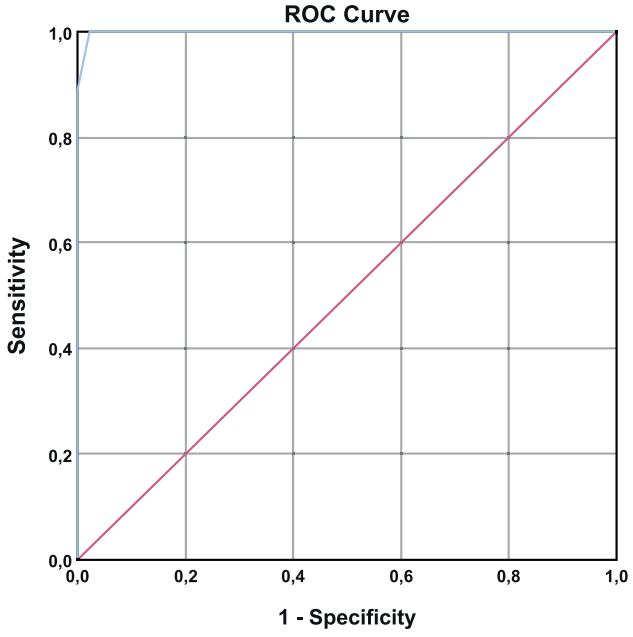

Figure 2. Receiver operating characteristic (ROC) analysis.

of ONSD can dynamically and sensitively evaluate real-time ICP. In their study, ONSD measurements were performed approximately 5 min prior to and after a lumbar puncture. They found significant correlations between ONSD and ICP before lumbar punctures and between the median change in ONSD and the change in ICP[17]. Padayachy et al. reported in child patients, the ONSD measurement with the best diagnostic accuracy for detecting an ICP ≥ 20 mmHg over the entire patient cohort was 5.5 mm, sensitivity 93.2 %, specificity 74 % and odds ratio of 39.3[18]. Tekin Orkun et al. also indicated the mean cerebrospinal fluid opening pressure (37.75 ± 12.64 cm H_2O) and the mean ONSD (5.94 ± 0.46 mm) were correlated in small sample size of pediatric IIH patients[19]. In contrast to these studies, Lochner et al. reported no correlation was demonstrated between ONSD and cerebrospinal fluid opening pressure in adult IHH patients. They also found no differences in optic nerve diameter values between patients and control groups[20].

In our study, in accordance with the literature, ONSD values were significantly higher in the IIH group than in the control group[2,9,10]. As frequently reported in the literature, IIH is mostly seen in young women with obesity[1,2]. Zheng et al. found a correlation between ONSD and BMI using high-resolution MRI. Their result indicates that the effects of BMI should be considered along with the ONSD during ICP monitoring. Meanwhile, the correlation index between ONSD and BMI was better than the ONSD in predicting IIH and could be used to obtain a more precise estimation of ICP[21]. As a different point of view, Lochner at al. claims to monitor the efficacy of diet and pharmacological treatment in IIH patients[22]. In our study, it was observed that the IIH group consisted mostly of young female patients with higher BMI values. In addition, a high level of correlation was observed between ONSD values and age (r: -0.416, p<0.001) and BMI (r: 0.437, p<0.001).

There is no single cut-off value for ONSD. This should be considered as a clear indication of abnormal or elevated ICP. In our study, the mean ONSD value was 6.40 mm in the IIH group and 4.90 mm in the control group. The best ONSD cut-off value indicating increased ICP was determined as 5.70 mm (100% sensitivity and 98% specificity) with an area under the curve (AUC) of 0.999. Shrestha et al. concluded that 95% of normal individuals in Nepal had an average ONSD value of 4.41 mm[23]. Dubourg et al., in their meta-analysis, concluded that ONSD had a cut-off value of 5.10 mm[24]. In a study conducted in China,

Wang et al. reported that the mean ONSD value was 4.33 ± 0.38 mm in normal individuals and 6.61 ± 0.39 mm in patients with IIH[25]. Kishk et al. measured the ONSD cut-off value as 6.05 mm (73.2% sensitivity and 91.4% specificity) with an AUC of 0.850[14]. Fernando et al. showed in their study in patients with increased intracranial pressure for various reasons, the pooled AUC curve for ONSD sonography was 0.94 (0.91 to 0.96)[26]. Li et al. reported in their study AUC analysis showed the ONSD of 5.6 mm was the best cutoff value with a sensitivity of 86% and a specificity of 71% for identifying high ICP[27]. Del Saz-Saucedo et al. found that the best cut-off point for detecting raised ICP was 6.3 mms, with a sensitivity, specificity and positive likelihood ratio of 94.7%, 90.9% and 10.4, respectively. After a therapeutic lumbar puncture an 87% of cases had a partial reduction of ONSD values[28]. According to the ROC analysis of our study, the cut-off point of 5.70 mm, showed 100% sensitivity and 98% specificity (AUC: 0.999 [0.996-1.000]). The sensitivity and specificity rates are the highest rates when compared to the other studies. Despite considerable debate on the normal and abnormal cut-off value of ONSD in different populations, this ultrasonographic measurement easy and noninvasive research method cannot be underestimated.

The limitation of our study is that when ONSD values are measured using USG, patients' ICPs are not measured, and they cannot be compared with ONSD values. Secondly, the distribution of age was different between the IHH and control groups. Some studies showed a correlation between age and ONSD[29], while others did not[30]. In our study, age was negatively correlated with ONSD. The heterogeneous distribution of age in the groups may also have affected the ONSD value. This was not taken into account when interpreting our results.

In conclusion, USG is a reliable, cheap, non-invasive and fast tool for measuring ONSD in the monitoring of patients with IIH. Although many studies have been conducted on the ONSD cut-off value as measured using USG, there is no consensus among authors yet. Our study made significant contributions to the literature in terms of determining ONSD cut-off values and demonstrating the diagnostic value of ONSD in patients with IIH. The values of the optic nerve sheath can replace cerebrospinal fluid pressure in the diagnosis or follow-up of these patients. Studies on this subject should be conducted on larger data sets and with a longer follow-up period. Considering the results of our study and comprehensive future studies, ONSD value may be considered as a preferable option in the diagnosis of IIH patients.

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ARTICLE

A study on the correlation between pain frequency and severity and vitamin B12 levels in episodic and chronic migraine

Estudo da correlação entre frequência e gravidade da dor e níveis de vitamina B12 em enxaqueca episódica e crônica

Sibel ÜSTÜN ÖZEK[1]

ABSTRACT

Background: It is believed that vitamin B12 deficiency and hyperhomocysteinemia cause endothelial cell damage by increasing the levels of free oxygen radicals, which may, in turn, be related to the onset of migraine episodes. **Objective**: The objective of our study was to ascertain a correlation between vitamin B12 levels and migraine attack frequency and pain severity. **Methods:** 127 patients with migraine and 45 healthy controls who presented to Okmeydanı Training and Research Hospital were included in the study. The migraine attack frequency and the duration and severity of pain in migraineurs were recorded. Pain severity was evaluated using a visual analogue scale (VAS). Vitamin B12 levels below 300 ng/L were considered low. **Results**: The vitamin B12 levels in migraineurs were found to be significantly lower than those in the control group (227.30 ± 104.72 ng/L vs 278.44 ± 149.83 ng/L; p = 0.047). The vitamin B12 levels of patients with chronic migraine (CM) were found to be lower than those in patients with less frequent migraine attacks (197.50 ± 69.16 ng/L vs 278.56 ± 147.91 ng/L; p = 0.019). The ratio of vitamin B12 levels of 300 ng/L and above in patients with CM was lower than that of patients with episodic migraine (p < 0.05). **Conclusions:** Along with attack frequency and pain severity assessment, it is important that migraine follow-ups should include regular measurement of vitamin B12 levels. We found lower vitamin B12 values in the CM group.

Keywords: Migraine Disorders; Headache, Vitamin B 12; Homocysteine.

RESUMO

Antecedetes: Acredita-se que a deficiência de vitamina B12 e a hiper-homocisteinemia causem danos às células endoteliais pelo aumento dos níveis de radicais livres de oxigênio, o que pode, por sua vez, estar relacionado ao aparecimento de episódios de enxaqueca. **Objetivo**: O objetivo do nosso estudo foi verificar a correlação entre os níveis de vitamina B12 e a frequência e a gravidade da dor nas crises de enxaqueca. **Métodos**: 127 pacientes com enxaqueca e 45 controles saudáveis que se apresentaram ao Okmeydanı Training and Research Hospital foram incluídos no estudo. A frequência das crises de enxaqueca, bem como a duração e a gravidade da dor nos pacientes foram registradas. A gravidade da dor foi avaliada usando-se uma escala visual analógica (EVA). Níveis de vitamina B12 abaixo de 300 ng/L foram considerados baixos. **Resultados**: Os níveis de vitamina B12 em pacientes com enxaqueca foram significativamente menores do que os do grupo controle (227,30 ± 104,72 ng/L vs 278,44 ± 149,83 ng/L; p = 0,047). Os níveis de vitamina B12 de pacientes com enxaqueca crônica (EC) foram menores do que aqueles em pacientes com crises de enxaqueca menos frequentes (197,50 ± 69,16 ng/L vs 278,56 ± 147,91 ng/L; p = 0,019). A proporção dos níveis de vitamina B12 de 300 ng/L e acima em pacientes com EC foi menor do que a de pacientes com enxaqueca episódica (p < 0,05). **Conclusões**: Juntamente com a avaliação da frequência das crises e da gravidade da dor, é importante que o acompanhamento da enxaqueca inclua a medição regular dos níveis de vitamina B12, pois encontramos valores mais baixos de vitamina B12 no grupo EC.

Palavras-chave: Transtornos de Enxaqueca; Cefaleia; Vitamina B 12; Homocisteína.

INTRODUCTION

Migraine is a condition that accounts for large patient volumes in daily neurology polyclinics. It causes obstacles to daily life activities and has an adverse impact on quality of life. The ratio of disability and workforce loss increases in parallel with an increase in the frequency and severity of pain[1]. The risk factors regarding migraine that cannot be changed are age, sex and family history. Other risk factors can be changed, and the most common of these are diet, stress, sleep changes,

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depression, medications and habits like alcohol consumption and caffeine intake[2]. Supplement intake is also considered to be a changeable factor[3,4].

Patients are diagnosed as having chronic migraine (CM) if pain occurs at a frequency of over 15 days a month, among which a minimum 8 days of pain have the characteristics of migraine[5]. Although transformation from episodic migraine is mostly blamed, it is considered that individuals' genetic predisposition and certain modifiable or non-modifiable risk factors play a role in this transformation. Although many factors are blamed for migraine becoming chronic and for increasing pain frequency, the underlying pathophysiological mechanisms are not yet altogether clear[6]. Identifying the factors that trigger migraine attacks is important for both diagnosis and preventive treatments. Therefore, modifiable factors need to be evaluated well, and the requirement for nutritional supplements need to be considered.

It is believed that vitamin B12 deficiency and hyperhomocysteinemia cause endothelial cell damage by increasing the levels of free oxygen radicals, which may, in turn, be related to the onset of migraine episodes. It is also believed that nitric oxide (NO) plays a role in the pathology of migraine[7,8]. However, vitamin B12 has an attenuating effect on NO[9].

There are many studies assessing migraine in relation to vitamin B12 levels. Some found normal levels of vitamin B12, whereas others found low levels in migraineurs[10-12]. In the study of İpekçioğlu et al., the level of vitamin B12 was found to be normal in serum, whereas the level of methylmalonic acid, which is a metabolite of vitamin B12, was found to be high in urine[13]. In other studies, apart from assessing vitamin B12 serum levels in migraine with aura and migraine without aura, vitamin B12 serum levels were assessed during the migraine attack and outside of the migraine attack[14]. There are many open-label and randomized control trial studies assessing prophylactic vitamin B12 and replacement treatments[15].

When browsing the literature, we found more studies concerning migraine with aura than migraine without aura, in correlation with vitamin B12 levels. These were mostly related to use of vitamin B12 in treatments. In studies concerning migraine with aura that were conducted among children and adolescents[16-18], vitamin B12 replacement was correlated with decreased pain frequency and intensity, along with decreased disability related to migraine. In a study that included migraine cases both with and without aura, pain frequency and use of drugs related to migraine diminished with vitamin B12 replacement, but there was no difference in the duration of attacks[9].

Even if there are studies proving the benefit of vitamin B12 replacement in cases of migraine with aura, there is a need for more randomized controlled trials regarding migraine without aura[19]. Vitamin B12 levels were found to be low in many studies concerning pediatric and adult groups of migraineurs[12,20]. In those studies, no evaluation of the frequency of attacks was conducted. In one study, evaluations was made during attacks and outside of attacks, and it was found that vitamin B12 levels were lower during the attacks. In one study evaluating vitamin B12 and MMA levels, there was no difference in levels between the episodic migraine group and the chronic migraine group. However, there was higher frequency of migraine among participants with low vitamin B12 levels[21].

Our study is valuable in these terms, in that it assesses vitamin B12 levels in correlation with pain frequency, mostly in a group of migraineurs without aura. The objective of our study was to ascertain a correlation between vitamin B12 levels and migraine attack frequency and pain severity.

METHODS

Patients who were diagnosed as having migraine according to the International Classification of Headache Disorders (ICHD-III), from among outpatients presenting to the Okmeydanı Training and Research Hospital neurology polyclinic between 2019 and 2020, were included in this study. Only patients who had complete medical data recordings and in whom vitamin B12 levels were assessed, were retrospectively scanned and included. Those with systemic diseases such as high blood pressure and diabetes mellitus, and those using vitamin replacements, were excluded. Clinical and demographic data such as age at disease onset, duration and frequency of headaches, clinical characteristics and location of the headaches, pain severity, triggering factors, presence of family history, presence of aura and visual analogue scale (VAS) scores were recorded.

The patients were divided into three groups according to attack frequency. These groups were identified as infrequent episodic, frequent episodic and chronic. Those with 1-3 migraine attacks per month and those having pain on 4-14 days per month were included in the infrequent and frequent episodic groups, respectively. CM was identified as headache attacks lasting over 4 hours on 15 or more days per month for a minimum period of three months, when the attacks on a minimum of eight of these days met the criteria for the diagnosis of migraine.

The control group consisted of patients who presented to our neurology outpatient clinic for general medical examination, and who were registered with the code Z00.0. Z00.0 is the code used to designate a group of patients who came in for 'general examination', who were not diagnosed as presenting any neurological disease and in whom no abnormal symptom was found. These patients had no headache symptoms. Their neurological, imaging and neurophysiological examinations were normal. Patients who had no additional systemic disease were chosen to form the control group. These patients had come in with non-specific complaints and their vitamin B12 assays was made within the context of a general check-up.

Pain severities were evaluated using VAS scores. From among the forms used in the interviews, a VAS was used by patients to subjectively score their pain severity on a horizontal or vertical 10-cm straight-line scale from 0 = no pain to 10 = most severe pain[22,23].

All the samples from the patients who were diagnosed with episodic and chronic migraine in accordance with the migraine diagnosis criteria were collected during an attack-free period. In our clinic, routine biochemical tests, along with the frequency and severity of pain are evaluated annually or biannually among patients diagnosed with migraine. The routine biochemical tests performed included renal and liver function tests, electrolyte values, hemogram, thyroid function tests, vitamin B12 and folate values. Samples were taken at the time of the first interview and only at this one time.

The vitamin B12 assays were done as follows: After 12 hours of fasting, 5 mL of blood was taken into a yellow serum separation gel tube. The samples were immediately centrifugated at +4 °C and 4000 rpm for 10 minutes. Vitamin B12 levels were assayed using a chemiluminescent immunoassay in a Roche Cobas Integra 400 Plus analyzer. Levels of below 300 ng/L were considered low for vitamin B12. The groups formed according to migraine frequency were compared with regard to vitamin B12 levels among each other and with normal healthy individuals.

Written informed consent was obtained from all participants in the study. Approval for the study was obtained from the Istanbul Prof. Dr. Cemil Taşçıoğlu City Hospital Clinical Research Ethics Board (Approval No. 32, dated February 9, 2021). This date is different from the selection data. Was the ethics send later?

Statistical analysis

The Number Cruncher Statistical System (NCSS) (Kaysville, Utah, USA) software was used for statistical analyses. Complementary statistical methods (mean, standard deviation, median, frequency, ratio, minimum and maximum) were used when evaluating the study data. The suitability of quantitative data for normal distribution was tested using the Kolmogorov-Smirnov test, Shapiro-Wilk test and graphic evaluations. Student's t test was used in two-group comparisons of quantitative data with normal distribution, and the Mann-Whitney U test was used in two-group comparisons of data without normal distribution. The Kruskal-Wallis test was used for comparing three or more groups that did not demonstrate normal distribution, and the Bonferroni-Dunn test was used for paired comparisons. Pearson's chi-square test and Fisher's exact test were used for comparing qualitative data. Binary logistic regression analyses were used. The significance level was taken to be a minimum of $p < 0.05$.

RESULTS

There were 127 patients with a diagnosis of migraine (121 females and six males); and 45 controls (43 females and two males) were included in the study. Patients with antecedents of chronic disease or who were using food supplements or any other drug were excluded from the study. The percentage of patients who were excluded was about 16%. None of the patients initially included in the study were lost later on. The mean ages of the patients with migraine and the control group were 37.6 ± 9.7 years and 42.3 ± 10 years, respectively. When gender and age were compared between the study and control groups, the p values detected were $p = 0.121$ and $p = 0.012$ respectively. The mean ages of the migraineur groups were 36.83 ± 2.1 in the infrequent episodic group, 35.65 ± 1.32 in the frequent episodic group and 40.14 ± 1.33 in the chronic group. When the migraineur groups were compared with each other, $p = 0.059$ was found and there was no significant difference according to the age.

The clinical features of migraine are shown in Table 1. Evaluation of the migraine demographic characteristics using the Pearson chi-square test after subtracting the cases of migraineurs with aura showed the following results: phonophobia $p = 0.100$, photophobia $p = 0.107$, nausea $p = 0.177$, vomiting $p = 0.599$ and family history $p = 0.299$. These data were comparable to those found from evaluating the group of migraineurs with and without aura all together. The Kruskal-Wallis test showed a statistically significant difference in comparing nonparametric distribution of disease duration and frequency of pain (between the infrequent episodic, frequent episodic and chronic migraine groups) ($p = 0.006$). Subgroup analysis showed that this difference was specifically between the frequent episodic and chronic groups ($p = 0.015$).

The mean vitamin B12 level of the study group was 240.68 ± 119.85 ng/L (range, 85–836). The vitamin B12 levels were ≥ 300 ng/L in 25.6% (n = 44) and < 300 ng/L in 74.4% (n = 128). The vitamin B12 levels in migraineurs were found to be significantly lower than in the control group (227.30 ± 104.72 ng/L vs 278.44 ± 149.83 ng/L; $p = 0.047$); and the vitamin B12 levels of those in the migraine group were lower than those of the control group. The ratio of encountering a vitamin B12 level over 300 ng/L was lower for the migraine group than for the control group ($p = 0.029$). Comparison of the duration of the disease and vitamin B12 levels using the Mann-Whitney test did not show any statistically significant difference ($p = 0.172$).

The Pearson chi-square test was used to compare pain frequencies according to vitamin B12 levels (below and above 300), in three groups of migraineurs: infrequent episodic, frequent episodic and chronic migraine. A statistically significant difference was found ($p = 0.044$). The infrequent episodic and frequent episodic groups were considered as one group because of the low number of cases. Comparison of the episodic pain and chronic pain groups showed that there was a significant difference ($p = 0.012$) between them. When the cases of migraine with aura were taken out, there was also a statistically significant difference ($p = 0.019$) (Table 1).

A statistically significant difference between vitamin B12 measurements was found when comparing groups according to migraine frequency (patients with infrequent episodic and frequent episodic migraine were included in a single group, while patients with chronic migraine were taken as a separate group) ($p = 0.011$). Paired comparisons revealed lower vitamin

Table 1. Demographic characteristics and B12 levels according to migraine frequencies.

		Migraine frequency			p
		Infrequent episodic (n = 18)	Frequent episodic (n = 59)	Chronic (n = 50)	
Vitamin B12		182-836 (239.5)	90-471 (214)	85-406 (184.5)	[e]0.020*
		278.56 ± 147.91	236.92 ± 108.14	197.50 ± 69.16	
Vitamin B12 level; n (%)	< 300	13 (72.2)	42 (71.2)	45 (90.0)	[d]0.044*
	≥ 300	5 (27.8)	17 (28.8)	5 (10.0)	
Disease duration (years)	Min-Max (median)	1-30 (8)	1-38 (6)	1-43 (10)	[e]0.006**
	Mean ± SD	10.50 ± 2.13	8.45 ± 1.10	13.42 ± 1.33	
Aura	None	16 (88.8)	53 (89.8)	50 (100)	[d]0.062
	Yes	2 (11.2)	6 (10.2)	0 (0)	
VAS	Min-Max (median)	5-10 (9)	5-10 (9)	7-10 (10)	[e]0.004**
	Mean ± SD	8.67 ± 1.71	8.68 ± 1.18	9.38 ± 0.88	
Family history; n (%)	None	6 (33.3)	28 (47.5)	23 (46.0)	[d]0.562
	Yes	12 (66.7)	31 (52.5)	27 (54.0)	
Nausea; n (%)	None	0 (0)	11 (18.6)	8 (16.0)	[d]0.147
	Yes	18 (100)	48 (81.4)	42 (84.0)	
Vomiting; n (%)	None	10 (55.6)	31 (52.5)	24 (48.0)	[d]0.825
	Yes	8 (44.4)	28 (47.5)	26 (52.0)	
Photophobia; n (%)	None	5 (27.8)	8 (13.6)	4 (8.0)	[d]0.107
	Yes	13 (72.2)	51 (86.4)	46 (92.0)	
Phonophobia; n (%)	None	5 (27.8)	5 (8.5)	8 (16.0)	[d]0.108
	Yes	13 (72.2)	54 (91.5)	42 (84.0)	

SD: standard deviation; [d]: Pearson chi-square test; [e]: Kruskal-Wallis test; *: $p < 0.05$; **: $p < 0.01$.

Table 2. Comparison of B12 levels according to migraine frequency and control groups.

		Migraine frequency		Control (n = 45)	p
		Episodic (n = 77)	Chronic (n = 50)		
Vitamin B12	Min-Max (median)	90-836 (227)	85-406 (184.5)	98-782 (223)	0.011*
	Mean ± SD	246.65 ± 118.88	197.50 ± 69.16	278.44 ± 149.83	
Vitamin B12 level; n (%)	< 300	55 (71.4)	45 (90.0)	28 (62.2)	[d]0.006**
	≥ 300	22 (28.6)	5 (10.0)	17 (37.8)	

SD: standard deviation; [d]: Pearson chi-square test; [e]: Kruskal-Wallis test; *: $p < 0.05$; **: $p < 0.01$.

B12 measurements in patients with chronic migraine than in the control group ($p = 0.012$) (Table 2).

Binary logistic regression analysis was done in order to investigate the effects of the vitamin B12 level (whether below or over 300), duration of the disease and presence or absence of aura on the frequency of pain. Logistic regression analysis showed a Nagelkerke ratio of 0.215 and a Hosmer-Lemeshow result of $p = 0.643$. We therefore came to the conclusion that the model that had been established was a good fit for the data. From the classification table, we determined that the logistic function was making classifications that were 66.9% correct. We also came to the conclusion that disease duration and vitamin B12 levels were independent factors for 'chronic migraine'. Low vitamin B12 levels increased the likelihood of chronic migraine 3.6-fold ($p = 0.022$; OR = 3.687; 95% CI 1.212-11.220). In addition, the disease duration was found to be 6% effective on chronic migraine ($p = 0.009$; OR = 1.063; 95% CI 1.016-1.113).

DISCUSSION

The main conclusion from our study was that serum vitamin B12 levels in migraineurs during migraine attack-free periods were lower than the levels in the healthy control group. These levels were also lower in patients with chronic migraine than in the episodic group. Comparison of vitamin B12 levels between migraineurs without aura and the controls did not show any significant difference[13]. There was a functional vitamin B12 deficiency, represented by elevated urine MMA levels, in patients presenting migraine without aura[13].

Bottini et al. found that vitamin B12 levels were normal in migraineurs[10]. However, in the studies by Nelson et al. and Acar et al., like in our study, vitamin B12 levels were found to be low[11,12]. Fenech et al. reported that DNA damage occurred in blood cells in patients with serum vitamin B12 levels < 300 pmol/L, and that, even if serum levels were normal, vitamin B12 deficiency could occur at a cellular level. They also reported that vitamin B12 levels should be kept at > 300 pmol/L[24]. Our results also identified the need to determine vitamin B12 deficiency in patients with migraine, and supported administration of vitamin B12 to decrease pain frequency.

Causes such as neurogenic inflammation, trigeminovascular system activation, vascular dysfunction and NO release, and increased release of homocysteine (Hcy), might be responsible for the onset of migraine. Hyperhomocysteinemia, NO release and vascular dysfunction are important pathways that play a role in the pathogenesis of migraine[25]. NO-related pain transmission, hyperalgesia, chronic pain, inflammation, central sensitization and cyclic guanosine play predominant roles in monophosphate-dependent pathways. It has been suggested that vitamin B12 has a regulatory effect on inflammation and that pro-inflammatory cytokine levels become increased in patients with vitamin B12 deficiency[26].

Homocysteine may be responsible for endothelial dysfunction in migraine[19]. Homocysteine causes endothelial damage through NO release. Low vitamin B12 levels are correlated with high homocysteine, which in turn triggers migraine[27]. A high homocysteine level has been correlated with B12 folate and, to a lesser degree, vitamin B6 deficiency[28]. These vitamins are quite important in inhibiting hyperhomocysteinemia. Van der Kuy et al. suggested that administration of intranasal hydroxocobalamin reduced the attack frequency. Vitamin B12 plays the role of a radical scavenger against NO. Accordingly, they recommended its use for migraine prophylaxis[9]. In another study, serum vitamin B12 and methylmalonic acid (MMA) levels in patients with migraine were compared with controls. Vitamin B12 levels were found to be significantly lower in patients with migraine. A greater proportion of migraine was found in patients having low vitamin B12 levels and high MMA levels[21].

A study conducted among patients with migraine accompanied by aura reported that vitamin supplementation (B6, B9 and B12) both significantly lowered homocysteine levels and reduced pain severity and disability, compared with placebo[16]. In another study, 51 patients with migraine with and without aura were evaluated, and decreased levels were found compared with controls. Additionally, by comparing patients with migraine during attacks and during periods without attack, it was found that vitamin B12 levels were lower during attacks. This was explained as induction of inflammation parameters by vitamin B12[12]. In that study, migraines were classified as aura or non-aura, but no remarks were offered regarding pain frequency[12]. All vitamin B12 samples from the cases included in our study were taken at times in between the attacks. We also found in our study that vitamin B12 levels were lower in cases with higher pain frequency.

In addition, we investigated the correlation between B12 levels and migraine pain frequency and severity. We found that vitamin B12 levels were lower in the chronic migraine group, which had greater frequency and severity of pain. Patients with chronic migraine are given analgesics that are more powerful, because of their pain. One possible cause of vitamin deficiency may be long-term and voluminous use of non-steroidal anti-inflammatory drug (NSAID) medication, thereby causing pathological conditions of the gastrointestinal system, which in turn disrupt vitamin absorption[14]. In our study, when patients with migraine were classified into subgroups, the vitamin B12 levels of patients with chronic migraine were found to be significantly lower than those of patients with infrequent and frequent episodic migraine. There was no significant difference between patients with frequent episodic and chronic migraine. Patients with infrequent and frequent episodic migraine were also similar. The vitamin B12 deficiency in chronic migraine cases may be caused by frequent use of analgesics. Prospective studies assessing analgesic use and vitamin B12 levels may be interesting. Use of analgesics was not taken into consideration in our present study.

Vitamin B12 and folic acid levels have been found to be lower in children with migraine than in normal controls[20]. Decreased frequency of migraine headache and improved hyperhomocysteinemia were reported after folic acid treatment was administered to 16 children with migraine, hyperhomocysteinemia and MTHFR gene mutations, followed by a three-month follow-up. From that result, it was recommended that children with hyperhomocysteinemia should be administered folic acid for migraine prophylaxis[17]. In the same way as for adults, vitamin B12 is also recommended in prophylactic treatment for pediatric and adolescent patients[10]. Our patient group consisted of patients aged over 18 years. The results from our study were comparable to those from studies assessing child populations.

Several studies have been demonstrating a relationship between migraine and nutritional deficiencies. In one study, vitamin D levels were found to be low in patients with migraine[29]. Low magnesium levels were reported in patients with migraine, especially during an attack[30]. Metabolic boosters such as riboflavin and coenzyme Q10 have been used to treat ketogenic migraine through diet, or pharmacologically[31]. In migraine, it is important to consider nutritional supplements from a wider perspective. Evaluating these parameters is important in terms of general health and preventive medicine. We only assessed vitamin B12 levels in our cases. We did not assess other nutritional deficiencies.

The limitation of our study was that it was a cross-sectional retrospective study conducted at a tertiary care training facility. This group reflects a small portion of a large migraine population. Due to the nature of our institution as a tertiary care

center, the majority of our cases comprised persistent frequent episodic migraine and chronic migration. Another limitation of the study was that folic acid, homocysteine and methylmalonic acid levels were not measured along with vitamin B12. Planning a study as multicentered, and for a larger patient group, may yield more useful results.

In conclusion, there is a negative correlation between migraine and vitamin B12 levels. In our study, we compared vitamin B12 values according to frequency of pain. We found lower levels in the chronic migraine group. When planning treatments for these patients, it is important to take a holistic approach when considering complementary treatments. There are many arguments in favor of the importance of B12 in cases of migraine with aura. However, more randomized-controlled studies are needed in relation to migraine without aura. With these data, controlled replacement treatment planning seems to be important. Controlled studies are needed in order to determine the direction to which the frequency and intensity of pain will tend when vitamin B12 is replaced in chronic migraine.

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ARTICLE

Does length of time since diagnosis in Parkinson's disease influence heart rate variability? A cross-sectional study

O tempo de diagnóstico na doença de Parkinson influencia a variabilidade da frequência cardíaca? Um estudo transversal

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ABSTRACT

Background: Intrinsic changes in Parkinson's disease (PD) affect the autonomic nervous system, and the disease course can aggravate the initial condition. Although the impact of time since disease onset on autonomic modulation has already been studied in other populations, this has not yet been investigated in PD. **Objective:** To investigate the impact of the length of time since diagnosis on the cardiac autonomic modulation of individuals with PD and compare with healthy individuals. **Methods:** Fifty participants were divided into three groups: a control group (CG; n = 24) and two groups with PD, divided according to the median length of time since diagnosis (median = 5.5 years): below the median (PG1; n = 13) and above the median (PG2; n = 13). To evaluate cardiac autonomic modulation, heart rate was obtained beat-to-beat in the supine position over a 30-min period, and heart rate variability (HRV) indices were calculated using linear methods in the time and frequency domains. **Results:** There were no significant differences in HRV indices between the PG groups, or between the three groups regarding Mean RR, LFun, HFun and LF/HF ratio. Significant reductions in the RMSSD, SDNN, pNN50, LFms^2 and HFms^2 indices were observed in PG1 and PG2, compared with CG. **Conclusions:** The cardiac autonomic modulation of individuals with PD was not influenced by the time since diagnosis. However, reduced parasympathetic and global modulation were observed in these individuals, compared with controls. These results emphasize the importance of aerobic exercise for improving autonomic modulation among individuals with PD.

Keywords: Parkinson Disease; Autonomic Nervous System Diseases; Neurodegenerative Diseases.

RESUMO

Antecedentes: As alterações intrínsecas da doença de Parkinson (DP) afetam o sistema nervoso autônomo, e a evolução da doença pode agravar o quadro inicial. Em outras populações, o impacto do tempo desde o início da doença na modulação autonômica já foi estudado, mas na DP isso ainda não foi investigado. **Objetivo:** Investigar o impacto do tempo de diagnóstico na modulação autonômica cardíaca de indivíduos com DP e comparar os valores aos de indivíduos saudáveis. **Métodos:** Cinquenta participantes foram divididos em três grupos: grupo controle (GC; n=24) e dois grupos com DP, divididos de acordo com a mediana do tempo de diagnóstico (5,5 anos): abaixo (GP1; n=13) e acima da mediana (GP2; n=13). Para a avaliação da modulação autonômica cardíaca, a frequência cardíaca foi captada batimento a batimento em posição supina durante 30 minutos, e os índices de variabilidade da frequência cardíaca (VFC) foram calculados utilizando métodos lineares nos domínios do tempo e frequência. **Resultados:** Não houve diferenças significativas para os índices de VFC entre os grupos GP, ou entre os três grupos para Mean RR, LFun, HFun e relação LF/HF. Foram observadas reduções significativas em RMSSD, SDNN, pNN50, LFms^2 e HFms^2, para GP1 e GP2 em comparação ao GC. **Conclusões:** A modulação autonômica cardíaca de indivíduos com DP não foi influenciada pelo tempo de diagnóstico, contudo, foi observada redução da modulação parassimpática e global nesses indivíduos em relação aos controles. Esses resultados reforçam a importância do exercício aeróbio para a melhora da modulação autonômica de indivíduos com DP.

Palavras-chave: Doença de Parkinson; Doenças do Sistema Nervoso Autônomo; Doenças Neurodegenerativas.

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INTRODUCTION

Parkinson's disease (PD), characterized by death of dopaminergic neurons located in the substantia nigra pars compacta[1], is considered to be the second most common neurodegenerative disease worldwide[2]. Its incidence in individuals aged over 50 years is increasing, such that it is expected to reach between 8.7 and 9.3 million people by 2030[3].

The cardinal motor symptoms of PD are postural instability, bradykinesia, rigidity and resting tremor[4]. During the course of the disease, abnormalities related to the autonomic nervous system (ANS)[5] may also be observed, which further worsen the overall clinical condition and lead to significant worsening of quality of life[6]. ANS alterations can be evaluated through heart rate variability (HRV)[7], a non-invasive method in which sinus beat intervals RR intervals) are analyzed. These intervals are associated with the influences of the ANS on the sinus node[7]. Studies using this analysis among individuals with PD have demonstrated that HRV is lower in this population[8,9,10]. This is an autonomic dysfunction that could be a consequence of autonomic regulatory degeneration in the brain and peripheral autonomic ganglia[9].

Several conditions may influence HRV, such as metabolic alterations[11], body composition[12], age[13], cardiovascular risk factors[12] and pathological conditions[11,12,14]. Specifically in PD, the stage of the disease[15], body mass index[16] and use of levodopa medication[17] may also influence HRV. However, through searching the literature, we were unable to find any studies that evaluated possible influences from the length of time since the diagnosis of PD was made, on autonomic dysfunctions.

In the literature, autonomic impairments in the PD population have been described. However, this raises a number of questions: Does the length of time since diagnosis influence the cardiac autonomic modulation of this population? Do individuals with longer times since diagnosis present worse cardiac autonomic modulation than individuals with shorter times? Does the cardiac autonomic modulation of individuals with PD with longer or shorter times since diagnosis differ from that of individuals without the disease? To fill these gaps in knowledge, the aim of the current study was to evaluate the impact of the length of time since diagnosis on the cardiac autonomic modulation of individuals with PD and compare these values with those of individuals without the disease.

The hypothesis of this study was that the length of time since the diagnosis of PD was made influences cardiac autonomic modulation, such that individuals with longer times since diagnosis would present worse cardiac autonomic modulation, and that these differences would be greater than those among healthy individuals. Understanding these matters is important for clinicians and researchers, given that these results could aid in elaboration of treatments aimed at promoting increased cardiac autonomic modulation and, thus, could reduce the risks induced in individuals with PD through autonomic alterations.

METHODS

Study design and ethical matters

This cross-sectional observational study was reported in accordance with the STROBE guidelines. The study was conducted in Presidente Prudente, São Paulo, Brazil, between August 2017 and April 2018. All procedures used were approved by the University's Human Ethics Committee. The participants were informed about the procedures and objectives of the study and, after agreeing to participate, provided written informed consent.

Population

The participants with PD were recruited from the neurology sector of the Center for Physical Therapy and Rehabilitation Studies and Treatment of São Paulo State University (UNESP) Faculty of Sciences and Technology, Presidente Prudente, Brazil, and the matching controls were recruited from health care centers and clinics in the same city. The participants with PD were required to have a medical diagnosis of PD, based on the presence of the clinical criteria[18], independent of the length of time since diagnosis, and to be classified in stages 1 to 3 of the *Hoehn and Yahr* (HY) scale[19]. The PD participants were divided into two groups according to the median length of time since diagnosis (median = 5.5 years): a group below the median (PG1; n = 13 participants) and a group above the median (PG2; n = 13 participants). Participants without the disease were considered for inclusion in the control group (CG; n = 24 participants) and were paired with individuals in the PG groups according to age.

The participants were required to present an absence of cognitive deficits, as evaluated though the Mini-Mental State Examination (MMSE)[20], in order to ensure understanding of the procedures performed during data collection. Current smokers, current heavy drinkers, individuals with active infections, cognitive deficits or cardiovascular and respiratory diseases and individuals who did not sign the informed consent statement were not included in the study. Participants with more than 5% error in the RR interval series recordings were excluded.

The sample size was based on the Root mean square of differences between adjacent normal RR intervals in a time interval, expressed in ms (RMSSD index). The significant difference assumed was 9ms and standard deviation 3ms with the number of participants analyzed, and a significance level of 5% (two-tailed), confirming a power > 80% to detect differences between the variables.

Study design

The study was divided into two steps, with intervals ranging from 24 hours to one week between them. Data collection was performed during the "on" period of levodopa medication of the participants with PD[21]. In the first step, personal data (to investigate the inclusion and exclusion criteria and identify age, sex, use of medication and length of time since diagnosis),

physical parameters (body composition) and clinical parameters (cardiovascular parameters of heart rate and blood pressure; PD stage; and cognition evaluation) were obtained. In the second stage, cardiac autonomic modulation was evaluated.

The data collection was performed in a room with a temperature of between 21 and 23 °C and humidity of 40 to 60%, at times between 8 am and 12 pm to minimize the influence of circadian rhythm[22]. The assessment was performed individually, and the participants were instructed not to consume alcohol and/or stimulant substances, such as coffee, tea, chocolate and soda, or perform physical exercise, for 12 hours prior to the assessments.

Experimental procedures

First step

After personal data had been collected and the cognitive assessment had been performed using the MMSE[20], body composition (height, weight and body mass index, BMI), cardiovascular parameters and PD stage were evaluated.

Body composition

To assess body composition, the participants were asked to wear appropriate clothes and no shoes. Height was measured using a stadiometer (Sanny; São Paulo, Brazil) and body weight was measured using a digital scale (Welmy R/I 200; Santa Bárbara D'Oeste/SP, Brazil). BMI was calculated using the following formula: weight/height^2 (kg/m^2)[23].

Body fat and lean mass were obtained through a Maltron bioimpedance device (Maltron BF 906 Body fat analyzer; Maltron, UK)[24].

Cardiovascular parameters

Systolic (SBP) and diastolic (DBP) blood pressures were indirectly measured using a stethoscope (Littman; Saint Paul, Minnesota, USA) and an aneroid sphygmomanometer (WelchAllyn – Tycos; New York, USA) on the left arm[25]. The resting heart rate was measured using the same heart rate monitor used for HRV assessment (Polar RS800CX, Polar Electro; Kempele, Finland).

Parkinson's disease stage

To determine the PD stage, the HY scale was used[19]. The classification of individuals with PD was made by a physiotherapist with specialization in neurology and in treatment of these individuals.

Second step

Cardiac autonomic modulation

To analyze cardiac autonomic modulation, heart rate was recorded beat-to-beat using a Polar RS800CX heart rate monitor (Polar, Finland). For the recording, the participants remained in a supine position for 30 minutes, while breathing spontaneously but avoiding conversation, during the procedure.

Outcomes

Cardiac autonomic modulation

The series of RR intervals was subjected to digital filtering using the Polar Precision Performance SW software (version 4.01.029), followed by manual filtering performed through the Excel software, to eliminate ectopic premature and artifact beats. Only series with more than 95% sinus beats were included in the study[26]. Cardiac autonomic modulation was analyzed using 1000 consecutive RR intervals, obtained from the most stable part of the series[26]. The Kubios HRV software, version 3.1, was used to calculate the HRV indices[27].

To analyze HRV in the time domain, the indices Mean RR, rMSSD, SDNN and pNN50 were used. Mean RR represents the mean value of the RR intervals. rMSSD is the root mean square of differences between adjacent normal RR intervals in a time interval, expressed in ms[7]. SDNN is the standard deviation of all normal RR intervals, expressed in ms. pNN50 is the percentage of adjacent RR intervals with a difference in duration > 50 ms[7].

For analysis on the frequency domain, the spectral components of low frequency (LF; 0.04 to 0.15 Hertz) and high frequency (HF; 0.15 to 0.4 Hertz), expressed in milliseconds squared (ms^2) and normalized units, and the LF/HF ratio, were calculated using a fast Fourier transform algorithm[7].

Data analysis

The normality of the data was tested using the Shapiro-Wilk test. A descriptive statistical method was used for data presentation, and the results were presented as means and standard deviations (for parametric data), medians and interquartile ranges (for nonparametric data) and confidence intervals, absolute frequencies and relative frequencies (for qualitative data). Sample characterization data and HRV indices were compared between the groups using covariance analysis (ANCOVA), adjusted for sex and BMI. Possible differences were assessed using the Bonferroni post-test. Data on medicines in use were compared using the chi-square test (Yates's correction was applied in 2 x 2 contingency tables).

The effect size of the differences between the groups was measured using partial eta squared. The effect size was defined as low (≤ 0.01), moderate (0.06 to 0.14) or high (≥ 0.14)[28]. The significance level was set at 5%. The analyses were performed using SPSS version 15.0 (SPSS Inc.; Chicago, IL, USA).

RESULTS

The distribution and sample losses during the steps of the study are demonstrated in Figure 1.

Table 1 presents the characteristics of the three groups studied and Table 2 demonstrates the medicines used by the participants. In Table 1, significant differences were observed for DBP, length of time since diagnosis and MMSE ($p < 0.05$). The groups were classified as overweight[23], pre-hypertension[25] and

absence of cognitive deficits[20]. In addition, most of the participants with PD were classified as having stage two of the disease[19]. In Table 2, significant differences were observed with regard to dopamine receptor blockers, levodopa and beta-blockers.

Comparisons of linear indices in the time and frequency domains between the control group (CG) and Parkinson groups (below the median – PG1; and above the median – PG2) can be observed in Tables 3 and 4, respectively. PG1 and PG2 presented statistically significant reductions in rMSSD, SDNN, pNN50, LFms^2 and HFms^2, compared with CG ($p < 0.05$). No significant differences were found between the groups regarding Mean RR, LFun, HFun and LF/HF ratio ($p > 0.05$).

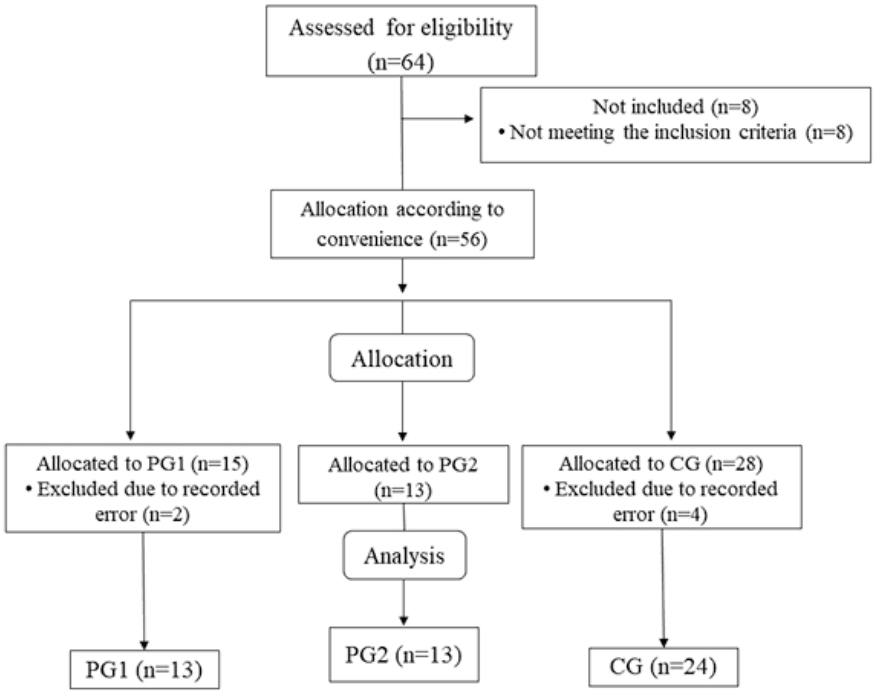

Figure 1. Flow diagram.

Table 1. Characterization of the control group (CG) and Parkinson's groups (PG1 and PG2) evaluated in this study.

	CG (n = 24)	PG1 (n = 13)	PG2 (n = 13)	P value
Age (years)	70.25 ± 8.03 66.86-73.64	70.23 ± 8.30 65.22-75.25	75.23 ± 6.09 71.64-79.01	0.13
SBP (mmHg)	130.42 ± 13.34 124.78-136.05	123.85 ± 10.44 117.54-130.15	128.46 ± 13.45 120.34-136.59	0.33
DBP (mmHg)	85.00 [10.00] 83.00-90.33	79.23 ± 9.54[a] 73.47-85.00	80.00 ± 11.55 73.02-87.08	0.045
HR (bpm)	63.50 [11.25] 57.29-68.21	64.15 ± 6.94 59.96-68.35	65.69 ± 11.10 59.08-72.40	0.75
BMI (kg/m^2)	29.43 ± 4.05 27.72-31.14	27.76 ± 3.11 25.88-29.63	26.39 ± 4.79 23.49-29.28	0.09
Body fat (%)	32.09 ± 9.58 28.06-36.12	31.98 ± 8.35 26.93-37.03	34.11 ± 9.10 28.61-39.61	0.78
Lean mass (%)	67.84 ± 9.48 63.83-71.84	68.02 ± 8.35 62.97-73.06	65.89 ± 9.10 60.39-71.39	0.79
Length of time since diagnosis (years)	–	2.62 ± 1.61 1.64-3.59	8.00 [7.50][b] 7.75-13.33	< 0.0001
HY scale	–	2.00 [1.00] 1.74-2.57	3.00 [1.00] 2.22-2.85	0.12
MMSE	27.50 [3.00] 25.56-28.19	28.00 [4.50] 23.39-28.30	23.31 ± 4.66[a] 20.50-26.12	0.03

Mean ± standard deviation; lower boundary – upper boundary of 95% confidence interval; median [interquartile range]; [a]value with difference in relation to control group; [b]value with difference in relation to PG1; CG: control group; PG1: Parkinson group below the median; PG2: Parkinson group above the median; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; BMI: body mass index; mmHg: millimeters of mercury; bpm: beats per minute; kg: kilogram; m: meters; m^2: square meters; MMSE: mini-mental status examination; HY: Hoehn and Yahr; %: percentage.

Table 2. Medication in use by the volunteers in the control group (CG) and Parkinson's groups (PG1 and PG2) evaluated in this study.

	CG (n = 24)	PG1 (n = 13)	PG2 (n = 13)	p value
Dopamine receptor blockers	0 (0.0)	3 (23.1)[a]	5 (38.5)[a]	< 0.01
Platelet anti-aggregate	5 (20.8)	4 (30.8)	2 (15.4)	0.62
Antiarrhythmic	0 (0.0)	1 (7.7)	2 (15.4)	0.16
Anticholinergic	0 (0.0)	0 (0.0)	2 (15.4)	0.05
Antidepressants	1 (4.2)	4 (30.8)	4 (30.8)	0.05
Beta blocker	2 (8.3)	5 (38.5)	0 (0.0)[b]	0.01
Biguanides	4 (16.7)	3 (23.1)	2 (15.4)	0.85
Ca + channel blocker	2 (8.3)	1 (7.7)	1 (7.7)	0.99
Angiotensin II blockers	10 (41.7)	6 (46.2)	3 (23.1)	0.42
Ciprofibrate	0 (0.0)	1 (7.7)	0 (0.0)	0.23
Amantadine hydrochloride	0 (0.0)	2 (15.4)	2 (15.4)	0.13
Diuretic	6 (25.0)	2 (15.4)	2 (15.4)	0.69
Entacapone	0 (0.0)	1 (7.7)	1 (7.7)	0.38
Statins	7 (29.2)	3 (23.1)	3 (23.1)	0.88
Gliclazide	2 (8.3)	2 (15.4)	0 (0.0)	0.35
ACE inhibitor	3 (12.5)	0 (0.0)	0 (0.0)	0.17
MAO inhibitor	0 (0.0)	2 (15.4)	2 (15.4)	0.13
Levodopa	0 (0.0)	9 (69.2)[a]	9 (69.2)[a]	< 0.01
Other	16 (66.7)	7 (53.8)	11 (84.6)	0.23
Vasodilator	1 (4.2)	3 (23.1)	1 (7.7)	0.17

[a]Value with difference in relation to control group; [b]value with difference in relation to PG1; CG: control group; PG1: Parkinson group below the median; PG2: Parkinson group above the median; n (percent); Ca^{+}: calcium; ACE: angiotensin-converting enzyme; MAO: monoamine oxidase.

Table 3. Comparison of the heart rate variability indices in the time domain between the control group (CG) and Parkinson's groups, divided by the length of time since diagnosis (below the median – PG1; and above the median – PG2).

	CG (n = 24)	PG1 (n = 13)	PG2 (n = 13)	p value	ES	EF
Mean RR (ms)	957.81 ± 87.96 920.67-994.95	972.08 ± 142.67 885.87-1058.30	1016.09 ± 157.29 921.04-1111.14	0.24	0.061	Low
SDNN (ms)	26.20 ± 11.72 21.25-31.14	14.10 ± 5.07[a] 11.03-17.17	14.63 ± 6.01[a] 11.00-18.27	< 0.001	0.302	High
rMSSD (ms)	24.48 ± 10.29 20.13-28.83	14.92 ± 6.08[a] 11.25-18.59	15.30 ± 6.49[a] 11.39-19.22	0.001	0.258	High
pNN50	4.95 [9.20] 3.27-9.17	0.80 [1.45][a] 0.30-1.92	0.80 [1.06][a] 0.29-1.57	0.003	0.229	High

Mean ± standard deviation; lower boundary – upper boundary of 95% confidence interval; median [interquartile range]; [a]value with difference in relation to CG ($p < 0.05$); ES: eta squared; EF: effect size; CG: control group; PG1: Parkinson group 1; PG2: Parkinson group 2; mean RR: RR interval mean; SDNN: standard deviation of all normal RR intervals, expressed in milliseconds; RMSSD: root mean square of differences between adjacent normal RR intervals in a time interval, expressed in ms; pNN50: percentage of adjacent RR intervals with a difference in duration > 50 ms.

Table 4. Comparison of the heart rate variability indices in the frequency domain between the control group (CG) and Parkinson's groups, divided by the length of time since diagnosis (below the median – PG1; and above the median – PG2).

	CG (n = 24)	PG1 (n = 13)	PG2 (n = 13)	p value	ES	EF
LF (nu)	60.95 ± 17.51 53.56-68.35	60.25 ± 17.27 49.82-70.69	53.68 ± 16.65 43.61-63.74	0.53	0.028	Low
HF (nu)	38.95 ± 17.46 31.58-46.33	39.62 ± 17.21 29.22-50.01	46.20 ± 16.58 36.18-56.22	0.53	0.028	Low
LF (ms^2)	309.00 [461.25] 246.63-586.87	62.00 [113.00][a] 35.04-179.73	95.38 ± 72.22[a] 51.74-139.03	0.003	0.230	High
HF (ms^2)	181.50 [231.50] 145.99-317.76	38.00 [90.50][a] 32.68-99.63	90.31 ± 74.61[a] 45.22-135.39	0.004	0.219	High
LF/HF (ms^2)	2.09 ± 1.38 1.50-2.67	2.03 ± 1.36 1.21-2.84	1.35 [1.03] 0.72-2.39	0.65	0.019	Low

Mean ± standard deviation; lower boundary – upper boundary of 95% confidence interval; median [interquartile range]; a value with difference in relation to CG ($p< 0.05$); CG: control group; PG1: Parkinson group 1; PG2: Parkinson group 2; ES: eta squared; EF: effect size; LF: low frequency; HF: high frequency; nu: normalized unit; ms2: milliseconds squared.

DISCUSSION

The results obtained through the linear HRV indices suggest that the length of time since diagnosis did not influence the cardiac autonomic modulation of individuals with PD. However, individuals with PD presented reduced global variability and parasympathetic modulation, compared with individuals without the disease.

This study predominantly included men and older adults, with cardiovascular risk factors such as overweight and prehypertension. It is known that the incidence of PD is higher among men[29] and individuals over 65 years of age[30], and that overweight and obesity are common among individuals with PD[31] and older adults without the disease[32]. Furthermore, blood pressure abnormalities can occur in the early stages of PD[33], as observed in our patients. Thus, we consider that the participants in this study represented the reality found in the general population[29–31,33].

Differences in the length of time since diagnosis were found between the PD groups. This was normal and expected according to the division of groups proposed in this study. Furthermore, statistical differences relating to the MMSE were found, but we do not consider that these differences were clinically important, because the individuals were classified according to their degree of schooling.

Regarding cardiac autonomic modulation, the rMSSD, pNN50 and $HFms^2$ indices that reflect parasympathetic modulation[7] were lower in both PD groups than in the CG, with a high effect size. These results demonstrate that parasympathetic modulation is reduced among individuals with PD, thus suggesting that the presence of PD is more important than the length of time since diagnosis, with regard to affecting parasympathetic modulation. This corroborates the findings of Rocha et al.[10], who reported that the rMSSD index was lower among individuals with PD than among those without the disease, thus indicating reduced parasympathetic modulation in these individuals. However, that study did not consider the influence of the length of time since diagnosis between individuals with PD, unlike the current study.

A reduction in parasympathetic modulation is associated with increased risks of mortality and morbidity, and with development of some risk factors[34] and can be a sign for predicting cardiovascular and metabolic health[13]. These results emphasize the importance of pharmacological and non-pharmacological interventions, such as aerobic exercise[35], among individuals with PD, regardless of the length of time since diagnosis, in order to promote better autonomic parasympathetic modulation response and mitigate possible damage to the organism, such as manifestation of gastrointestinal malfunction, cardiovascular dysregulation, urinary disturbance or sexual dysfunction[36].

The global variability represented by the SDNN index is reduced in individuals with PD, regardless of the length of time since diagnosis, in comparison with individuals without the disease. Studies have shown that the reduction in the SDNN index can occur at the beginning of the disease, thus indicating involvement of the ANS physiology[37]. Ke et al.[38] also demonstrated that a significant reduction in global variability occurred among individuals with PD, compared with individuals without the disease. Those authors reported SDNN values of 45.50 ms for the control group and 34.50 ms for the Parkinson group, which were higher than the values found in the current study, which were 26.19 ms for the control group, 14.10 ms for the group with shorter time since diagnosis and 14.63 ms for the group with longer time since diagnosis. The duration of the HRV analysis may explain these differences, since it was 24 hours in the study by Ke et al.[38] and 30 minutes in the current study. In addition to evaluation of the length of time since diagnosis, our study also suggests that these differences can be identified with less duration of analysis, which is clinically important.

Parasympathetic modulation and HRV reduction have been shown to present vagal sympathetic imbalance[39] in subjects with PD. This could be caused by degeneration of the central and autonomic nervous system interaction regions, such as

the hypothalamus, dorsal vagal nucleus, nucleus ambiguous, postganglionic sympathetic neurons in the pre-vertebral region and paravertebral ganglia, and in the dopaminergic nigrostriatal pathway[37]. This HRV reduction also demonstrates insufficient ANS adaptation[7].

No differences were observed between the groups with regard to LFun, HFun and the LF/HF ratio. These results were expected since these indices are calculated from the power spectrum area and a reduction in these spectra is found in individuals with PD, when analyzed in ms^2. As these indices are normalized with regard to the power spectrum area, no differences are observed. The reduced $LFms^2$ and $HFms^2$ in individuals with PD, with a high effect size, also explains the absence of significant differences in the LF/HF ratio between the groups.

The RR interval analysis has a relationship with HR values, and no differences between the groups were observed in relation to either index. These results corroborate those of Soares et al.[39], who also observed reduced parasympathetic and HRV indices with no significant HR reduction[39]. These results are in agreement, particularly because HRV is observed in terms of precise units of time that present greater sensitivity than HR values.

Reduced $LFms^2$ was observed in individuals with PD in comparison with the control group. Given the association with reduced parasympathetic and global modulation, this result may suggest that individuals with PD have increased sympathetic modulation, as reported by other authors[17]. Nevertheless, the data in the literature are divergent regarding the predominance of high sympathetic modulation quantified through the LF index[40]. In this regard, we take the view that further studies are needed in order to evaluate sympathetic modulation directly, in order to confirm any alterations among individuals with PD.

To complete the information discussed above, the use of medicines should be considered to be a limitation. Nevertheless, we described all the medicines used in detail, and only a few differences were observed. Statistically significant differences were observed with regard to DBP, which could be related to the difference found in beta-blocker medication. It is also important to emphasize that due to the average age of our participants, it was common for them to use drugs to control risk factors, which reflects the reality of this population. Two other differences were found, one in relation to dopamine receptor blockers, which are medicines for psychiatric treatment, and the other to Levodopa, which is specific medication for PD treatment. To minimize this limitation, all participants with PD were evaluated during the "on" period of Levodopa. Moreover, the length of time since diagnosis was defined through analysis on medical records, which may represent a source of error, since these patients may have started to feel the symptoms before seeking a clinic to obtain the diagnosis. Despite the limitations, it is important to highlight the originality of this study. Although there was already some information in the literature about factors that might influence the cardiac autonomic modulation of other populations[11–14], or even factors such as the stage of the disease, specifically with regard to PD[15], this was the first study to investigate the influence of the length of time since diagnosis on the cardiac autonomic modulation of individuals with PD. This is important because this time period has a relationship with the damage caused by this degenerative disease.

In summary, our results suggest that the presence of PD, regardless of the length of time since diagnosis, can influence cardiac autonomic modulation. Furthermore, individuals with PD present reductions in global and parasympathetic modulation, compared with individuals without the disease. These issues emphasize the need for prevention and treatment among individuals with PD, along with the importance of aerobic exercise interventions[10], which may promote increased HRV among individuals with PD, independent of the length of time since diagnosis.

In conclusion, the length of time since the diagnosis of PD was made did not influence cardiac autonomic modulation. However, PD promotes reductions in parasympathetic modulation and global variability.

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ARTICLE

Diagnosis of Guillain-Barré syndrome and use of Brighton criteria in Peruvian hospitals

Spanish title: Diagnóstico del Síndrome de Guillain-Barré y uso de los criterios de Brighton en hospitales Peruanos

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ABSTRACT

Background: Guillain-Barré syndrome (GBS) is an autoimmune disease of the peripheral nervous system that caused multiple epidemiological outbreaks in Peru during 2018 and 2019. It is usually diagnosed using the Brighton criteria (BC). **Objective:** We aimed to determine the performance of Peruvian neurologists in diagnosing GBS based on the BC, along with its associated factors. **Methods:** This was a retrospective multicenter cohort study. We included patients diagnosed with GBS between 2007 and 2018 in three public hospitals in Lima, Peru. We collected data regarding demographic, clinical and management characteristics. We evaluated the use of the BC for confirmatory diagnosis of GBS and developed a logistic regression model to identify factors associated with its use. **Results:** Out of 328 cases, we reviewed 201 available charts. The median age was 48 years, with male predominance. Over half of the patients presented an inadequate motor examination according to their Medical Research Council (MRC) score. Additional testing included lumbar puncture and electrophysiological testing, in over 70% of the cases. The BC showed certainty level 1 in 13.4% and levels 2 and 3 in 18.3%. Neither the quality of the motor examination nor the type of institution showed any association with the BC. **Conclusions:** Level 1 diagnostic certainty of the BC was met in less than one quarter of the cases with a GBS diagnosis in three centers in Lima, Peru, between 2007 and 2018. This level was not significantly associated with being treated in a specialized institute, rather than in a general hospital.

Keywords: Guillain-Barré Syndrome; Evidence-Based Practice; Evidence-Based Medicine.

RESUMEN

Antecedentes: El Síndrome de Guillain-Barré (SGB) es una enfermedad autoinmune del sistema nervioso periférico, causante de brotes epidemiológicos en Perú entre el 2018 y el 2019. El diagnóstico se realiza a través de los Criterios de Brighton (CB). **Objetivo**: Determinar el desempeño de neurólogos peruanos en diagnosticar SGB basándose en los CB, así como factores asociados. **Métodos:** Cohorte retrospectiva multicéntrica. Incluimos pacientes diagnosticados con SGB del 2007-2018 en 3 hospitales públicos en Lima, Perú. Recolectamos sus características demográficas, clínicas y de manejo. Evaluamos el uso de los CB para el diagnostico de SGB y empleamos un modelo de regresión logística para identificar los factores asociados con su uso. **Resultados:** De 328 casos, revisamos 201 historias disponibles. La edad mediana fue 48 años, con predominancia masculina. Mas del 50% de pacientes presento un examen motor inadecuado acorde con el puntaje MRC. Se realizaron exámenes auxiliares como punción lumbar y estudios electrofisiológicos en mas del 70% de pacientes. Se obtuvo un nivel de certeza 1 para los CB en un 13.4% de casos , y un nivel 2 o 3 en un 18.3%. El nivel no estuvo asociado con la calidad del examen motor ni el tipo de institución de atención. **Conclusiones:** Un diagnostico nivel 1 de certeza acorde con los BC se obtuvó en menos de un cuarto de casos diagnosticados como SGB. Este nivel no estuvo asociado con la atención en una institución especializada, comparado con un hospital general.

Palabras clave: Síndrome de Guillain-Barré; Práctica Clínica Basada en la Evidencia; Medicina Basada en la Evidencia.

INTRODUCTION

Guillain-Barré syndrome (GBS) is an autoimmune disease of the peripheral nervous system that presents with axonal or demyelinating neuropathy, with ascendent centrifugal progression. GBS affects around 1.1 patients per 100,000 inhabitants annually around the globe[1]. In Peru, multiple epidemiological outbreaks were reported during 2018 and 2019, which raised

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Authors' contributions: MM, ARC: contributed to study design, data collection, data analysis and interpretation; VVR, CAD: contributed to study design, data analysis and provided review of scientific content. All authors contributed to the writing and review of the original draft.

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the incidence from 0.62 to 0.92 patients per 100,000 inhabitants and led to declaration of a healthcare emergency in five regions of the country[2].

The first diagnostic criteria for GBS were developed in 1976 and were expanded by Asbury and Cornblath in 1990[3,4]. However, the criteria elaborated by the Brighton Collaboration have been recommended in national and international clinical-practice evidence-based guidelines since 2010[5,6]. These criteria include flaccid limb weakness, areflexia in the affected limbs, a monophasic course of less than 28 days, albuminocytological dissociation in cerebrospinal fluid (CSF), suggestive findings in electrophysiological studies (EPS) and the absence of an alternative diagnosis[7].

Use of the Brighton criteria (BC) extends around the world. Countries such as the Netherlands, India, Bangladesh and China have reported that the proportion of patients at diagnostic certainty level 1, which indicates fulfillment of all the BC criteria, was near to or greater than 60%[7–10]. A complete diagnostic workup for patients with these criteria is important because they present severe weakness and possible imminent death[9]. However, additional testing such as EPS and CSF studies may be difficult in low-resource settings[9], which means that it is more likely that the BC would be applied in centers in which these specialized tests are available.

Here, we aimed to determine the performance of Peruvian neurologists in diagnosing Guillain-Barré syndrome (GBS) based on the Brighton criteria (BC), along with factors associated with GBS, in three Peruvian referral institutions between 2007 and 2018.

METHODS

Patients

We included a retrospective multicenter cohort from three referral institutions in Lima, Peru: the *Instituto Nacional de Ciencias Neurológicas* (INCN), an institute that specializes in neurological diseases; and two national hospitals, the *Hospital Nacional Dos de Mayo* (HNDM) and *Hospital Nacional Arzobispo Loayza* (HNAL). Clinical records from patients diagnosed with GBS between January 1, 2007, and December 31, 2018, were reviewed. We excluded patients for whom clinical records were not available and also those with neuropathy secondary to diabetes mellitus, alcohol intoxication, malignancy or human immunodeficiency virus.

Variables

The following variables were analyzed: age, sex, institution, clinical presentation, motor assessment at admission using the Medical Research Council (MRC) score, level of diagnostic certainty according to the BC, length of time between disease onset (from onset of motor symptoms) and obtaining EPS and lumbar puncture (LP) results.

The level of diagnostic certainty was classified into four levels according to the BC: level 1 fulfills all diagnostic criteria; level 2 fulfills all clinical parameters, without the final results from LP and EPS; level 3 fulfills only clinical parameters; and level 4 does not fulfill the criteria of level 3, but all other diagnoses are excluded (Table 1)[7].

The MRC score establishes a score of 0-5 for each muscle group, with an overall maximum score of 60[11]. The quality of the motor examination is categorized as "complete" if at least 6 of the 12 muscle groups included in the MRC score were assessed (necessarily more than three muscle groups for each hemibody). It is considered "incomplete" in the remaining cases[11].

The time between disease onset and LP was categorized as ≤ 7 days or > 7 days, whereas for EPS the cutoff point was 14 days, in accordance with the Peruvian guidelines for diagnosis and treatment of patients with GBS[6]. We categorized the facilities at which care took place into two groups: national hospital (HNAL or HNDM) and specialized institute (INCN), taking into account the differences in the capacity and expertise for management of neurological diseases.

Statistical analysis

STATA version 16.0 was used for the analysis. For quantitative and qualitative variables, measurements of statistical dispersion and frequency were used, respectively. Categorical data for each institution were compared using the chi-square test if normally distributed and the Fisher exact test if not normally distributed. A logistic regression model was used to determine whether clinical characteristics (cranial nerve involvement, dysautonomia and electromyographic subtype) or care-related characteristics (care facility, quality of motor examination and length of time until LP or EPS) were associated with use of the BC to confirm the diagnosis with certainty level 1. These factors were entered into the model in a stepwise fashion if they had a p-value less than or equal to 0.2.

This study was approved by the Institutional Review Boards of the three participating institutions (INCN-IRB, HNDM-IRB and HNAL-IRB) before data collection. The confidentiality of participants' identities was maintained.

RESULTS

We identified 328 GBS cases and included 201 patients whose charts were available for review. The median age was 48 years (interquartile range [IQR]: 18-86), and 54.2% were male. Among the 201 patients, 86.2% presented bilateral flaccid weakness at admission, 90% had a monophasic course of disease (< 28 days) and 45.2% had areflexia in the affected limbs. Cranial nerve involvement and dysautonomia were present in 39.2% and 13.4% of patients, respectively. The axonal and demyelinating subtypes were also observed in 64.6% and 35.4% of the patients, respectively (Table 2).

According to the BC, the proportion of confirmed cases (certainty level 1) was 13.4% and the proportion of suspicious cases (certainty levels 2 and 3) was 18.3%. The remaining 68.3% of the patients met level 4 of certainty. There was no statistically

Table 1. Diagnostic criteria and level of diagnostic certainty for Guillain-Barré syndrome.

Diagnostic criteria	Level of diagnostic certainty			
	1	2	3	4
Bilateral and flaccid weakness of limbs	+	+	+	+/-
Decreased or absent deep tendon reflexes in weak limbs	+	+	+	+/-
Monophasic course and time between onset and nadir of 12 h to 28 days	+	+	+	+/-
CSF cell count < 50/ml	+	+[a]	-	+/-
CSF protein concentration > 0.45 g/L	+	+/-[a]	-	+/-
NCS findings consistent with one of the subtypes of GBS	+	+/-	-	+/-
Absence of alternative diagnosis for weakness	+	+	+	+

[a] If CSF is not collected or results not available, nerve electrophysiology results need to be consistent with the diagnosis of Guillain-Barré syndrome; +: present; -: absent; +/-: present or absent; CSF: cerebrospinal fluid; NCS: nerve conduction studies; GBS: Guillain-Barré syndrome.

Table 2. Clinical characteristics of patients diagnosed with Guillain-Barré syndrome.

Clinical characteristics of patients		Fr	%	N (%)	
				Hospital †	Institute
Sex	Female	92	45.8	57 (40.4)	35 (58.3)
	Male	109	54.2	84 (59.6)	25 (41.8)
Monophasic course < 28 days	No	20	10.1	11 (7.9)	9 (15)
	Yes	179	90	128 (92.1)	51 (85)
Bilateral and flaccid weakness	No	26	13.8	18 (14)	8 (13.6)
	Yes	162	86.2	111 (86.1)	51 (86.4)
Areflexia in weak limbs	No	103	54.8	72 (55.8)	31 (52.5)
	Yes	85	45.2	57 (44.2)	28 (47.5)
Cranial nerves affection	No	121	60.8	83 (59.7)	38 (63.3)
	Yes	78	39.2	56 (40.3)	22 (36.7)
Dysautonomia	No	174	86.6	116 (82.3)	58 (96.7)
	Yes	27	13.4	25 (17.7)	2 (3,.3)
Increased protein in CSF	No	46	30.5	29 (27.9)	17 (36.2)
	Yes	105	69.5	75 (72.1)	30 (68.8)
Normal CSF cell count	No	1	0.6	1 (0.9)	0 (0)
	Yes	155	99.4	106 (99.1)	49 (100)
Albuminocytological dissociation	No	47	31.1	30 (28.9)	17 (36.2)
	Yes	104	68.8	74 (71.2)	30 (63.8)
Electrophysiological subtype	Demyelinating	51	35.4	29 (31.6)	22 (42.3)
	Axonal	93	64.6	63 (68.5)	30 (57.7)
Total				141 (70.2)	(29.9)

†Hospital Nacional Dos de Mayo and Hospital Nacional Arzobispo Loayza; CSF: cerebrospinal fluid; Fr: frequency.

significant difference between the institutions at any of the certainty levels (p = 0.396). Most patients at certainty level 4 met most of the clinical criteria except for altered tendon reflexes (84.3%) (Table 3).

In the three institutions, a mean proportion of 35.8% of the patients was adequately examined using the MRC score. At the specialized institute, this percentage was 78.3%, with a statistically significant difference compared with the national hospitals (p < 0.000) (Table 4).

An LP was performed on 74.1% of the patients, among which 76% of the procedures were carried out within the first seven days after admission. No significant differences were observed between the care facilities (p = 0.559). EPS was performed on 76.6% of patients and was used more frequently in the specialized institute (91.7%; p = 0.001). In 62.8% of the cases, EPS was carried out within 14 days after admission.

In the bivariate analysis, patient age and the timing of LP and EPS showed p-values greater than the cutoff. In multivariate logistic regression, we found that use of both early LP (< 7 days) and late EPS (> 14 days) increased the likelihood of application of the BC for confirmatory diagnosis. The remaining clinical or care characteristics were not significant (Table 5).

Table 3. Brighton criteria and diagnostic certainty level among patients diagnosed with Guillain-Barré syndrome.

	BC	Certainty level			
		1	2	3	4
Bilateral and flaccid weakness of limbs	No	0 (0.00%)	0 (0.00%)	0 (0.00%)	26 (21.67%)
	Yes	29 (100.00%)	30 (100.00%)	7 (100.00%)	94 (78.33%)
Decreased or absent deep tendon reflexes	No	0 (0.00%)	0 (0.00%)	0 (0.00%)	102 (84.30%)
	Yes	29 (100.00%)	30 (100.00%)	7 (100.00%)	19 (15.70%)
Monophasic course with 12 h to 28 days from onset to nadir	No	0 (0.00%)	0 (0.00%)	0 (0.00%)	20 (16.53%)
	Yes	29 (100.00%)	30 (100.00%)	7 (100.00%)	101 (83.47%)
Normal CSF cell count	No	–	–	–	–
	Yes	29 (100.00%)	17 (100.00%)	–	99 (100.00%)
Increased CSF protein concentration	No	0 (0.00%)	7 (43.75%)	–	37 (38.54%)
	Yes	29 (100.00%)	9 (56.25%)	–	59 (61.46%)
NCS findings consistent with one subtype	No	0 (0.00%)	10 (33.33%)	7 (100.00%)	35 (28.93%)
	Yes	29 (100.00%)	20 (66.67%)	0 (0.00%)	86 (71.07%)

BC: Brighton criteria.

Table 4. Characteristics of a diagnosis of Guillain-Barré syndrome.

Characteristics		Fr	%	N (%)		p-value
				Hospital	Institute	
Level of diagnostic certainty	1	25	13.4	17 (13.3)	12 (20.3)	0.396‡
	2	28	15.1	23 (18)	7 (11.9)	
	3	6	3.2	6 (4.7)	1 (1.7)	
	4	127	68.3	82 (64.1)	39 (66.1)	
Motor examination	Incomplete	129	64.2	116 (82.3)	13 (21.7)	< 0.000*†
	Complete	72	35.8	25 (17.7)	47 (78.3)	
Lumbar puncture	No	52	25.9	40 (28.4)	12 (20)	0.215 †
	Yes	149	74.1	101 (71.6)	48 (80)	
Time until lumbar puncture	Early (≤ 7)	111	76	74 (74.8)	37 (78.7)	0.559 †
	Late (> 7)	35	24	25 (25.3)	10 (21.3)	
Electrophysiological studies	No	47	23.4	42 (29.8)	5 (8.3)	0.001*†
	Yes	154	76.6	99 (70.2)	55 (91.7)	
Time until electrophysiological studies	≤ 14	96	62.8	62 (63.3)	34 (61.8)	0.859 †
	>1 4	57	37.3	36 (36.7)	21 (38.2)	

*p < 0.05; †Chi-square test; ‡Fisher exact test; FR: frequency.

Table 5. Factors associated with application of the Brighton criteria with diagnostic certainty level 1 for Guillain-Barré syndrome.

Variables		Brighton criteria diagnostic certainty level 1				
		No	Yes	Crude PR (95% CI)	p	Adjusted PR (95% CI)
		N (%)	N (%)			
Institution	National hospital	111 (86.7)	17 (13.3)	Ref	0.218	Ref
	Specialized institute	47 (79.7)	12 (20.3)	1.67 (0.74 – 3.76)		0.73 (0.23 – 2.35)
Age†	< 65	132 (83.0)	27 (17.0)	Ref	0.200	Ref
	≥ 65	26 (92.9)	2 (7.1)	0.38 (0.08 – 1.68)		0.28 (0.03 – 2.39)
Sex	Female	69 (82.1)	15 (17.9)	Ref	0.424	Ref
	Male	89 (86.4)	14 (13.6)	0.72 (0.33 – 1.60)		‡
Complete medical research council	No	101 (87.1)	15 (12.9)	Ref	0.216	Ref
	Yes	57 (80.3)	14 (19.7)	1.65 (0.75 – 3.67)		1.29 (0.42 – 4.01)

Table 5. Cont.

Variables		Brighton criteria diagnostic certainty level 1				
	No	Yes	Crude PR (95% CI)		p	Adjusted PR (95% CI)
	N (%)	N (%)				
Cranial nerve involvement	No	97 (86.6)	15 (13.4)	Ref	0.311	Ref
	Yes	60 (81.1)	14 (18.9)	1.51 (0.68 – 3.35)		‡
Dysautonomia	No	136 (83.4)	27 (16.6)	Ref	0.309	Ref
	Yes	22 (91.7)	2 (8.3)	0.46 (0.10 – 2.06)		‡
Lumbar puncture	Early	80 (76.9)	24 (23.1)	Ref	0.090	Ref
	Late	30 (90.9)	3 (9.1)	0.33 (0.09 – 1.19)		0.16 (0.04 – 0.65)
Electrophysiological studies	Early	78 (83.9)	15 (16.1)	Ref	0.197	Ref
	Late	39 (75.0)	13 (25.0)	1.73 (0.75 – 4.00)		3.46 (1.20 – 9.97)
Electrophysiological subtype	Demyelinating	36 (76.6)	11 (23.4)	Ref	0.691	Ref
	Axonal	70 (79.5)	18 (20.5)	0.84 (0.36 – 1.97)		‡

†Median ± SD; ‡Variables did not require adjustment; MRC: medical research council; LP: lumbar puncture; EPS: electrophysiological studies.

DISCUSSION

This study assessed the diagnostic management of GBS and use of the BC in three Peruvian institutions between 2007 and 2018. We found that level 1 diagnostic certainty was met in only 13.4% of the GBS cases, and complementary tests were used in the cases of 75% of the patients. Likewise, more than half of the patients presented an incomplete motor examination using the MRC score.

The proportion of patients with affected reflexes in our cohort was lower (45%) than what was reported in a previous Peruvian study (84%)[12]. It was also the main clinical criteria missing among patients with certainty level 4. This difference may have been a consequence of inadequate examination, inadequate recording or "normal" reflexes, which have been associated with higher frequency of the axonal variant of GBS, as in our cohort. Although there is still divergence of opinions regarding the predominant variant in Latin America, there are reports from pediatric cohorts showing that the axonal subtype made up to 40-65% of the cases of GBS. This stands in contrast to findings from Europe and North America, where AIDP has a frequency of 60-80%[13,14]. However, we did not observe any association between the electrophysiological variant and use of the BC with level 1 diagnostic certainty.

In the present study, the rate of application of the BC for GBS diagnosis with level 1 diagnostic certainty was lower (13.4%) than in studies conducted in the Netherlands, India and Bangladesh, which met the criteria for level 1 in 61%, 62% and 58% of the patients, respectively[7–9]. This finding might be explained by lack of knowledge of these criteria and the recommendations for its use, or by physicians' disagreement with their use[15,16]. In addition, the lower proportion of Peruvian neurologists, in contrast with the World Health Organization recommendations, may have contributed to lower use of the BC[17]. Complementary tests such as LP and EPS were frequently used (in around 75% of the cases) in our study: thus, availability does not seem to have been an influencing factor.

The quality of motor examination with the MRC score was incomplete in most patients (64.2%), while complete quality of examination predominated in the specialized institute (78.3%). A higher proportion of neurologists with greater experience of using these scores could likely explain this finding[18,19].

CSF analysis is helpful for confirming the diagnosis and for ruling out another differential diagnosis[20]. Most of our patients (76%) underwent LP during hospitalization, within seven days of disease onset. An early LP shows albuminocytological dissociation in 50-66% of GBS patients, and this proportion rises to 75% of the cases if the procedure is performed more than three weeks after disease onset. Thus, it is recommended that this test is repeated if negative[21]. Since most LPs in our study were performed within the first seven days, during which the hallmark findings of GBS are typically less frequently found, this could explain the low fulfillment of the BC among these patients.

EPS findings reinforce the diagnosis and allow differentiation of the variants of GBS[22]. The relevance of performing EPS after the second week of the disease lies in the fact that more than 85% of patients present consistent signs of GBS after this time[23]. We observed that after 14 days, EPS was less frequently used (37.3%). This could be a consequence of patients' refusal to undergo the procedure[24], lack of consideration of this test among neurologists or lack of availability of this equipment in the public sector[25].

We found that being treated in a specialized institution was not associated with a higher rate of certainty level 1 of GBS diagnosis, despite the greater use of LP, EPS and complete motor examinations. Apart from these institutional factors, none of the patient-related factors assessed showed any association. We believe that physicians' familiarity with and acceptance of

the BC should be explored in order to determine whether these are associated with the lower rate of use of the BC observed in our population.

Our study was limited by lack of access to patient records, due to unavailability of old paper records in one of the centers. However, our sample still had sufficient power and, as the only common factor among the factors excluded was the date on which these patients were treated, we do not believe that this resulted in a high risk of selection bias. Likewise, due to the retrospective design of this study, there was a risk of bias in data collection, which we reduced by using strict case definitions, standardized case report forms and exclusion of cases with missing data from the univariate analysis.

In conclusion, level 1 diagnostic certainty of the BC was met in less than one quarter of the cases with a GBS diagnosis between 2007-2018 in three national centers in Lima, Peru. This level was not significantly associated with being treated in a specialized institute, compared with a general hospital. Additionally, less than half of the patients presented a complete motor evaluation using the MRC score. Further research should assess whether neurologists' preferences or institutional factors can explain the low use of the BC and how this can be increased.

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ARTICLE

HIV-associated painful neuropathy: where are we?

Neuropatia dolorosa associada ao HIV: onde estamos?

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ABSTRACT

Background: After the advent of combination antiretroviral therapy, infection with the human immunodeficiency virus (HIV) ceased to be a devastating disease, but sensory neuropathy resulting from the permanence of the virus and the side effects of treatment have worsened the morbidities of these patients. **Objective:** To investigate the quality of life of 64 HIV-positive patients: 24 with painful neuropathy (case group) and 40 without painful neuropathy (control group). The impact of other factors on quality of life was also assessed. **Methods:** To assess painful neuropathy, the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale, Douleur Neuropathique 4 (DN4) questions and Neuropathy Disability Score (NDS) were used. The Short Form Health Survey (SF-36) scale was used to assess quality of life. Factors related or unrelated to HIV were obtained through the medical history and analysis on medical records. **Results:** The quality of life of patients with neuropathic pain was worse in six of the eight domains of the SF-36 scale. The number of clinical manifestations related to HIV, length of time with detectable viral load since diagnosis, length of time since the diagnosis of HIV infection and length of time of HAART use had a negative impact on quality of life. Higher levels of CD4, education and family income had a positive impact. **Conclusions:** Painful neuropathy related to HIV is a factor that worsens the quality of life of patients infected with this virus and should be included in the clinical evaluation.

Keywords: Morbidity; HIV; Quality of Life.

RESUMO

Antecedentes: Após o advento da terapia antirretroviral combinada a infecção pelo vírus da imunodeficiência humana (HIV) deixou de ser uma doença devastadora, porém a neuropatia sensitiva consequente à permanência do vírus e ao efeito colateral do tratamento piora a morbidade desses pacientes. **Objetivo:** Investigar a qualidade de vida de 64 pacientes com HIV, 24 com neuropatia dolorosa (grupo caso) e 40 sem neuropatia dolorosa (grupo controle). Avaliou-se também o impacto de outros fatores relacionados e não relacionados ao HIV na qualidade de vida. **Métodos:** Para avaliação da neuropatia dolorosa foram utilizadas as escalas *Leeds Assessment of Neuropathic Symptoms and Signs* (LANSS), *Douleur Neuropathique 4* (DN4) e Escore de Comprometimento Neuropático (ECN). Para avaliação da qualidade de vida foi utilizada a escala *Short Form Health Survey* (SF-36). Fatores relacionados e não relacionados ao HIV foram obtidos através da anamnese e análise de prontuário. **Resultados:** A qualidade de vida dos pacientes com dor neuropática foi pior em 6 dos 8 domínios da escala SF-36. O número de manifestações clínicas relacionadas ao HIV, tempo de carga viral detectável desde o diagnóstico, tempo de diagnóstico da infecção pelo vírus e tempo de uso de TARVC impactaram negativamente na qualidade de vida. Maior nível de CD4, da escolaridade e da renda familiar impactaram positivamente. **Conclusões:** A neuropatia dolorosa relacionada ao HIV é fator de piora da qualidade de vida dos pacientes infectados por esse vírus devendo ser incluída na avaliação clínica desses pacientes.

Palavras-chave: Morbidade; HIV; Qualidade de Vida.

INTRODUCTION

Infection by the human immunodeficiency virus (HIV) has been challenging healthcare authorities since the 1980s. In Brazil,882,810 cases of acquired immunodeficiency syndrome (AIDS) were identified between 1980 and June 2017[1]. In 2014, with the inclusion of HIV infection in the list of compulsorily notifiable diseases, better understanding of the epidemiological profile of HIV/AIDS cases was achieved, thus enabling redirection of public healthcare policies. Many advances have been observed over recent years with regard to diagnosis and treatment of infection by this virus, but this remains an important public health problem.

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In 2015, mortality due to HIV/AIDS was 42.3% lower than in 1995[1]. Neurological impairment has a major impact on both morbidity and mortality. It has been estimated that 40 to 70% of these patients have both central and peripheral neurological manifestations[2]. With the advent of antiretroviral therapy (ART), there was a reduction in mortality, but the length of exposure to the virus and to ART increased. Thus, there was a reduction in neurological impairment secondary to opportunistic infections related to severe immunodepression states. In contrast, the symptoms associated with the permanence of the virus and exposure to ART, such as peripheral neuropathy, remain the main neurological changes[2–5].

The incidence rate for sensory neuropathy (SN), and particularly distal symmetric polyneuropathy (DSP), ranges from 30 to 60% among HIV-positive patients[5]. SN has been found to be the most frequent form of neuropathy among HIV-positive individuals[6–8]. Its clinical manifestations are variable but include burning pain, numbness and paresthesia, which can be disabling and irreversible, with an important impact on quality of life[9,10].

Some studies have assessed the influence of factors either related or unrelated to infection, on quality of life[11,12]. However, these studies did not assess the impact of neuropathic pain on the quality of life of HIV-positive patients. The aim of the present study was to investigate the quality of life of HIV-infected patients with neuropathic pain.

METHODS

This study was approved by the Research Ethics Committee of Federal Fluminense University. Written informed consent was obtained from all study participants before enrollment into the study.

This was an observational and descriptive cross-sectional study. A convenience sample of adult HIV-infected patients either with or without neuropathic pain was evaluated between March and July 2017. Right after their consultations at the HIV/AIDS immunology clinic, patients who presented with pain in the lower limbs and/or upper limbs were referred for neurological evaluation. In this evaluation, anamnesis, physical examination and application of three neuropathic pain scales were used to characterize whether the referred pain was neuropathic or not. These scales were the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale, Douleur Neuropathique 4 (DN4) questions and Neuropathy Disability Score (NDS).

Next, a review of the medical records of patients with neuropathic pain was carried out to collect test results and epidemiological and disease-related data. Patients who had neuropathic pain on the three pain scales and who met the inclusion criteria were evaluated regarding quality of life (SF-36 scale). Patients without any type of pain, and with sociodemographic characteristics similar to those of the group with neuropathic pain, were selected as a control group to be evaluated using the SF-36 scale.

The inclusion criteria for both groups were that the participants needed to be between the ages of 18 and 65 years; have a positive HIV test on the blood sample; have complementary test results within the normal range, including normal TSH, FT4, B12 vitamin, cholesterol and glycated hemoglobin; and have no history of treatment for HIV/AIDS.

For the HIV-positive group with neuropathic pain, the additional inclusion criteria were that the participants needed to present the following; sensory neuropathic symptoms such as paresthesia, numbness and pain in the extremities; the criteria for neuropathic pain of two scales: LANSS ≥ 12 and DN4 ≥ 4; neuropathy on the clinical scale (NDS > 3); and a neurological examination compatible with peripheral neuropathy.

For the HIV-positive control group, there was the additional inclusion criterion of not presenting any neurological symptoms.

The exclusion criteria for both groups were the following situations: presence of an opportunistic disease that was either active or under treatment; presence of cognitive deficits, as assessed using the Mini-Mental State Examination (MMSE), with a score lower than 20[11]; presence of sensory deficits that prevented scoring of scales or that impaired test performance; and/or a history of drug-induced neuropathy.

For the control group, there was one further exclusion criterion: use of medication with action against neuropathic pain.

Statistical analysis

Fisher's exact test was used to assess statistical significance between categorical variables, and between groups with and without painful neuropathy. Continuous variables were categorized so that statistical associations could be assessed using Fisher's exact test. Continuous variables were described in terms of means, medians and standard deviations using the nonparametric Mann-Whitney test. Statistically significant differences regarding the domains of the SF-36 scale, for groups with and without painful neuropathy, were calculated using the Mann-Whitney nonparametric test. The magnitude of differences between the means of the groups with and without painful neuropathy, in relation to each domain of the SF-36 scale, was evaluated by calculating Cohen's effect size. Statistical correlations within each group, between the domains of the SF-36 scale and the continuous and categorical variables, were performed using the Spearman correlation coefficient (rs) and the Mann-Whitney method, respectively. The statistical procedures were performed using the Statistical Package for the Social Sciences software, version 16.0.

Description of the variables analyzed

The patients were divided into two groups (with and without neuropathy), and the variables analyzed were: sex, age, education, family income, practicing of physical activity, history of depression, BMI (body mass index), viral load (detectable or undetectable), duration of HIV infection, number of

ARV drugs used, length of ART use, number of clinical manifestations related to HIV, CD4 value in the last six months and length of time for which a viral load (VL) had been detectable since diagnosis.

RESULTS

Sixty-four patients were evaluated, among whom 24 presented painful neuropathy in accordance with the clinical criteria. The other 40 patients did not present painful neuropathy through the same criteria and thus composed the control group. In the group with painful neuropathy, 54.2% were female, 50% were between 40 and 49 years old, 41.7% had attended school for up to 5 years and 45.8% had a family income of 3 to 4 minimum monthly wages. In the control group, 55% were female, the predominant age group was 31 to 49 years (70%), the schooling level was higher in this group than in the other group (72.5% of the patients were aged 6 to 9 years of schooling) vs 41.7% with up to 5 years of schooling in the other group and 50% had a family income of between 3 and 4 minimum monthly wages. Table 1 characterizes the sociodemographic variables in relation to the two groups studied.

Only the educational level variable showed a statistically significant difference (p-value < 0.05) between the groups, such that lower levels of education were concentrated in the group with neuropathy. There was a predominance of patients between 40 and 49 years old in the group with neuropathy, thus suggesting that increasing age may be related to a greater chance of developing neuropathy.

Comparison of non-HIV-related variables between the groups with and without neuropathy

Considering the variables not related to HIV (Table 2), there was no statistically significant difference between the groups regarding the practice of physical activity, or regarding histories of depression. Despite this, 54.2% had a history of depression, as opposed to 47.5% in the control group. BMI showed a statistically significant difference, such that overweight predominated in the group with neuropathy.

Comparison of HIV-related variables between the groups with and without painful neuropathy

The analysis of variables related to HIV is shown in Table 3. The only variable that demonstrated statistical significance between the groups was the length of time with a diagnosis of HIV infection. In the group without painful neuropathy, 60% of the patients had had this infection for less than 10 years. In the group with painful neuropathy, 58.4% of the patients had had it for more than 10 years.

Analysis of numerical variables using the Mann-Whitney test

Descriptive statistics on numerical variables among the HIV-positive patients with and without painful neuropathy are presented in Table 4. Only the variables of the number of clinical manifestations and the length of time with detectable viral load since diagnosis showed statistically significant differences between the groups studied, such that they were greater in the group with neuropathy.

Table 1. Sociodemographic characteristics of the groups with and without neuropathy.

Sociodemographic variables		HIV-positive patients				P-value of Fisher's exact test
		WITH painful neuropathy (n = 24)		NO painful neuropathy (n = 40)		
		n	%	n	%	
Sex	Female	13	54.2	22	55.0	1.000
	Male	11	45.8	18	45.0	
Age	31 – 39 years	5	20.8	14	35.0	0.396
	40 – 49 years	12	50.0	14	35.0	
	50 – 55 years	7	29.2	12	30.0	
Educational level	Up to 5 years of schooling	10	41.7	9	22.5	0.001
	6 – 9 years of schooling	7	29.2	29	72.5	
	10 or more years of schooling	7	29.2	2	5.0	
Income (minimum monthly wages)	1 – 2 mw	3	12.5	1	2.5	0.353
	2 – 3 mw	9	37.5	14	35.0	
	3 – 4 mw	11	45.8	20	50.0	
	> 4 mw	1	4.2	5	12.5	

Source: HUGG HIV/AIDS immunology outpatient clinic; mw: minimum monthly wages.

Table 2. HIV-positive patients with and without painful neuropathy, according to variables not related to HIV.

Variables not related to HIV		HIV+ patients				P-value of Fisher's exact test
		WITH painful neuropathy (n = 24)		NO painful neuropathy (n=40)		
		n	%	n	%	
Physical activity	Yes	5	20.8	16	40.0	0.170
	No	19	79.2	24	60.0	
BMI (kg/m²)	Up to 24.9 (normal)	7	29.2	25	62.5	0.003
	25 – 29.9 (overweight)	14	58.3	7	17.5	
	30 or more (obesity)	3	12.5	8	20.0	
History of depression	Yes	13	54.2	19	47.5	0.797
	No	11	45.8	21	52.5	

Source: HUGG HIV/AIDS immunology outpatient clinic; BMI: body mass index.

Table 3. Patients with and without painful neuropathy, according to variables related to HIV.

Variables related to HIV		HIV-positive patients				P-value of Fisher's exact test
		WITH painful neuropathy (n = 24)		NO painful neuropathy (n=40)		
		n	%	n	%	
Length of time with the diagnosis of HIV infection	Up to 4 years	5	20.8	3	7.5	0.006
	5 – 9 years	5	20.8	21	52.5	
	10 – 14 years	7	29.2	14	35.0	
	15 or more	7	29.2	2	5.0	
Number of ARV used	Up to 5	18	75.0	34	85.0	0.341
	6 or more	6	25.0	6	15.0	
Length of HAART use	Up to 9 years	11	45.8	26	65.0	0.192
	10 or more	13	54.2	14	35.0	
Number of hospitalizations	0	9	37.5	23	57.5	0.071
	1	6	25.0	12	30.0	
	2 or more	9	37.5	5	12.5	
Number of clinical manifestations related to HIV	0	3	12.5	14	35.0	0.130
	1	9	37.5	13	32.5	
	2 or more	12	50.0	13	32.5	
History of abandonment of HAART use	Yes	8	33.3	14	35.0	1.000
	No	16	66.7	26	65.0	
CD4 cell count	Up to 499	6	25.0	13	32.5	0.583
	500 or more	18	75.0	27	67.5	
Viral load	Undetectable	20	83.3	35	87.5	0.718
	Detectable	4	16.7	5	12.5	
Time of VL detectable since diagnosis	1 year	8	33.3	26	65.0	0.051
	2 years	7	29.2	6	15.0	
	3 years or more	9	37.5	8	20.0	

Source: HUGG HIV/AIDS immunology outpatient clinic; ARV: antiretrovirals; HAART: highly active antiretroviral therapy; VL: viral load.

Table 4. Descriptive statistics for numerical variables among HIV-positive patients with and without painful neuropathy.

Variables	HIV-positive groups	Descriptive statistics					Mann-Whitney test p-value
		Average	Standard deviation	Minimum	Median	Maximum	
Age (years)	With painful neuropathy	46.7	5.8	35.0	47.5	55.0	0.296
	No painful neuropathy	44.2	7.4	31.0	43.5	55.0	
Years of study	With painful neuropathy	6.7	3.0	4.0	6.0	13.0	0.583
	No painful neuropathy	6.6	1.7	4.0	6.0	12.0	
Income (MW)	With painful neuropathy	2.4	0.8	1.0	2.5	4.0	0.155
	No painful neuropathy	2.7	0.7	1.0	3.0	4.0	
BMI (kg/m^2)	With painful neuropathy	26.2	5.4	18.3	26.0	42.3	0.291
	No painful neuropathy	25.7	6.1	18.0	24.7	40.0	
Infection duration (years)	With painful neuropathy	10.7	5.5	2.0	11.5	21.0	0.117
	No painful neuropathy	8.7	4.0	4.0	8.0	21.0	
Number of ARV used	With painful neuropathy	4.5	1.5	3.0	4.0	9.0	0.522
	No painful neuropathy	4.2	1.2	3.0	4.0	7.0	
Duration of use of HAART (years)	With painful neuropathy	9.3	4.8	2.0	10.5	19.0	0.185
	No painful neuropathy	7.8	3.1	4.0	7.0	14.0	
Number of clinical manifestations	With painful neuropathy	1.8	1.3	0.0	1.5	4.0	0.026
	No painful neuropathy	1.1	1.1	0.0	1.0	5.0	
CD4	With painful neuropathy	670	345	14	682	1.257	0.321
	No painful neuropathy	760	313	221	814	1.327	
Detectable VL duration (years)	With painful neuropathy	2.9	2.7	1.0	2.0	12.0	0.019
	No painful neuropathy	1.9	1.6	1.0	1.0	8.0	

Source: HUGG HIV/AIDS immunology outpatient clinic. MW: minimum monthly wage; BMI: body mass index; ARV: antiretrovirals; HAART: highly active antiretroviral therapy; VL: viral load.

Differentiation of the groups with and without neuropathy in relation to the domains of the SF-36 quality-of-life scale

Descriptive statistics for the domains of the SF-36 scale in HIV positive patients with, and without painful neuropathy are represented in Table 5 and Figure 1.

The domains that most differentiated the groups were: pain, social aspects, functional capacity, emotional aspects and physical aspects. Vitality was the domain that showed the least difference between the groups.

Correlation between numerical variables and the SF-36 domains among patients with painful neuropathy

The greater the number of years of schooling was, the smaller the impact of the domains of emotional aspects, general health, vitality and mental health was on the quality of life of patients with painful neuropathy. In addition, the higher the income was, the lower the impact of pain, general health, vitality and mental health was on quality of life. The number of clinical manifestations related to HIV showed a negative correlation

with general health status. The CD4 value showed a positive correlation with the scores for physical aspects, emotional aspects, vitality and mental health.

Description of the correlation between categorical variables and the SF-36 scale domains

- Sex: there was no statistically significant difference between the sexes, for any of the domains of the SF-36 scale. However, all domains showed better averages for males.
- Practicing of physical activity: Practicing of physical activity improved the quality of life of patients with neuropathic pain, especially in the functional capacity domain.
- History of depression: Although there was no statistically significant difference between the groups, presence of this comorbidity had a significant negative influence on the following domains in the group with pain (taking into account the difference between the means): pain, general state of health, vitality and mental health.
- Viral load: Only the physical aspects domain showed a statistically significant difference between patients who had detectable VL and those with undetectable VL, in the group with neuropathic pain.

Table 5. Descriptive statistics for the domains of the SF-36 quality-of-life scale among HIV-positive patients with and without painful neuropathy.

SF-36 domains	HIV-positive groups	Descriptive statistics					d = effect size	Mann-Whitney test p-value
		Average	Standard deviation	Minimum	Median	Maximum		
Functional capacity	With painful neuropathy	46.9	24.1	10.0	45.0	100.0	-2.9	0.008
	No painful neuropathy	95.4	9.7	60.0	100.0	100.0		
Physical aspects	With painful neuropathy	36.5	29.5	0.0	25.0	100.0	-2.1	< 0.001
	No painful neuropathy	91.3	24.4	0.0	100.0	100.0		
Pain	With painful neuropathy	40.2	12.4	20.0	41.0	52.0	-4.2	< 0.001
	No painful neuropathy	93.5	12.9	51.0	100.0	100.0		
Emotional aspects	With painful neuropathy	24.9	32.4	0.0	25.0	100.0	-2.5	< 0.001
	No painful neuropathy	90.5	22.0	0.0	100.0	100.0		
General health status	With painful neuropathy	52.5	23.8	27.0	42.0	92.0	-1.9	< 0.001
	No painful neuropathy	87.3	14.2	40.0	89.5	100.0		
Vitality	With painful neuropathy	39.5	21.8	15.0	32.5	90.0	-1.5	< 0.001
	No painful neuropathy	75.9	26.6	0.0	87.5	100.0		
Social aspects	With painful neuropathy	39.0	26.5	12.0	25.0	100.0	-3.5	< 0.001
	No painful neuropathy	98.1	6.7	75.0	100.0	100.0		
Mental health	With painful neuropathy	51.0	20.3	24.0	42.0	92.0	-1.8	< 0.001
	No painful neuropathy	84.3	16.9	32.0	91.0	100.0		

Source: HUGG HIV/AIDS immunology outpatient clinic.

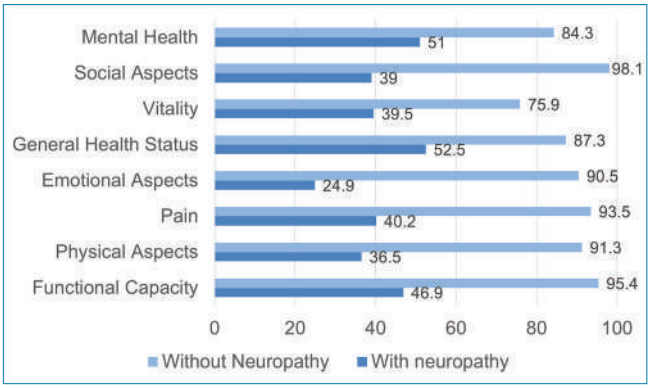

Figure 1. Mean of the domains of the SF-36 quality-of-life scale among HIV-positive patients with and without painful neuropathy.

DISCUSSION

Thirty-seven years after the discovery of the HIV virus, much progress has been made in combating the disease caused by this virus, which without treatment is devastating. However, even today, AIDS is a public health problem that can have a major impact on morbidity among patients who live with it[13].

Out of the sociodemographic variables studied, only the level of education showed a statistically significant difference between the groups. In an evaluation on HIV-positive patients with neuropathy, Kabongo et al., 2016, had already identified that lower educational levels correlated with worse symptoms and quality-of-life scores[14].

Although not statistically significant, it was noted that, in relation to age, 79.2% of the patients in the group with neuropathy were older than 40 years. In this group, the patients were predominantly between 40 and 49 years old because of the inclusion and exclusion criteria. Data on increasing age as an independent risk factor for neuropathy among patients with HIV have been previously reported[15–17]. Watters et al., 2004, in a study that evaluated HIV-associated DSP patients who were older than 50 years, observed that the thin sensory fibers became less tolerant to cumulative neuropathic effects with increasing age. In addition, patients with a longer life span were unable to regulate the neuroprotective astroglial response[18,19]. Among the variables not related to HIV, the only one that showed a statistically significant difference was BMI, which was higher in the group with neuropathy. Tumusiime et at., 2014, mentioned in their study that weight gain would be related to an increased risk of developing neuropathy[20].

Analysis on the HIV-related variables described in Table 3 showed that only the length of time with the diagnosis of HIV infection was statistically significant, such that it was higher in the group with neuropathy. Another variable that deserves to be highlighted, considering the percentage data for each group, is the length of use of ART. According to Robinson-Papp et al., 2013, and Tumusiime et al., 2014, the longer the time since the diagnosis of HIV infection, and the longer the use of ART are, the greater the risk of developing peripheral neuropathy is[20,21]. The length of use of ART was greater than 10 years for more than 54% of the patients with neuropathic pain, whereas in the group without this symptom, 65% had less than 9 years of use of ART.

Regarding CD4 and VL, in this study there was no statistically significant correlation between these variables and the presence of neuropathy. This information is in agreement with Keltner et al., 2014[22], and Navis et al., 2018[23].

Patients with and without neuropathic pain differ greatly with regard to almost all aspects of quality of life assessed by the SF-36 scale. Data relating to quality of life and neuropathic symptoms have already been reported from other recent studies such as Phillips et al., 2014, and Kaku and Simpson, 2014[19,15]. The findings from our study are in agreement with the results found by Phillips et al., 2014[19], who evaluated HIV-positive patients with and without painful neuropathy using the SF-36 scale. According to these authors, the domains that showed the greatest difference between the groups were functional capacity, physical aspects, vitality and social aspects. In addition to these, in our study, the domain of emotional aspects also showed an important difference.

There were statistically significant positive correlations between the number of years of schooling, family income and BMI, and several domains of the SF-36 scale in both groups (Table 2). The age variable did not show any statistical difference. Despite this, we observed that this variable showed a negative correlation in all domains of the SF-36 scale, from which it can be inferred that increasing age may contribute to worse quality of life. Cherry et al., 2009, reported that increasing age would be related to a higher risk of developing neuropathy among patients using Stavudine[17]. Hays et al., 2000, correlated increasing age with worsening quality of life, especially when the physical aspects were evaluated[24].

In evaluating the numerical variables related to HIV among patients with painful neuropathy and among the controls, it was observed that longer times with the diagnosis of HIV infection were correlated with worse quality-of-life scores in all the domains evaluated, and in both groups. This result is in agreement with the study by Miners et al., 2014[9]. Additionally, in our study, patients with neuropathic pain had had their diagnoses of HIV infection for longer times than the control group, and this difference was statistically significant.

The CD4 value had a positive impact on quality of life. The higher the CD4 values were, the higher the scores in all the domains assessed also were. There was a greater number of statistically significant correlations in the group with neuropathy. In this group, the correlation between CD4 and the domains of physical aspects, emotional aspects, vitality and mental health presented p values < 0.05. In the group without neuropathy, only the domain of social aspects showed a statistically significant association in relation to CD4. Thus, maintenance of adequate CD4 levels has a positive impact on several aspects of the quality of life of patients with neuropathic pain. In the literature,

the data correlating CD4 and quality of life are inconsistent[25]. However, our data are concordant with those of Duncan et al., 2005, and Briongos et al., 2011[26,27].

Practicing of physical activity had an important impact on quality of life, especially in the group with neuropathic pain. In this group, there was a statistically significant difference in the mean for the domain of functional capacity, such that it was higher among patients who were practicing physical activity. In the group without pain, no domain presented statistically significant p-values and the difference in the mean value, between those who were practicing physical activity and those who were not, was much smaller than in the preceding group. According to O'Brien et al., 2008, and O'Brien et al., 2016, aerobic physical exercise or a combination of aerobic and resistance exercises at least three times a week, and for at least 20 minutes, improved the quality of life of adult HIV patients[28,29]. According to Maharaj and Yakasai, 2018, who evaluated the influence of physical activity among HIV-positive patients with neuropathic pain, a rehabilitation program with physical exercise helps to control neuropathic pain[30].

Jin et al., 2014, and Mannheimer et al., 2005, observed that patients with undetectable VL and better adherence to ART had better quality of life[25,31]. Our study adds that, in addition to better HIV control, prevention of risk factors for neuropathic pain helps to improve morbidity given that even patients with undetectable VL had worse quality-of-life scores when neuropathic symptoms were present.

In conclusion, the quality of life of HIV-positive patients was worse in all domains of the SF-36 scale. The domains that showed the greatest difference were pain, social aspects, functional capacity, emotional aspects, physical aspects and general health status. In assessing differences in non-HIV-related variables between groups, most patients with painful neuropathy were found to have higher BMI (overweight). Regarding the variables related to HIV, the length of time with the diagnosis of HIV infection, presence of detectable VL, use of ART and number of clinical manifestations were higher in the group with painful neuropathy.

In evaluating the influence of variables associated with HIV on the scores of the quality-of-life scale of patients with painful neuropathy, we found that:

- Greater numbers of clinical manifestations correlated with worse general health.
- Increased CD4 levels had a positive impact on social aspects, emotional aspects, vitality and mental health.
- Detectable VL had a significant negative influence on physical aspects.
- Regarding the impact of variables not related to HIV on the quality of life of this same group, we found that:
- Higher levels of education were correlated with less impact of pain on quality of life.
- Individuals who had higher family income had better general states of health, vitality and mental health.

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ARTICLE

Translation and adaptation of the sleep apnea quality of life index (SAQLI) to Brazilian Portuguese

Tradução e adaptação cultural do questionário de qualidade de vida (SAQLI) para o português brasileiro

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ABSTRACT

Background: Obstructive sleep apnea syndrome (OSAS) is characterized by episodes of upper airway obstruction during sleep, with a risk of cardiovascular and cerebrovascular diseases. There is no tool in Brazil to measure the impact of treatment on patients with OSAS. **Objective:** To translate and culturally adapt the Sleep Apnea Quality of Life Index (SAQLI) into Brazilian Portuguese. **Methods:** The translation and cultural adaptation were carried out in five steps: translation, synthesis of the translations, back translation, review committee and pretesting. **Results:** A version of a culturally compatible SAQLI was constructed after lexical changes, along with changes to the sentence structures, visual format, instructions and cards. The essence of the questionnaire and its social, emotional, and disease impact in treatment measures was maintained, with 80% understanding. **Conclusions:** The questionnaire was translated and adapted culturally to Brazilian Portuguese, and presented good comprehension in the study population.

Keywords: Quality of Life; Sleep Apnea, Obstructive; Translating.

RESUMO

Antecedentes: A síndrome da apneia obstrutiva do sono (SAOS) é caracterizada por episódios de obstrução da via aérea superior durante o sono, com risco para doenças cardiovasculares e cerebrovasculares. Não há ferramenta no Brasil para medir o impacto do tratamento em pacientes com SAOS. **Objetivo:** Traduzir e adaptar culturalmente o Índice de Qualidade de Vida em Apneia do Sono (SAQLI) para o português brasileiro. **Métodos:** A tradução e adaptação cultural foram realizadas em cinco etapas: tradução, síntese das traduções, retrotradução, comitê de revisão e pré-teste. **Resultados:** Uma versão de SAQLI culturalmente compatível foi construída após mudanças lexicais, bem como mudanças nas estruturas das frases, formato visual, instruções e cartões, mantendo a essência do questionário e seu impacto social, emocional e da doença nas medidas de tratamento, com 80% de compreensão. **Conclusões:** O questionário foi traduzido e adaptado culturalmente para o português brasileiro apresentando bom índice de compreensão na população estudada.

Palavras-chave: Qualidade de Vida; Apneia Obstrutiva do Sono; Tradução.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a disorder characterized by recurrent episodes of upper airway (UA) obstruction during sleep. It is a multifactorial disease and occurs due to thickening of the UA structures and increased collapsibility of the pharynx[1].

A study carried out in the city of São Paulo, Brazil, using polysomnography, identified that the prevalence of OSAS was 32.8%. This may have serious consequences for long-term health, such as: cardiovascular disease, systemic arterial hypertension[2,3], stroke, sexual impotence, cognitive deficit, poorer quality of life and sleep[3,4], decreased work activity and automobile accidents[5].

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Several instruments have been used[6,7] to assess the quality of life and sleep[6] among patients undergoing treatment for OSAS[8,9]. However, the Sleep Apnea Quality of Life Index (SAQLI) is the first instrument to specifically measure the quality of life of patients with OSAS, before and after treatment. It enables assessment of the impact of treatment on patients' lives, including the negative aspects of using CPAP, intraoral appliances and surgical treatment[10].

In Brazil, there is a lack of translated and formally adapted quality-of-life assessment questionnaires to aid healthcare professionals in decision-making and clinical follow-up. Most patients give up on treatment[11] because of discomfort. The SAQLI has been useful for detecting impairments of quality of life, compared with other questionnaires[12].

The purpose of this study was to carry out the translation and cultural adaptation of the SAQLI into Brazilian Portuguese.

METHODS

Participants

Thirty patients of both genders and 18 to 77 years of age participated in this study. They were recruited from our sleep disorders clinic. The study was conducted from August to November 2015.

Instrument

After receiving authorization from the original authors of the SAQLI for its translation and cultural adaptation, we started this process in accordance with a standardized guide for this purpose[10].

The SAQLI is an instrument with four domains that aims to assess the quality of life of patients with OSAS after undergoing some type of treatment5: CPAP, surgery, intraoral device or weight loss. These four domains are as follows: A: daily functioning (11 items); B: social interactions (13 items); C: emotional functioning (11 items); and D: symptoms (5 items). For domains A to D, each item is scored from 1 to 7, with 1 corresponding to the least impairment and 7 to the greatest impairment. An additional domain, E, titled treatment-related symptoms, was added to be used post-treatment and domain F measures the impact of treatment-related symptoms. The translation and cultural adaptation were carried out in five stages: translation, synthesis of translations, back-translation, review committee and pre-test.

Procedure

The translation was done by two independent evaluators who were fluent in English and Portuguese. A conceptual rather than a literal translation was emphasized. Next, a meeting was held between the main author, two psychologists and a neurologist specializing in sleep, in order to compare the two translations and reach a consensual synthesis from them: this then constituted version A of the translation. Version A was then back-translated by two other independent evaluators who were native English speakers and fluent in Portuguese[13].

This was followed by another meeting, of a review committee for synthesis of versions, at which discrepancies between the original English-language instrument, the Portuguese translation and the back translation were documented and analyzed. This process ultimately led to reaching a consensus translation (version B) that would be applied to the population. The instructions for the questionnaire and its items were adapted considering semantic, conceptual, cultural and idiomatic equivalences. Two pretests were then conducted, one in the period from November 2014 to June 2015, among 10 adults, and the other in the period from August to November 2015, among 20 adults.

Ethical considerations

This study was approved by the Ethics Committee of UNIFESP, São Paulo, Brazil, and all participants signed a consent form.

RESULTS

Version B of the translated instrument underwent adaptations relating to semantic equivalences (four changes), cultural equivalences (18) and conceptual equivalences (37), but none with regard to idiomatic equivalences. These modifications are described below.

Semantic equivalence

In item A (daily functions), "I. Most important daily activity. Regarding the execution of your most important daily activities (for example, work, school, childcare, housework, etc.) during the last four weeks", was modified to: "I. Choose a daily activity that is most important to you (for example, work, school, childcare, housekeeping, etc). Tell us how things have been in the last four weeks regarding this activity".

Questions 1, 2, and 3 of item I underwent alterations to the verb tense of the sentence, with use of a simpler and more usual verb structure, to facilitate understanding of the question. In question 3 of item III, the word "conflito" was omitted and only the word "discussões" was used, which is more colloquial in Brazilian Portuguese[14].

Conceptual equivalence

In questions 2, 3, and 4 of item I, the expressions "com que frequência" and "quanto tempo" were changed to "por quanto tempo" in order to give a sense of continuity. Some words in the instructions and questions of items 1, 2 and 4 of item II were suppressed, in order to make the sentence more objective and adapt it to the interviewees' understanding. In question 3 of item III, the word "brigar" was changed to "lutar", to achieve the meaning that the person strives to stay awake. In question 2, the word "quarto" was replaced by the word "cômodo" because

the home may not always have a bedroom available. In question 6, "quão culpado você se sentiu" was modified to "quanto você se sentiu culpado" because it is the most used and best understood way to ask that question in Brazilian Portuguese. In sentences 7, 8, and 9 of item III B, the phrase "com que frequência" was replaced by "quantas vezes". In question 11 of item III B, a structural change was made, from "quanto você teve de problema por não estar envolvido....." to "quanto você teve de problema por não participar", because this way of asking the question allows respondents to demonstrate whether or not they were willing to participate in activities with family members.

In item C, in the instructions, the sentence was simplified to facilitate understanding. In the questions relating to this item (1, 2, 3, 4, 5, 6, 7, 8 and 9), the structure "com que frequência" was changed "quanto tempo" because this is a phrase more commonly used by patients. The instructions of item D were modified in order to make them more direct. In question 7, the word "frequentemente" was removed in order to simplify the question; while in question 19, the words "relutância" and "incapacidade" were suppressed. In the instructions for item E, the word "circule" was replaced by "indique", and in question 18, the word "autoconsciência" was changed to "sensação de aumento da percepção do rosto/boca". The instructions for item F were simplified by using fewer words and making them more objective.

Cultural equivalence

In the initial instructions of the questionnaire, the word "impacto" was replaced by "como .... afeta" in order to reach a more direct explanation and demonstrating how OSAS influences the lives of the respondents. In question 3 of item II, the structure of the question was changed from "Quanta dificuldade você teve relacionada à sua capacidade para exercitar e/ou fazer atividades que você não considera relaxantes" to "Quanto você não se sentiu capaz para.... (atividade que escolher)", thereby making the question more objective and colloquial. In order to ascertain whether the ability to do leisure activities is still preserved, the instructions for item II B were modified to allow respondents to think about the activities that would be asked about next. In questions 1, 2, 3, 4, 5, 10, 12 and 13 of item III B and questions 10 and 11 of item C, the structure "Quão apreensivo..." was changed to "Quanto você ficou chateado... ." because these words are more appropriate to the colloquial vocabulary of Brazilian Portuguese.

In question 2, the word " fadiga " was changed to " cansaço ", because in the technical test the patients did not understand the word " fadiga ". In question 5, the words " adormecer se não for estimulado " were changed to " adormecer quando não está fazendo nenhuma atividade", both from item D. In the instructions for item E, the word "circule" was changed to "indique", so as to have a simpler way of informing the alternative. The format of the instructions in item A was also changed, as reported in item I of the Results.

The application of the questionnaire was maintained, but the scoring of the cards was simplified. In the original questionnaire, the points go from 1 to 7; however, the sort order is descending. The modification made was that the naming of the classification, i.e. the points from 1 to 7, was kept, but there was no correlation with the naming of any of the points except for points #1 and #7. There was also an inversion regarding the classification. In the original SAQLI in English, the score is presented in descending order; in our study, after application of the pretest and the consensus meeting, it was decided that an ascending order of classification would be adopted, because this meant that the understanding of the response measurements became more direct and did not confuse the interviewees.

Version B was pretested but required changes. Therefore, version C was applied in the technical test, and this version was shown to have an 80% understanding rate in the population to which it was applied. Thus, no further modifications were deemed necessary (Supplemental material).

DISCUSSION

In this process of translation and cultural adaptation to Brazilian Portuguese, changes were made that were related to cultural, semantic, conceptual and idiomatic equivalences[13–15]. The SAQLI has now undergone validation, translation and cultural adaptation in several western and eastern countries. Several of these studies have demonstrated the internal validity, reliability and sensitivity of this instrument, through measurements that identify impairments[16,17] in different areas relating to quality of life, including OSAS specifically[18–22].

Validation, translation and cultural adaptation studies have shown that the translation from English into the language in which the questionnaire will be used should not be literal but should "convey the spirit of the items of the questionnaire in different languages and cultures"[23,24].

In addition, the adaptations should encompass different social classes, with different cultural and socioeconomic levels, as seen throughout Brazil, so as also to include functionally illiterate individuals[14].

A few semantic changes were made in the present study, and the results from this adaptation give the instrument the possibility of being sensitive to the target population. The first measure that was used to achieve conceptual equivalence was to consult the lexical references of Canadian and Brazilian cultures, which provided the conditions for changes, such as in the expression "com que frequência" and "quanto tempo", which were modified to "por quanto tempo" in order to give a sense of continuity; and likewise, from "com que frequência" to "quantas vezes". In addition, the phrase "quanto você teve de problema por não estar envolvido..." was changed to "quanto você teve de problema por não participar".

The word "impacto" was replaced by "como...afeta" and "quão apreensivo..." was replaced by "quanto você ficou chateado...",

in order to achieve cultural equivalences. This change was needed because these terms did not maintain a correlation with the cultural context within which they were being applied[14].

Although the study sample encompassed a heterogeneous population in socioeconomic and cultural terms, it was not very large in terms of quantity.

In conclusion, the SAQLI was translated and culturally adapted to Brazilian Portuguese from the original in English and was shown to have a good comprehension index in the population studied.

SUPPLEMENTARY MATERIAL

SAQLI Version C (final version) is available at: https://www.arquivosdeneuropsiquiatria.org/wp-content/uploads/2022/06/1678-4227-anp-80-06-0275-suppl.pdf

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VIEW AND REVIEW

Autism and Down syndrome: early identification and diagnosis

Autismo e síndrome de Down: identificação precoce e diagnóstico

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ABSTRACT

Background: The diagnosis of autism spectrum disorder (ASD) in Down syndrome (DS) is underestimated because it is necessary to understand which aspects of the behavioral phenotype are related to DS and which are related to ASD. **Objective:** To conduct a systematic review of the literature on early identification and diagnosis of ASD in patients with DS. **Data source:** The VHL, MEDLINE, Cochrane, CINAHL, Scopus, Web of Science and Embase databases were searched and data were evaluated using PRISMA. **Data synthesis:** Out of 1,729 articles evaluated, 15 were selected. Although well studied, identification of ASD in DS can be difficult because of the need to understand which aspects of the behavioral phenotype are related to Down syndrome and which to autism. In this review, the prevalence of ASD was found to range from 12% to 41%. Early identification of autism risk in individuals with Down syndrome is still poorly studied, even though there are screening instruments for infants. Several instruments for diagnosing autism in individuals with Down syndrome were found, but a developmental approach is fundamental for making a clear diagnosis. **Conclusions:** Screening procedures are important for detecting early signs of autism risk in the first year of life. Careful evaluation methods are needed to establish the diagnosis, which include choosing appropriate tools for evaluation of development and cognition, and analysis of qualitative aspects of social interaction, among others. It has been indicated in the literature that early detection and timely accurate diagnosis, in association with an intervention, may benefit development, quality of life and social inclusion.

Keywords: Autism Spectrum Disorder; Down Syndrome; Diagnosis.

RESUMO

Antecedentes: O diagnóstico de autismo na síndrome de Down é subestimado, sendo necessário entender quais aspectos do fenótipo comportamental estão relacionados à síndrome de Down e quais são do autismo. **Objetivo:** Revisão Sistemática da Literatura sobre identificação precoce e diagnóstico do Transtorno do Espectro Autista em pacientes com síndrome de Down. Fonte de dados: Busca nas bases BVS, MEDLINE, Cochrane, CINAHL, Scopus, Web of Science e Embase e avaliação pelo PRISMA. **Síntese dos dados:** De 1.729 artigos avaliados, foram selecionados 15. Apesar de ser bastante estudada, a identificação do transtorno do espectro do autismo na síndrome de Down pode ser difícil devido a compreensão de quais aspectos do fenótipo comportamental estão relacionados à síndrome de Down e quais são do autismo. Nessa revisão foi encontrada variação na prevalência de 12% a 41%. A identificação precoce de risco de autismo na síndrome de Down é pouco estudada mesmo existindo instrumentos de triagem para lactentes. Sobre o diagnóstico do autismo na síndrome de Down foram encontrados diversos instrumentos, mas é necessária abordagem desenvolvimental para um diagnóstico apurado. **Conclusões:** É destacada a importância de procedimentos de triagem de sinais precoces de risco de autismo ainda no primeiro ano de vida. São para estabelecimento do diagnóstico a escolha de instrumentos para a avaliação do desenvolvimento e cognição, análise dos aspectos qualitativos da interação social, dentre outros. A detecção precoce e o diagnóstico preciso no tempo correto e uma intervenção poderão beneficiar o desenvolvimento, a qualidade de vida e inclusão social.

Palavras-chave: Transtorno do Espectro Autista; Síndrome de Down; Diagnóstico.

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INTRODUCTION

Down Syndrome (DS) is a common chromosomal anomaly and affects around 1 in 1000 individuals[1,2]. Recent research has indicated that the prevalence of autism spectrum disorder (ASD) is higher among individuals with DS[1].

ASD consists of a heterogeneous group of neurodevelopmental disorders that are characterized by disorders of social relations and communication, repetitive behaviors and restricted interests[3]. According to data from the CDC, this disorder affects approximately 1 in 54 individuals[4]. Another study showed that the ASD rate was 1 in 100 children born in the United States[5]. Data on the prevalence of ASD in DS vary, since studies have indicated that ASD affects between 2% and 10% of the population with DS, a rate that is higher than in the general population[2,6].

The diagnosis of ASD in Down syndrome is underestimated, because it is necessary to understand which aspects of the behavioral phenotype are related to DS and which are related to ASD[7].

Several standardized scales have been used to evaluate the ASD criteria[8,9]. Some researchers have recommended a developmental approach to the diagnosis of ASD among cognitively impaired children, i.e. the social or communication function needs to be qualitatively different and more impaired than the general cognitive function, for an additional ASD diagnosis to be made. Researchers taking this approach have generally reported lower ASD prevalence. Epidemiological studies using a developmental approach to estimate the prevalence of autism among children with Down syndrome are scarce[8,10].

The discussion about which criteria and instruments should be used to diagnose ASD in DS has been the subject of some studies, because the tools generally used have been validated considering individuals who do not have specific syndromes but who do have different levels of development. Furthermore, these tools do not exclude individuals with functional disorders, such as are present in DS[2].

In such cases, professionals should consider whether individuals' communicative social functioning corresponds to their basal level of development. In the absence of a developmental perspective, delays that are symptoms of a social disorder, e.g. ASD, can be misinterpreted[1,2].

Another aspect of ASD is that, when early signs of risk of this disorder are identified and the intervention occurs in the first year of life, the chances of successful therapies are greater[11-13]. Intervention at earlier ages is favored because this is the time of greatest potential for neural plasticity. Studies on detection and intervention mechanisms are increasingly necessary[14,15]. Identification of early signs of autism risk (before one year of age) occurs at a developmental point at which the diagnosis is more difficult to make. Intervention at this point will aim to modify the trajectory and change the prognosis[16].

Identification of early signs of autism risk has been widely studied, since no biomarker for the diagnosis of autism currently exists. The diagnosis is still made late, at around three years of age, even though symptoms are present in the first years of life[17]. In cases of DS, the diagnosis tends to be made even later[18].

With increasing numbers of studies on the early signs of autism risk, screening tools such as M-CHAT R have been created and tested at younger ages. In Brazil, law 13.438 recommends that formal evaluation of child development should be conducted on all infants using the *Caderneta da Criança* (Children's Booklet), which contains data that can guide ASD screening. Nonetheless, even with the increase in research, diagnostic tools for children, such as CARS, ADI-R and ADOS, are mainly concentrated around the age of two years. There are also tools that evaluate children in the first year, but few before the first year of life[17].

Identification of early signs of autism risk may lead to interventions at the most appropriate time and with better results[17]. Children with DS often present considerable delay in receiving the diagnosis of ASD, and this may result in inadequate strategies[13,11]. Attending to the need for earlier interventions, tools have been used to detect signs of autism in the first months of the child's life[17].

These interventions can prevent or minimize autism symptoms, such as premature appearance of stereotypes, isolation and communication delay. These are the symptoms that can subsequently lead to a diagnosis of ASD, particularly among children with DS[19].

In this regard, understanding how to identify early signs of autism risk among infants and make the diagnosis of autism in the population of people with DS is important, given the propositions that are necessary in these contexts. Faced with this issue, we conducted a systematic review on ASD in DS.

METHODS

This was a systematic review of the literature based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[20]. A search was conducted in the BVS, MEDLINE, Cochrane, CINAHL, Scopus, Web of Science and Embase databases to identify the main studies that evaluated autism spectrum disorder in Down syndrome.

Search strategy

To search for articles, specific descriptors linked to Boolean operators (AND and OR) were used with the aid of parentheses – ( ) – to delimit intercalations within the same logic and quotation marks (") to identify compound words. Therefore, the descriptors were applied as follows: "Autistic Disorder" OR "Trastorno do Espectro do Autismo" OR "Transtorno do Espectro Autista" OR autismo OR "Autismo Infantil" OR "Síndrome de Kanner" OR autism OR "Autism, Early Infantile" OR "Disorder, Autistic" OR "Disorders, Autistic" OR "Early Infantile Autism" OR "Infantile Autism" OR "Infantile Autism, Early" OR "Kanner Syndrome" OR "Kanners Syndrome" OR "Autism, Infantile" OR "Kanner's Syndrome") AND (tw: "Down Syndrome" OR

"Síndrome de Down" OR "Síndrome de Down" OR "Down Syndrome, Partial Trisomy 21" OR "Down's Syndrome" OR "Partial Trisomy 21 Down Syndrome" OR "Downs Syndrome" OR "Syndrome, Down" OR "Syndrome, Down's". This search was conducted in June and July 2019.

No filters such as article language, target audience or publication deadline were added. No such limitation were imposed because the objective was to include the largest number of articles relating to the prevalence of ASD in DS.

Recruitment and selection bias

To select potentially eligible articles, after exporting the studies selected from the databases, the Rayyan software was used. This is specific software for systematic reviews, in the form of a web and mobile app[21]. After importing the search results, the following steps were conducted: a) identification - recruitment of studies; b) selection - exclusion of duplicates and exclusion through reading of titles and abstracts; c) eligibility - exclusion through full reading of the studies; and d) inclusion - eligible studies, according to pre-established inclusion criteria.

The whole process was carried out by two independent researchers and was assessed by a third reviewer by reading the titles and abstracts. It should be noted that two inclusion or exclusion criteria were followed: a) articles selected by both researchers were included; and b) articles selected by only one researcher were analyzed by the third reviewer and, if these fitted the criteria, they were included. A further search was performed through reading the reference lists of the studies included in the eligibility phase (full reading of the articles).

Inclusion criteria

The criteria for inclusion of articles were the following: a) eligible cross-sectional epidemiological studies describing the prevalence of autism in the population with Down syndrome; b) eligible studies that presented the specificities of the diagnosis of autism in Down syndrome, with a detailed approach to diagnostic methods; c) eligible studies that showed the identification of signs of autism risk in the population of infants with Down syndrome; and d) no restrictions regarding age, gender, class of healthcare professional or the date of use of the service. Studies in English and Spanish were included.

Studies that did not demonstrate the criteria for the diagnosis of autism and those conducted prior to 2000 were excluded.

Data extraction

The data from each article were distributed in a table. The following information was included: country, year of publication, study design and data collection tools.

The quality of the evidence was evaluated in accordance with the criteria proposed by the EPHPP (Effective Public Health Practice Project – Quality Assessment Toll for Quantitative Studies – Annex 3)[22]. These criteria evaluate the selection bias, study design, potential confounding factors, blinding of the investigator and participant, method of data collection, loss of follow-up, integrity of the intervention and appropriate analysis of the research question. Based on these criteria, studies were then classified as having weak, moderate or strong quality of evidence.

RESULTS

The search based on the proposed content resulted in retrieval of 1,729 articles. Out of these, 577 duplicates were excluded, and 1,149 articles were selected for reading the titles and abstracts. Through this first analysis, 37 articles were selected for full reading. Out of these, 15 articles met the inclusion criteria for review. Figure 1 shows the selection flowchart for the studies. Table 1 shows the general characteristics of the articles included in this review.

Out of the studies included in the systematic review, 13 were cohort studies[7,18,23-28,30,32], among which one was retrospective[23], and two were cross-sectional[29,33]. These studies were published between 2005 and 2019. The ages of the subjects ranged from two to 40 years and the sample sizes ranged from 12 to 293 people. Seven studies were conducted in European countries and eight in the United States. Regarding outcomes, only one study identified early signs of autism risk[22]. In addition, nine diagnosed autism[6,7,18,24-29] and five, the diagnosis and prevalence of ASD in DS[8,28,30-32]. The quality of the evidence was evaluated in accordance with the criteria proposed by the EPHPP and the articles were classified as having weak quality of evidence.

Among these fifteen studies included, the use of screening assessment tools and autism diagnosis varied. In the study by Ortiz et al.[22], which was the only one that aimed to identify early signs of autism risk (Table 2), we opted to use a tool based on other standardized ones, although there are mechanisms for this purpose that have already been validated. In the fourteen studies (Table 3) that presented the diagnosis of ASD as an outcome, only Capone et al.[29] did not show any use of tools validated for evaluation. Also, in relation to the diagnosis, the reference criterion varied. Six studies[24-28,30,32] used the DSM-IV as the reference and four[6-8,18] used the DSM-IV TR. One[24] additionally used the ICD-10 and another[26] additionally used the DSM-IIIR. Two studies[28,32] used the DSM-V. Three studies[28,29,31] did not report the diagnostic criterion.

Regarding prevalence, there was variation in the results among the studies, as well as in the proportions of men and women in the sample composition. There was also heterogeneity among diagnostic outcomes, such as invasive developmental disorder (according to DSM-IV), ASD and autism, which were also related to the use of each diagnostic criterion.

Among the internationally validated scales for diagnosing ASD, eleven were used in the fifteen studies included in the systematic review. Seven of the tools used have a questionnaire format, for application to the children's guardians (ADI-R, AutBC, ABC, SCQ, SCQ-L, PDD-MRS and SDQ), and the other four tools present the possibility of observation of the individual and interviewing the person responsible for the subject (ADOS,

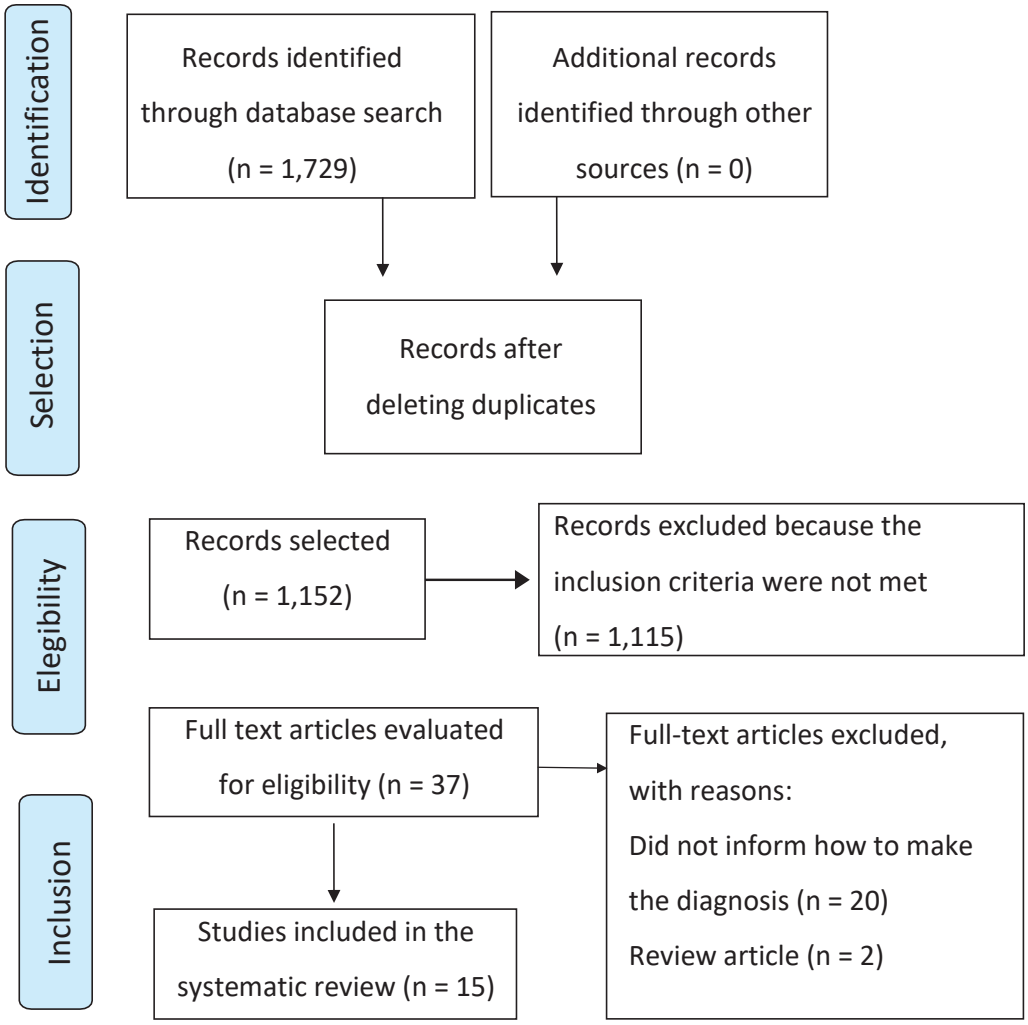

Figure 1. Flow of studies included in the review – PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

A-PL-ADOS, CARS and MCHAT). Among the tools used, four presented the diagnostic proposal (ADI-R, ADOS, A-PL-ADOS and CARS) and seven, the screening proposal (AutBC, ABC, SCQ, SCQ-L, PDD-MRS, M-CHAT and SDQ).

The minimum age at which subjects could be evaluated using these tools was 12 months, and two tools (A-PL-ADOS and PDD-MRS) were developed to evaluate individuals with cognitive impairments. There were differences in sensitivity and specificity, as presented in the table 4. It is important to highlight that sensitivity and specificity data may vary according to the study and the number of applications of the tool.

DISCUSSION

Several studies in this review evaluated identification of autism in the population with Down syndrome. It has been suggested in the existing literature that children with DS are different from those with DS and ASD[28].

In the present study, 15 studies with poor quality of evidence, according to the criteria proposed by EPHPP (Effective Public Health Practice Project – Quality Assessment Toll for Quantitative Studies), were included. Their poor quality was mainly due to the selection bias and confounding factors present in them. In these studies, 11 different assessment tools were used, two of which are specifically directed to analysis of people with intellectual disabilities. No specific tool or scale for evaluating ASD in DS was found. The studies evaluated show that there is a need for greater dissemination of standardized scales for diagnosing ASD, since screening scales are not diagnostically definitive. It is also worth noting that in three studies it was not possible to identify the diagnostic criteria used.

Identification of early signs of autism risk has been widely studied in the general population, since the diagnosis tends to be made at the age of around three years. However, parents already report changes in the first year of life[44].

Studies have reported that the stability of the ASD diagnosis in the general population reaches the rate of 75% around the age of three years. Identification of early signs of autism risk thus appears to provide a possibility for prevention and reduction of this disease[45].

Table 1. General characteristics of the studies included in the systematic review.

Author, year	Location	Study design	Origin and sample size	Age range	Study outcome	Quality of evidence
Ortiz et al., 2017[22]	Catalonia, Spain	Retrospective cohort	Down's Medical Centre (12)	0 to 5 years	Identification of early signs of ASD in DS	Weak
Starr et al., 2005[23]	Manchester, Liverpool and Leeds, England	Cohort	Down Syndrome Association, UK (13)	7 to 31 years	Diagnosis of ASD in DS	Weak
Carter et al., 2006[24]	USA	Cohort	Not informed (127)	2 to 24 years	Diagnosis of ASD in DS	Weak
Hepburn et al., 2007[6]	Denver, USA	Cohort	Mile High Down Syndrome Association (20)	2 to 3 years	Diagnosis of ASD in DS	Weak
Dressler et al., 2011[18]	Pisa, Livorno, Bologna and Pistoia, Italy	Cohort	IRCCS Stella Maris Foundation, University of Pisa (24)	6 to 34 years	Diagnosis of ASD in DS	Weak
Ji et al., 2011[25]	USA	Cohort	Kennedy Krieger Institute Down Syndrome Clinic (293)	2 to 13 years	Diagnosis of ASD in DS	Weak
Magyar et al., 2012[26]	USA	Cohort	Participants in a prevalence study (71)	4 to 14 years	Diagnosis of ASD in DS	Weak
Pandolfi et al., 2017[7]	USA	Cohort	Participants in a prevalence study (71)	3 to 15 years	Diagnosis of ASD in DS	Weak
Godfrey et al., 2019[27]	USA	Cohort	Parents' association (18)	Born between 1996 and 2003	Diagnosis of ASD in DS	Weak
Oxelgren et al., 2019[28]	Uppsala, Sweden	Cohort	Uppsala University Children's Hospital (60)	5 to 17 years	Diagnosis of ASD in DS	Weak
Capone et al., 2005[29]	Baltimore, USA	Cohort	Kennedy Krieger Institute (131)	2 to 21 years	Diagnosis of ASD in DS	Weak
DiGuiseppi et al., 2010[8]	Colorado, USA	Cross-sectional	General population and the Mile High Down Syndrome Association (123)	2 to 11 years	Diagnosis of ASD in DS	Weak
Moss et al., 2013[30]	Birmingham and London, UK	Cross-sectional	Down Syndrome Association, UK (108)	4 to 62 years	Diagnosis of ASD in DS	Weak
Warner et al., 2014[31]	England and Wales	Cohort	Down Syndrome Association, UK (160)	4 to 40 years	Diagnosis of ASD in DS	Weak

Table 2. Methodological characteristics of the studies, for identifying early signs of autism risk.

Author, year	Study design	Inclusion criteria	Sample size	Age range (years)	Autism assessment tools	Information source	Proportions of men/women
Ortiz et al., 2017[22]	Retrospective cohort	Individuals with DS and with SD and autism	Down's Medical Centre (12)	0 to 5	Modified Checklist for Autism in Toddlers (M-CHAT) and Autism Diagnostic Interview-Revised (ADI-R)	Analysis of home videos	2:1

Table 3. Methodological characteristics of studies on the diagnosis and prevalence of autism in DS.

Author, year	Inclusion criteria	Sample size	Age range (years)	Autism assessment tools	Information sources	Reference criterion for diagnosis	Diagnostic benchmark prevalence	Proportions of men/ women
Starr et al., 2005[23]	Individuals with DS and severe intellectual disability	13	7 to 31	Autism Diagnostic Interview-Revised (ADI-R) and Adapted Pre-Linguistic Autism Diagnostic Observation Schedule (A-PL-ADOS)	Parents	DSM-IV and CID-10	-	1.16:1
Carter et al., 2007[24]	Individuals with DS	127	2 to 24	Autism Behavior Checklist and Aberrant Behavior Checklist	Parents	DSM-IV	-	2.33:1
Hepburn et al., 2007[6]	Children with SD	20	2 to 3	Autism Diagnostic Interview-Revised and Autism Diagnostic Observation Schedule-Generic	Parents	DSM-IV TR	-	2.45:1
Dressler et al., 2011[18]	Individuals with DS and/or autism living with their family	24	6 to 34	Childhood Autism Rating Scale (CARS)	Parents	DSM-IV TR	-	0.84:1
Ji et al., 2011[25]	Individuals with DS	293	2 to 13	Autism Behavior Checklist	Not informed	DSM-IIIR and DSM-IV	-	3.16:1
Magyar et al., 2012[27]	Individuals with DS	71	4 to 14	Archival Social Communication Questionnaire (SCQ), Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule	Not informed	DSM-IV	-	1.29:1
Pandolfi et al., 2017[7]	Individuals with DS	71	3 to 15	Pervasive Developmental Disorder in Mental Retardation Scale (PDD- MRS), Social Communication Questionnaire – Lifetime Version (SCQ-L) and Autism Diagnostic Interview-Revised (ADI-R)	Parents	DSM-IV- TR	-	1.15:1
Godfrey et al., 2019[27]	Individuals with DS born between January 1, 1996, and December 21, 2003, and who had a caregiver who spoke English or Spanish fluently	33	born between 1996 and 2003	Autism Diagnostic Observation Schedule (ADOS) and Autism Diagnostic Interview-Revised (ADI-R)	Parents	DSM-V	-	2.01:00
Oxelgren et al., 2019[29]	Individuals with DS	60	5 to 17	Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS)	Parents	Not informed	-	1.8:1
Capone et al., 2005[29]	Individuals with DS	131	2 to 21	Behavior questionnaires, semi-structured neurological development assessment and observation during play or social interactions	Parents	DSM-IV	12.9%	2.7:1
DiGuiseppi et al.,2010[8]	Individuals with DS born between January 1, 1996, and December 21, 2003, and who had a caregiver who spoke English or Spanish fluently	123	2 to 21	Behavior questionnaires, semi-structured neurological development assessment and observation during play or social interactions	Parents	DSM-IV TR	AUT 6.4% TEA 11.8% Total 18.2%	1.86:1
Moss et al., 2013[30]	Participants were included if there was information on the date of birth and diagnosis of DS from a professional (physician, clinical geneticist, pediatrician or other), if at least 75% of the SCQ (Rutter et al., 2003) had been completed and if the participant with SD was at least 4 years of age.	108	4 to 62	Social Communication Questionnaire (SCQ)	Parents	Not informed	19%	0.7:1
Warner et al., 2014[31]	Individuals with DS	160	4 to 40	Lifetime version of the Social Communication Questionnaire (SCQ) and Strengths and Difficulties Questionnaire	Parents	Not informed	AUT 16,5% TEA 37.7%	1.2:1

Table 4. General characteristics of the tools used for ASD evaluation*, **, ***.

Tool	Description	Age	Sensitivity	Specificity	Amount of use (n = 15)
Autism Diagnostic Interview- Revised (ADI-R)[34]	[Diagnosis] Standardized questionnaire in accordance with DSM-IV criteria. This is an early childhood evaluation that checks social relationships, communication and repetitive behaviors.	from 18 months	0.52	0.84	8
Autism Diagnostic Observation Schedule (ADOS)[34,35]	[Diagnosis] This is a semi-structured evaluation tool that enables observation of four areas: social interaction, communication, play and repetitive behaviors.	from 12 months	0.94	0.80	5
Adapted Pre-Linguistic Autism Diagnostic Observation Schedule (A-PL-ADOS)[36]	[Diagnosis] Tool developed for diagnosing autism that enables observation of children and adults with severe/profound cognitive impairments	from 3 years	0.82	0.85	1
Autism Behavior Checklist (AutBC)[37]	[Screening] Tool based on parents' responses that evaluates behaviors associated with autism, in five subscales: sensory; interaction; body and object use; language; and social and self-help.	from 24 months	0.77	0.91	2
Aberrant Behavior Checklist (ABC)[38]	[Screening] This is a 58-item questionnaire that evaluates the severity of behaviors on five subscales: irritability; lethargy/social impairment; stereotyping; hyperactivity; and inadequate speech.	from 5 years	0.4-0.74	0.3-0.75	1
Childhood Autism Rating Scale (CARS)[34]	[Diagnosis] This is an tool for behavioral observations. It evaluates 15 items taking into account the symptoms for diagnosing ASD that are described in the DSM-IV	from 24 months	0.80	0.88	2
Archival Social Communication Questionnaire (SCQ)[39]	[Screening] This is a tool for evaluating individuals who are considered at risk of autism. It evaluates qualitative deficiencies in reciprocal social interaction and communication, as well as repetitive and stereotyped behavior	from 4 years	0.88	0.72	6
Social Communication Questionnaire – Lifetime Version (SCQ-L)[40]	[Screening] This version of the SCQ focuses on the child's development history, providing a total score that identifies individuals who may have autism and should be referred for a more thorough evaluation. The evaluation is practically unaffected by age, gender, language level and IQ performance	from 4 years	0.78	0.47	1
Pervasive Developmental Disorder in Mental Retardation Scale PDD- MRS[41]	[Screening] This is an ASD assessment tool that was developed for people with DS based on the DSM-IV-R criteria. It assesses the quality of social interactions with adults and colleagues, language and speech problems and aspects of behavior	from 2 years	0.92	0.92	1
Modified Checklist for Autism in Toddlers (M-CHAT)[42]	[Screening] This is a tool that is easy to apply and accessible, and it assesses psychometric properties. The caregiver responds to 23 yes/no items. Failure in three items or 2 out of 6 critical items (focus on joint attention, social orientation and imitation) indicates a risk of autism.	18 to 24 months	0.34	0.93	1
Strengths and Difficulties Questionnaire (SDQ)[43]	[Screening] This is an evaluation of 25 items that assesses the psychological condition of children and young people. It generates scores for emotional symptoms, behavioral problems, hyperactivity, peer problems and social behavior.	3 to 16 years	0.63	0.94	1

*Tests may vary according to more current versions, such as age references and values for specificity and sensitivity; **Sensitivity and specificity data may vary according to studies and the way in which the tests are applied (single or double application); ***This table reports the ASD assessment tools contained in the studies included that are standardized.

With the growing recognition through studies that a portion of the population with DS will present ASD in association with this, there is a need to identify early signs of risk and implement treatment as soon as these signs have been identified. This important for reducing the impacts of this comorbidity[7].

Despite the persistent interest of the scientific community in this subject, only the study by Ortiz et. al[22] presented an outcome related to identification of early signs of autism risk in the population with DS.

In that retrospective study, the most significant early signs from the perspective of expert evaluators were identified through home videos of children who had already been diagnosed with autism. These evaluations were made through an instrument based on the Modified Checklist for Autism in Toddlers (M-CHAT) and the Autism Diagnostic Interview-Revised (ADI-R). The main findings were associated with absence of shared attention, reduced interest in other people, lack of eye contact, absence of imitation and the presence of repetitive and stereotyped movements. It was also pointed out in that study that, even with the difficulty of the DS population in processing stimuli, the clinician's watchful eye is needed in order to detect difficulties regarding shared attention and interest in social contact, and thus enable early diagnosis of ASD and effective intervention.

Screening tests are indicated for all children, including those with DS, since it is already possible to start intervention at an early age, for rehabilitation of children with a probable diagnosis of autism as a comorbidity[17]. One of the differential diagnoses of autism is intellectual disability, but it is noteworthy that both in children with DS and in those with ASD, the comorbidity of intellectual disability is also frequent, thus requiring assessment using specific cognitive scales. This differential diagnosis becomes more difficult as the cognitive impact increases[7,24,28]. Because of this complexity, it has been reported that the diagnosis of ASD in DS is made at older ages than in the general population[13,16].

The diagnostic criteria most used as a reference, according to the studies included in the present review, were the DSM criteria. Most of the studies included in the present review used the DSM-IV and DSM-IV-TR as references, consequent to the years in which they were published [6-8,18,24,25,27,30,32].

It is known that there is a relationship between intellectual disability and ASD and that, when the intellectual limitation is more significant, autism symptoms will be more evident. Thus, according to the DSM-V criteria, the individual must present a difference between these two impairments for there to be an additional diagnosis of ASD in cases of DS[32].

In the ICD version 11, which is still in a preliminary version that is available on the WHO website, infantile autism and Asperger's syndrome are incorporated into ASD. Furthermore, categories have been created for this disorder, with and without intellectual and functional impairment[45].

In the studies included in this review, wide variation in the prevalence of ASD in cases of DS was observed. All studies evaluating the prevalence of ASD in cases of DS found higher rates of the disorder than in the general population[8,28,30-32]. These studies also indicated that there was higher prevalence of ASD among men[8,28,30,32] and among DS individuals with greater cognitive impairment.

Several factors may influence the data on the prevalence of ASD in DS. The studies included point to possible influences relating to the diagnostic criterion used, sample recruitment method, socioeconomic aspects of the population studied, age, evaluation method (direct observation or interviews with parents or teachers), proportions between men and women and intellectual functioning. Because of all these different factors, it is not yet possible to specify the prevalence of the disorder in cases of DS. However, there is still consensus that the prevalence is higher than in the general population. This causes us to remain alert to occurrences of this comorbidity in the population with DS.

In this systematic review, the importance of applying a validated instrument for formal evaluation of ASD during the follow-up of children with DS was observed. One important point in choosing instruments is that screening tests show higher rates of false-positive ASD diagnoses in the population with DS[7,8,28]. This occurs because the screening instruments are affected by cognitive impacts and other conditions associated with DS[8].

It has been shown that the Social Communication Questionnaire (SCQ) has higher sensitivity and lower specificity rates, when used in the population with DS. However, performance data regarding ASD assessment tools remain limited among individuals with DS[7,8].

In the studies included in this systematic review, the tools most used were the Autism Diagnostic Interview-Revised (ADI-Re) and the Autism Diagnostic Observation Schedule (ADOS), which are diagnostic tools that have not yet been validated in Brazil. Also used was the Archival Social Communication Questionnaire (SCQ), which is a screening tool already validated for use in Brazilian populations. When using these tools, it is important to verify the necessary adjustments for lower levels of intellectual functioning, as seen in cases of intellectual disability, whenever possible[24].

Studies have indicated that screening tools such as M-CHAT R and SCQ should be used only for initial evaluations, since they are not sufficient to determine the diagnosis[24,27,31]. Even though it has been shown that the SCQ presents good convergence with gold standard tools, this application alone is not enough for the diagnosis. Thus, the diagnosis should be reached by also considering anamnesis, interviews, physical examinations, detailed observation and application of validated diagnostic scales[27,31].

Star et al.[24] evaluated individuals with DS in association with severe or profound intellectual disability. The Autism Diagnostic Interview-Revised (ADI-R) and Adapted Pre-Linguistic Autism Diagnostic Observation Schedule (A-PL-ADOS) were used as tools. The latter is an instrument for evaluating nonverbal

children and adults who have severe and profound intellectual limitations. In a sample of 13 individuals who had DS with serious intellectual impairments, five met the diagnostic criterion for autism. That study, despite its small sample, demonstrated that not all individuals who have serious intellectual impediments will be diagnosed with ASD.

Several studies have compared the profiles of individuals with ASD and DS, and those with DS only. These data show that individuals with ASD and DS have greater social withdrawal, aggressive behaviors and anxiety and worse social engagement than children with DS[7,18,25,27,28,30,31]. In addition, individuals with both diagnoses show lower levels of adaptive functioning[18] and higher levels of repetitive and stereotyped behaviors, compared with those with DS alone[6,25,27].

At younger ages, when verbal communication skills are still developing, and especially in cases of DS (since delayed communication is expected in such cases), these characteristics will be more related to the qualitative aspects of communication (shared attention, interest, eye contact and imitation). Repetitive movements and stereotyping may also occur[23].

In older children, when speech is present, more stereotyped and repetitive speech is expected. When speech is absent, limitation or absence of gesticulation with communicative objectives is observed. Greater aggressiveness in social contact, lack of symbolic and functional play, as well as a tendency to align objects and have restricted interests, can also be observed[7,9,25].

To make the diagnosis of ASD in DS, it is also necessary to consider the interference of factors associated with the syndrome. Sensory conditions, such as hearing loss and motor difficulties, for example hypotonia, can affect the time and fluidity of these individuals' social and communicative behaviors. These signs are identified through screening methods, but differ qualitatively from the difficulty in basic social relationships seen in autism and may be misinterpreted if the examiner is not aware of the aspects relating to DS. Furthermore, it has been suggested that individuals with DS demonstrate executive function deficits that affect social and communicative relationships, but in a different way from the reciprocity problems associated with autism[8].

Moreover, regarding the diagnosis of ASD, it is important to consider the conditions within which a differential diagnosis is necessary. Down Syndrome Disintegrative Disorder (DSDD) has been described as a clinical syndrome in which people with DS may experience adaptive, social and cognitive regression. Although DSDD may present symptoms similar to those of ASD, its onset is later, generally occurring between the first and third decades of life. Also, in DSDD there are other symptoms such as catatonia and insomnia. The differential diagnosis should be based on a comprehensive psychosocial and medical assessment of possible secondary causes of behavioral change and regression[46].

Thus, to diagnose ASD in DS, clinicians should select appropriate tools, conduct analysis on intellectual development and functioning, make direct observations and conduct analysis on communication and social interaction and other aspects of social engagement, which are fundamental for distinguishing ASD from other developmental delays[8].

It is also worth mentioning the challenges faced by families with regard to the diagnosis of ASD. In a systematic review of the literature, it was observed that these challenges start with the search for a diagnosis, which may take a long time to be reached. There is the difficulty in dealing with the symptoms, and even in achieving access to rehabilitation, education and leisure services. These data emphasize the need to seek a systematic approach, starting from the time at which ASD is diagnosed, through appropriate care plans and support networks for children with ASD and their families[47]. These challenges are observed in the general population and may become greater in cases in which there is already a diagnosis of DS.

The present study had limitations with regard to the methodological and diagnostic system variations present in the 15 studies included, given that these factors interfere with identifying the best diagnostic practices. Future studies should use meta-analyses to address methodologies, in order to extract psychometric data from diagnostic practices in the population with DS.

Although we were unable to identify the most appropriate tool for evaluating ASD in DS, since the psychometric qualities of these tools are not well delimited for this population, this systematic review allowed us to understand that the clinical diagnosis of ASD in DS should not focus only on test results. Clinical experience and interdisciplinary evaluation will allow greater understanding of whether there is any qualitative difference in social engagement and cognitive impairment that would justify the second diagnosis of ASD in DS.

We highlight the need for early evaluation and intervention in cases of ASD associated with DS, since these will be determinants for better development, quality of life and social inclusion.

In conclusion, individuals with DS have higher prevalence of ASD than the general population, and screening should be universal, to enable early detection of signs and effective intervention, thus improving the prognosis in relation to the potential for development and better quality of life. The present systematic review showed that use of ASD diagnostic tools in the population with DS requires careful complementary and multidisciplinary clinical evaluation. In addition, there is a need to evaluate the psychometric properties of these tools in the population with DS, and whether tools that were created to evaluate people with intellectual disabilities present more affirmative results for the population with DS.

The need for additional diagnoses of ASD among individuals with DS should be determined based on the qualitative difference between social and cognitive impairments. It is also important to highlight the need to assess signs of autism risk in the first year of life, so that it becomes possible to analyze the qualitative aspects of social interaction and thus to initiate more timely intervention.

It is necessary to provide tools for early detection of autism risk among infants and for diagnostic evaluation of ASD in DS, based on developmental analyses in healthcare services, so that better results can be achieved with earlier interventions.

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My journey after a mild infection with COVID-19: I want my old brain back

Minha jornada após uma infecção leve por COVID-19: eu quero meu cérebro antigo de volta

Clarissa Lin YASUDA[1, 2]

ABSTRACT

Although neurocognitive dysfunction has been observed after infection by SARS-CoV-2, few studies have detailed these alterations or demonstrated their impact on daily life activities and work. Here, I describe the sequence of events following a mild COVID-19 infection in August 2020 (which now is described as "post-COVID syndrome") and comment on my ensuing limitations associated with cognitive difficulties, headache, fatigue and sleepiness. Furthermore, I discuss the efforts that I have made to recover from my infection since its beginning and the strategies adopted for living with persistent restrictions in terms of cognitive performance.

Keywords: COVID-19; Cognitive Dysfunction; Post-COVID Syndrome; Fatigue.

RESUMO

Embora a disfunção neurocognitiva tenha sido observada após a infecção por SARS-Cov2, poucos estudos detalharam essas alterações ou demonstraram seu impacto nas atividades de vida diária e trabalho. Aqui eu descrevo a sequência de eventos após uma infecção leve por COVID-19 em agosto de 2020 (agora considerada Síndrome pós-COVID) e comento as limitações associadas às dificuldades cognitivas, dor de cabeça, fadiga e sonolência. Além disso, eu caracterizo o esforço de recuperação desde o início e as estratégias para conviver com restrições persistentes em termos de desempenho cognitivo.

Palavras-chave: COVID-19; Disfunção Cognitiva; Síndrome Pós-COVID; Fadiga.

I am a 46-year-old neurologist working as an assistant professor of neurology at a tertiary hospital in Brazil. In March 2020, I designed the NeuroCovid study at the University of Campinas, combining MRI analyses, neuropsychological and clinical evaluation and immunological analyses. I chose this multimodal approach because I was involved in epilepsy research and neuroimaging (neuroimmunology of multiple sclerosis was the focus of my undergraduate research project for five years) before the pandemic. We started evaluating post-COVID volunteers in July 2020, and I became infected in August 2020. It was a mild infection without fever, dysgeusia, anosmia or respiratory symptoms. I presented headache (worsened migraine), severe abdominal pain, sleepiness, diarrhea, vomiting and hiccups; it was winter, and I felt unusually cold in Campinas, Brazil (I have experienced -45 Celsius during winter in Canada). These symptoms terminated within ten days (except the headache), and I truly believed it was over. I was happy to be back at the hospital to continue to evaluate the post-COVID subjects.

Approximately 3-4 weeks after the acute stage, I knew my migraine had worsened, and I could not tolerate the atenolol (50 mg) that I had been using as a prophylactic for migraine and hypertension treatment. This intolerance was mainly during swimming practice. At the same time, I noticed excessive somnolence during the day, associated with an increase of 1.5-2.0 hours of night sleep. It felt awkward because I had always been an energetic person who usually had 6-7 hours of sleep. Now I needed 8-9 hours of rest, yet I was also experiencing daytime somnolence. I realized that I was having difficulties writing a grant proposal and performing more complex statistical analyses. I tried modafinil because I had daytime somnolence; it improved the somnolence but not my cognitive performance.

At that moment, I realized that I had some cognitive dysfunction impairing my academic tasks. There were no difficulties

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with daily tasks or patient care, except the fatigue and somnolence. I knew my difficulties were mainly in relation to more complex tasks (sophisticated statistical models and writing papers). I missed deadlines; I could not write papers as fast as before. I also missed some meetings (I was distracted and sleepy) and could no longer perform simultaneous tasks, as I used to. I noticed that I had slower brain processing speed and inattention. I had to struggle with excessive daytime sleepiness and fatigue, along with a combination of difficulties and frustration associated with symptoms of depression and anxiety.

However, I am grateful for the support of my team of postgraduate students and colleagues. I never tried to hide my symptoms and difficulties; they have supported me since the beginning. We have discussed the drugs that I have been trying because this is a new virus[1] and almost nothing about any persistent neurocognitive dysfunction that it might cause is known[2]. I decided to use levetiracetam for migraine prophylaxis[3] because I knew it could somehow improve my brain connectivity[4]. It was a good choice because it reduced the migraine attacks and somehow reduced the excessive night sleep by 0.5-1.0 hour. Nevertheless, I had to adjust the dose due to worsening symptoms of depression with the high dose; therefore, I combined it with an antidepressant (agomelatine).

At the end of 2020, I realized I had to adjust to the new situation and slow down my pace of life and academic activities. I had already resumed my swimming workouts (2000 m, with variable intensity and snorkel) 2-3 times/week, combined with Pilates and one day of strength exercise. There was hope that intensive aerobic exercise would help recover the cognition[5].

In January 2021, I decided to try low doses of lisdexamfetamine, which finally helped me work, although not as fast or efficiently as before COVID-19. However, I do not tolerate it well and only use it 2-3 times on weekdays, especially on busy days at work. I manage my routine with an online agenda (which I never needed before). I need to sleep more than before; I do my swimming workouts and respect my fatigue and tiredness. I take drugs that I never imagined I would need. After each dose of vaccine (COVID-19 and meningitis), it was intriguing that I felt I lost each slight improvement for approximately four weeks.

After 16 months (end of 2021), I finally thought that part of my old brain was coming back. Some automatic connections (part of my personality) that I had lost are now back, such as the names of several patients and their histories. It seems that I have a slight improvement in brain processing speed. Roughly, if I lost 30% of my natural speed after COVID-19, I think that I have recovered 10%. It is sad and disappointing. It is embarrassing and painful not to recognize myself.

I believe that transparency about all the uncertainties surrounding the new coronavirus is needed[1]. Not much data on the negative impact of prolonged symptoms is available, nor are the effects of SARS-CoV-2 on either the central or the peripheral nervous system understood[6]. I am frightened because previous studies showed the vulnerability of the hippocampus to coronavirus[2]. I have studied hippocampal atrophy in epilepsy for almost 20 years, and now I face the risk that the new coronavirus will act as an initial precipitating injury and eventually cause hippocampal atrophy and epilepsy. Or it may accelerate a neurodegenerative process with dementia[2].

In an article now submitted (in collaboration with other researchers), we already observed grey matter atrophy in the orbitofrontal cortex of mildly infected individuals (81 individuals with an average age of 37 years), which was associated with poor performance in the trail-making test[7]. This has also been recently reported in a larger group (401 subjects with an average of 62 years)[8]. In our study[7], we identified that there was higher frequency of symptoms of anxiety and depression approximately two months after the COVID-19 diagnosis, which was in line with findings from an extensive study of survivors[9].

I fear for the numerous survivors of COVID-19 who do not have access to medical attention for their post-COVID symptoms. I have received several emails from individuals with similar (or worse) symptoms; they complain that most physicians do not understand or believe in the multitude of symptoms. It is frustrating because I know all these symptoms are real and compromise our life and work. As well described previously by other doctors[1] and in another study[10], the mental health system needs to become prepared to receive survivors with different neuropsychiatric symptoms, including anxiety and depression.

Longitudinal studies on these symptoms need to be continued in order to more precisely understand the predisposing factors for neurocognitive and cerebral alterations associated with SARS-CoV-2. Given the uncertainties about the underlying mechanisms, COVID-19 cannot be prevented or treated specifically; nor can it be predicted whether the alterations that it causes are temporary, permanent or progressive.

We are starting a new project to offer cognitive rehabilitation to survivors with post-COVID dysfunction. It is a small, local project. Nevertheless, we expect to bring hope to individuals and simultaneously collect multimodal data to understand possible mechanisms behind neurocognitive dysfunction.

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Brazilian Academy of Neurology practice guidelines for stroke rehabilitation: part I

Diretrizes da Academia Brasileira de Neurologia para reabilitação do acidente vascular cerebral: parte I

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ABSTRACT

The Guidelines for Stroke Rehabilitation are the result of a joint effort by the Scientific Department of Neurological Rehabilitation of the Brazilian Academy of Neurology aiming to guide professionals involved in the rehabilitation process to reduce functional disability and increase individual autonomy. Members of the group participated in web discussion forums with predefined themes, followed by videoconference meetings in which issues were discussed, leading to a consensus. These guidelines, divided into two parts, focus on the implications of recent clinical trials, systematic reviews, and meta-analyses in stroke rehabilitation literature. The main objective was to guide physicians, physiotherapists, speech therapists, occupational therapists, nurses, nutritionists, and other professionals involved in post-stroke care. Recommendations and levels of evidence were adapted according to the currently available literature. Part I discusses topics on rehabilitation in the acute phase, as well as prevention and management of frequent conditions and comorbidities after stroke.

Keywords: Stroke; Guideline; Neurological Rehabilitation; Practice Guidelines as Topic.

RESUMO

As Diretrizes Brasileiras para Reabilitação do AVC são fruto de um esforço conjunto do Departamento Científico de Reabilitação Neurológica da Academia Brasileira de Neurologia com o objetivo de orientar os profissionais envolvidos no processo de reabilitação para a redução da incapacidade funcional e aumento da autonomia dos indivíduos. Membros do grupo acima participaram de fóruns de discussão na web com pré-temas, seguidos de reuniões por videoconferência em que as controvérsias foram discutidas, levando a um consenso. Essas diretrizes, divididas em duas partes, focam as implicações de recentes ensaios clínicos, revisões sistemáticas e metanálises sobre reabilitação do AVC. O objetivo principal é servir de orientação a médicos, fisioterapeutas, fonoaudiólogos, terapeutas ocupacionais, enfermeiros, nutricionistas e demais profissionais envolvidos no cuidado pós-AVC. As recomendações e níveis de evidência foram adaptados de acordo com a literatura disponível atualmente. Aqui é apresentada a Parte I sobre tópicos de reabilitação na fase aguda, prevenção e tratamento de doenças e comorbidades frequentes após o AVC.

Palavras-chave: Acidente Vascular Cerebral; Guia; Reabilitação Neurológica; Guias de Prática Clínica como Assunto.

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INTRODUCTION

Stroke is the second leading cause of death and disability worldwide[1,2]. It is estimated that in 2016, there were almost 260,000 stroke cases, approximately 107,000 deaths, and more than 2.2 million adjusted life years lost due to disability following a stroke in Brazil[3,4]. Worldwide, stroke is the most prevalent neurological disease that needs rehabilitation, with 86 million disabled individuals[5]. More than two-thirds of individuals after stroke receive rehabilitation services after hospitalization[6]. Despite the development and support of stroke centers and national societies in Brazil to raise awareness of stroke symptoms, only a minority of stroke patients in the acute phase receive thrombolytic therapy or thrombectomy. Consequently, many stroke survivors have residual functional deficits. Stroke rehabilitation differs in many regions in Brazil according to socio-economic conditions. In large urban centers stroke patients are referred to a rehabilitation center by the time of discharge; however, in most parts of the country stroke survivors have few opportunities to initiate or continue rehabilitation after the acute phase. This data is lacking in Brazil and has been evaluated by the Access to Rehabilitation Study across 17 public health centers in Brazilian cities in the North, Northeast, West, Southeast and South of Brazil[7]. Therefore, the need for effective rehabilitation of stroke patients remains an essential part of the continuum of stroke treatment.

Considering this premise, the Scientific Department of Neurological Rehabilitation of the Brazilian Academy of Neurology made efforts to draft the first Brazilian Guidelines for Stroke Rehabilitation to guide professionals involved in the rehabilitation process to reduce functional disability and increase the autonomy of individuals. The members of the group participated in discussion forums on the web with predefined themes, followed by videoconference meetings in which

controversies were discussed, leading to a consensus. For the preparation of the Brazilian Guidelines for Stroke Rehabilitation, several national co-authors, with prior knowledge in their areas of expertise, were asked to write the suggested topics following criteria defined by the coordinators of these guidelines. The original texts were adapted to follow a format in which, after the general information, the Recommendations for each intervention were added.

The present work focuses on recent clinical trials, meta-analyses, and systematic reviews in stroke rehabilitation literature. The main objective of this paper is to guide physicians, physiotherapists, speech therapists, occupational therapists, nurses, nutritionists, and other professionals involved in post-stroke care. Recommendations and levels of evidence have been adapted according to currently available literature.

We have sought to provide visibility to broader rehabilitation aspects based on the intervention concepts proposed in the International Classification of Functioning, Disability, and Health[8]. The rehabilitation strategies included in this guideline cover the different stroke phases: hyper-acute (0-24 hours), acute (1-7 days), early subacute (7 days-3 months), late subacute (3-6 months), and chronic phases (> 6 months)[9]. Most studies in stroke rehabilitation include participants over the age of 18 years[10]. In clinical practice, the same interventions are used for all ages. Therefore, the Recommendations of this guideline can be applied to all individuals after a stroke. In addition, these guidelines also aim to highlight the issues of accessibility and palliative care. The guidelines have been divided into two groups. Part I includes topics on rehabilitation in the acute phase as well as prevention and management of the most frequent conditions and comorbidities after stroke. A section on Secondary Stroke Prevention was included in Part I because the incidence of stroke recurrence is higher in the first months after stroke[9] and it is a potential and preventable complication that impairs the process of rehabilitation as do falls, deep vein thrombosis and others. More detailed information about Secondary Stroke Prevention is available at https://www.ahajournals.org/doi/pdf/10.1161/STR.0000000000000375. Table 1 shows daily doses, adverse effects, and duration of follow-up during the study periods of drugs used in the management of central pain, mood disorder, sleep disorder, and epilepsy after stroke. Part II covers the topics on rehabilitation of neurological deficits and disabilities after stroke, and transitions to community rehabilitation and palliative care. A table with validated scales to assess neurological impairment, disability, and quality of life is included in Part II. At the end of Part II, supporting material includes suggestions for patients, caregivers, and other health professionals, including legal rights after stroke,

Table 1. Daily doses, adverse effects, and duration of follow-up during the study periods of drugs used in the management of central pain, mood disorder, sleep disorder, and epilepsy after stroke.

Comorbidities	Drug	Daily dose	Duration of study follow-up	Adverse effects
Central Pain	Amitriptyline[39]	Start with 25 mg, up to 75 mg	4 weeks	Dry mouth, urinary retention, drowsiness, and confusion
	Lamotrigine[39]	Start with 25 mg, up to 200 mg	8 weeks	Rash and severe headache
	Duloxetine[42]	Start with 30 mg, up to 60 mg	3 weeks	Nausea, agitation, and drowsiness
	Pregabalin[43]	Start with 150 mg, up to 600 mg	12 weeks	Somnolence, and peripheral edema
	Gabapentin[39]	Start with 900 mg, up to 2400 mg	8 weeks	Dizziness and drowsiness
	Fluvoxamine[44]	Start with 50 mg, up to 125 mg	2 to 4 weeks	Drowsiness, insomnia, and restlessness
Mood disorder	Nortriptyline[79]	Start with 25 mg, up to 100 mg	6 weeks	Dry mouth, urinary retention, drowsiness, and confusion
	Trazodone[79]	Start with 25 mg, up to 200 mg	32 days	Dry mouth, urinary retention, drowsiness, and confusion
	Citalopram[79]	Start with 5 mg, up to 10 mg	6 weeks	Nausea, drowsiness, weakness, dizziness, anxiety, trouble sleeping, and sexual dysfunction
	Fluoxetine[79]	Start with 10 mg, up to 10 mg	6 weeks to 3 months	Nausea headaches, insomnia, diarrhea, weakness, and anxiety
	Reboxetine[79]	4 mg	16 weeks	Dry mouth, constipation, and sexual dysfunction
Sleep disorders	Trazodone[110]	100 mg	1 week	Dry mouth, urinary retention, somnolence, and confusion
Epilepsy	Levetiracetam[157]	Start with 500 mg up to 300 mg	52 weeks	Fatigue, drowsiness, skin eruptions or allergies
	Lamotrigine[157]	Start with 25 mg up to 200 mg	52 weeks	Dizziness and rash
	Controlled release carbamazepine[157]	Start with 200 mg up to 1600 mg	52 weeks	Confusion, skin eruptions or allergies, nausea, and vomiting

as well as functional accessibility laws and the care network. We have also included a chapter on the possibilities of paths to be followed in the future, based on promising approaches to rehabilitation after stroke.

We hope that this pioneering Brazilian work will soon be followed by new versions that can improve and update the content presented here.

RECOMMENDATION RATING AND LEVEL OF EVIDENCE

The recommendation rating and level of evidence used in these guidelines is an adaptation of the framework established by the American Heart Association[10].

Recommendations

Class I: There is evidence and/or consensus that intervention is effective.

Class II: There is conflicting evidence and/or divergence of opinions about the effectiveness and usefulness of intervention.

a) Although there is divergent evidence on the usefulness and effectiveness of intervention, the Recommendations are in favor of intervention;

b) Utility and effectiveness are less established by the evidence or opinions.

Class III: There is evidence and/or consensus that intervention is not useful or effective and may cause harm.

Levels of evidence

A: Data are obtained from multiple randomized clinical trials or meta-analyses.

B: Data are obtained from a single randomized or non-randomized study.

C: Consensus and expert opinion, case studies, or usual (standardized) treatments.

ORGANIZATION OF POST-STROKE REHABILITATION CARE (LEVELS OF CARE)

The ideal organization of post-stroke rehabilitation care includes rehabilitation during the acute phase in stroke units, nursing home facilities, inpatient, home-based and outpatient rehabilitation services[11]. The level of care to which patients will be referred depends on the status of clinical conditions and the degree of neurological impairment and disability. These services should be delivered by a multidisciplinary team with physicians, physical, occupational, speech and language therapists, physical educators, social workers, psychologists, and psychiatrists[10]. Integration within the whole system of health and social community care is necessary. At all levels of care, specific needs should be assessed, such as swallowing, hydration and nutrition, continence, mobility, activities of everyday life, communication, cognition, alertness and engagement, vision, hearing, perception, behavior, emotional, need for assistance, and social engagement[11].

The level of care after stabilization of the acute phase will depend on the degree of dependence in activities of daily living, status of comorbidities and neurological impairments and disabilities. It is suggested that the Assessment for Rehabilitation Tool (ART)[12], a pathway and decision tool that considers individual particularities, such as age, prognosis, neurological impairment and disability domains, level of function, and management level available, i.e., inpatient, home or outpatient rehabilitation. ART also considers exceptions where there is no need to initiate rehabilitation, such as the patient returning to pre-morbid function, coma and/or unresponsiveness or palliative care.

Recommendation

- Organized, coordinated, and multidisciplinary care should be available to patients after stroke. (Recommendation I-A).

REHABILITATION IN THE ACUTE PHASE

This topic will address themes of relevance to rehabilitation in the acute phase of stroke that do not involve reperfusion or clinical stabilization interventions, as there are specific guidelines for that purpose[13,14].

All patients must be evaluated by a multidisciplinary team using an objective framework, through the application of scales to assess the risk of pulmonary aspiration, malnutrition, pressure ulcers, deep vein thrombosis, neurological deficits, focal and global disabilities, and psychiatric disorders [9]. A multidisciplinary team should include physicians, physical, occupational, speech and language therapists, physical educators, social workers, psychologists, and psychiatrists[11].

All rehabilitative interventions should be initiated as soon as the impairments and disabilities after stroke are diagnosed and should be continued as outpatient rehabilitation in the community[11,15]. Some conditions are contraindications to the commencement of rehabilitation: early deterioration, immediate surgery, another serious medical illness or unstable coronary condition, systolic blood pressure lower than 110 mm Hg or higher than 220 mm Hg, oxygen saturation lower than 92% with oxygen supplementation, resting heart rate of less than 40 beats per min or more than 110 beats per min, and temperature higher than 38·5°C[16]. Mobilization out of bed or any other intervention should be initiated only if the patient's blood pressure does not drop by more than 30 mm Hg on achievement of an upright position[16].

Regarding mobilization in the acute phase, the AVERT[16] multicenter trial showed that the group that received very early mobilization, within 24 hours of stroke onset, had a lower chance of favorable results at three months. Mobilization to maintain range of motion, sensory stimulation and body posture

change is not considered intensive rehabilitation[16]. A multicenter study (HeadPoST)[17] did not find differences between outcomes when comparing a group that rested with the head in the horizontal position, without elevation (i.e., 0º) in the first 24 hours post-randomization and another group in which the head was elevated to at least 30º.

COMPREHENSIVE STROKE CENTER

The Comprehensive Stroke Center (CSC), a combined and integrated service for acute-phase care and rehabilitation, offers the best outcomes[18]. Care in a CSC reduces deaths by two and dependence by six in every 100 patients and promotes the return home of six individuals[18]. It is a cost-effective intervention[15,18,19]. The benefits of CSCs apply to all stroke cases, regardless of severity, age, sex, and whether the stroke is ischemic, hemorrhagic, or a transient ischemic attack[18].

Despite the limited number of CSCs in Brazil, patients must be admitted to these units in the acute phase, preferably within the first hours of the stroke[20]. A suspicious case evaluated in a service not dedicated to stroke must be immediately transferred to the nearest qualified unit. All services must offer protocols for managing fever, blood pressure, blood glucose, and dysphagia[20]. Additionally, patients must have their rehabilitation needs assessed within 24-48 hours of admission by members of a multidisciplinary team[11,15].

There is evidence that individuals with mild stroke may have impairments neglected by professionals in multidisciplinary teams[21]. On the other hand, severely affected patients are not referred to rehabilitation services[22] . To avoid these situations the ART[12] can be used to provide an appropriate course of post-stroke rehabilitation.

Recommendations

- All patients in the acute stroke phase must be admitted to specialized stroke care units where they can receive care from a multidisciplinary team. (Recommendation I-A);
- All patients in the acute stroke phase must be seen by specialized professionals and objectively assessed, with the use of scales, for risk of pulmonary aspiration, malnutrition, pressure ulcers, deep vein thrombosis, neurological deficits, focal and global disabilities, and psychiatric disorders. (Recommendation I-A);
- Very early and high-intensity mobilization within 24 hours of stroke onset is not recommended. (Recommendation III-A);
- Keeping the head in the horizontal position, without elevation, did not show benefit in the acute post-stroke phase. (Recommendation III-A).

CONTRACTURES

Contractures are defined as the shortening or stiffening of muscles, skin, or connective tissue resulting in decreased movement and range of motion[23]. Observational studies have shown the incidence of contractures to be between 15% and 60%, mainly in patients with greater motor impairment[24]. The predictors of contractures include spasticity, muscle weakness, upper limb dysfunction, impaired dexterity, and pain[23].

Few studies have addressed the treatment of contractures after stroke. Systematic reviews and randomized studies evaluating passive movement and positioning with limb resting orthoses have shown little evidence of benefits in prevention and treatment of contracture[25-29]. A dynamic, progressive orthosis fixed in the forearm to lengthen the wrist in extension in post-stroke hemiplegic patients improved the range of motion and resistance to passive movement, but this benefit was not sustained[30]. A recent meta-analysis of several neurological conditions, including those found in post-stroke patients, for interventions to reduce muscle contractures, did not find convincing evidence in favor of non-surgical interventions, such as stretching, botulinum toxin, electrical stimulation, physical activity, and robot-assisted therapies[31]. Surgical release of the brachial, brachioradialis, and biceps muscles improved pain, passive range of motion, and decreased spasticity of the elbow with a contracture[32].

Recommendations

- Progressive casting and adjustable orthotics may be considered to reduce mild to moderate contractures of the elbow joints. (Recommendation IIb-B);
- Resting ankle and wrist orthotics may be used to prevent contractures. (Recommendation IIb-B);
- The effects of stretching, botulinum toxin, electrical stimulation, physical activity, and robot-assisted therapies have not been well established. (Recommendation IIb-B);
- Surgical interventions in the brachial, brachioradialis, and biceps muscles in elbow contractures might be considered. (Recommendation IIb-B).

PHYSICAL DECONDITIONING

People who have had a stroke spend 81% of the day in sedentary time, increasing the risk of glucose intolerance, diabetes, heart disease, mood disorders, cognitive decline, decreased muscle mass, increased dependency for daily activities, stroke recurrence, and death. Physical activity (PA) plays a central role in reducing these risks and improving cardiovascular performance[33]. PA also has benefits for bone structure, fatigue, cognition, mood, wellness, sensation, gait speed, social isolation, and has the potential to reduce treatment costs[34].

The Recommendations below are based on the American and Canadian guidelines[33,35].

Recommendations

- It is recommended that all post-stroke individuals participate in PA interventions once they are clinically stable. (Recommendation I-A);
- Assessment of PA must be performed by qualified professionals. (Recommendation I-B);
- Monitoring of heart rate, blood pressure, and rating of perceived exertion before, during, and after completion of the test is recommended. Cardiac monitoring is recommended if stress testing is performed. (Recommendation I-A);
- Aerobic training is recommended in a rehabilitation program with the addition of muscle strengthening, task-oriented activities of motor control, balance, gait, and functional use of the upper limb. (Recommendation I-C);
- It is recommended that a PA program be developed and supervised by physical therapists or cardiovascular rehabilitation specialists. (Recommendation I-C);
- Exercises to activate a large group of muscles for a sufficient period to produce aerobic effort are recommended. (Recommendation I-B);
- A minimum period of eight weeks is recommended to obtain significant effects, followed by PA being maintained indefinitely. (Recommendation I-B);
- A frequency of three times a week of PA and lighter physical activities on other days is recommended. (Recommendation I-B);
- Sessions lasting more than 20 minutes are recommended, with a period of five minutes of warm-up and relaxation before and after each session. (Recommendation I-B);
- It is recommended that exercise intensity has individualized parameter values based on the percentage of heart rate reserve, percentage of maximum heart rate, and individual perceived exertion. (Recommendation I-B);
- It is recommended that the effects of PA be monitored by measures of cardiovascular capacity, blood pressure, lipid profile, fasting blood glucose, waist circumference, medication adherence, tobacco use, cognition, mood, and sleep quality. (Recommendation I-B);
- A PA program is recommended to be continued by the patient so that he/she can practice on their own. (Recommendation I-B);
- Clinical dates and stress tests with sub-maximal limits of tolerance should be used for prior evaluation of PA as a reference. (Recommendation IIa-C).

CENTRAL PAIN

Central pain after stroke is defined as neuropathic pain resulting from spinothalamic or thalamocortical tract lesions in the central nervous system (CNS), affecting patients in the acute or chronic phase after a stroke[36]. As a diagnostic criterion, it is necessary that the pain that occurs after a stroke should be located in a body area corresponding to the CNS lesion and not caused by peripheral neuropathic pain or nociceptive stimuli[37]. Numbness, tingling, or needling sensations may also be present. The onset of symptoms is always gradual, coinciding with improvement in sensory perception and the onset of dysesthesia[38]. The pain can be intermittent or constant and can manifest as hyperalgesia or allodynia[36].

Amitriptyline and lamotrigine can be first-line pharmacological treatments[39-41]. Duloxetine, as an adjuvant treatment, has shown positive effects in pain reduction[42]. Pregabalin and gabapentin can be considered second-line medications, and pregabalin has a favorable secondary effect of reducing anxiety and improving sleep[43]. Fluvoxamine reduced pain in an open observational study[44]. Levetiracetam and carbamazepine do not improve post-stroke neuropathic pain symptoms[39]. There is no evidence for the use of opioids in the treatment of central post-stroke pain[45]. Table 1 shows the drugs with favorable outcomes.

Steroids, intravenous infusions of lidocaine, ketamine propofol, repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation, and spinal electrical stimulation showed favorable results[46,47]. However, they should be reserved for refractory cases[48].

Recommendations

- Amitriptyline and lamotrigine should be used as first-line treatments for neuropathic pain. (Recommendation I-A);
- Duloxetine can be considered as an adjuvant treatment. (Recommendation IIa-B);
- Pregabalin and gabapentin can be used as second-line medication. (Recommendation IIa-B);
- Fluvoxamine can be considered. (Recommendation IIb-B);
- rTMS, deep brain, or spinal electrical stimulation may be considered in refractory cases. (Recommendation IIb-B);
- Levetiracetam, carbamazepine, and opioids are not recommended. (Recommendation III-B).

PAINFUL SHOULDER

Painful shoulder (PS) after stroke has an incidence range of 9% to 73%, depending on the diagnostic criteria used in the studies[49]. It can appear in the first two weeks but is more frequent between the second and fourth months after stroke[50].

The most frequent causes are spasticity, adhesive capsulitis, and glenohumeral subluxation[49].

Evidence for the use of shoulder orthoses to prevent dislocation, decrease pain, and improve function is conflicting[50,51]. These orthoses can improve gait efficiency[51]. Placing an orthosis on an already dislocated shoulder can reduce vertical subluxation on imaging examinations, but the improvement is not maintained after removing the orthosis[52].

Gentle joint alignment movements and mobilization with external rotation and abduction may be beneficial[49]. Analgesics, such as acetaminophen and ibuprofen, and neuromodulators can be used[49]. Botulinum toxin has positive effects on pain reduction and functional improvement and increases the range of motion[53]. Subacromial corticosteroid injections can be used if the pain is caused by trauma or inflammation of the subacromial region[54]. Suprascapular nerve blocks, with and without corticosteroids, increased passive range of motion[55]. A functional bandage reduced shoulder subluxation, improved upper limb motor function and activities of everyday life, and reduced pain when compared to placebo[56,57].

Conventional acupuncture and electroacupuncture have shown uncertain benefits[58]. Electrical functional stimulation can be beneficial in reducing pain and regaining independence in activities of everyday life[59]. The pulley system should not be used[60].

Recommendations

- Functional bandages are recommended for PS after stroke. (Recommendation I-A);
- Botulinum toxin injection in the subscapular and pectoral muscles is recommended, mainly if PS is associated with spasticity. (Recommendation I-A);
- Arm position and support during rest, arm protection, and support during functional movements can be considered to prevent PS. (Recommendation IIa-C);
- Functional electrical stimulation can be considered in the prevention of PS. (Recommendation IIa-A);
- PS can be treated with gentle alignment movements and mobilization with external rotation and abduction. (Recommendation IIa-B);
- Analgesics, such as acetaminophen and ibuprofen, and neuromodulators, can be used. (Recommendation IIa-A);
- Subacromial corticosteroid injections and suprascapular nerve block are reasonable options for hemiplegic PS. (Recommendation IIb-B);
- Acupuncture, as an adjunctive treatment, has an uncertain value. (Recommendation IIb-B);
- The use of orthotics to prevent dislocations is uncertain. (Recommendation IIb-B);
- The pulley system should not be used for the prevention of PS. (Recommendation III-A).

PRESSURE INJURY

Pressure injury (PI) is defined as localized injury to the skin and/or underlying tissues, usually over a bony prominence, resulting from pressure or pressure in combination with shear[61]. Its etiology is multifactorial and can include advanced age, cognitive, physical, and sensory impairment, comorbid conditions, malnutrition, and limited mobility.

The PI classification of the Associação Brasileira de Estomatoterapia (SOBEST) and Associação Brasileira de Enfermagem em Dermatologia (SOBENDE) is recomended in these guidelines[62].

Although not specific to patients after stroke, the Braden Scale is a widely used tool for assessing pressure injury risk and had moderate predictive validity[63]. The Sunderland Scale and the Cubbin & Jackson Revised Scale can also be used and have been translated and validated in Portuguese[64].

The Recommendations for the prevention and care of PI after stroke are based on an adaptation of the latest version of the Prevention and Treatment of Pressure Ulcers/Injuries Quick Reference Guide published by the European Pressure Ulcer Advisory Panel, National Pressure Injury, Advisory Panel, and Pan Pacific Pressure Alliance[65].

Recommendations

- Skin assessment for the risk of pressure injuries over pressure points is recommended in subjects with impaired mobility, sensory perception, older age, and diabetes. (Recommendation I-A);
- Structured PI risk assessment and PI classification are recommended. (Recommendation I-C);
- The skin of individuals at risk of PI should be inspected to identify the presence of erythema. (Recommendation I-A);
- The skin of individuals at risk of PI should be kept clean and appropriately hydrated. (Recommendation I-C);
- Full-thickness excision of pressure sores, including abnormal skin as well as granulation and necrotic tissues, should be performed. (Recommendation I-B);
- The following factors should be considered for PI surgery: comorbidities, surgical risk, the individual's clinical condition, and the likelihood of healing with non-surgical versus surgical interventions. (Recommendation I-C);
- Airflow mattresses can be considered for stroke patients at risk of developing PI. (Recommendation IIa-B);
- Pulsed current electrical stimulation to facilitate wound healing in recalcitrant PI should be considered. (Recommendation IIa-A);
- High absorbency incontinence products can be used to protect the skin in stroke patients with urinary incontinence at risk of PI. (Recommendation IIa-B);

- Post-stroke individuals at risk of PI can undergo nutritional assessment. (Recommendation IIa-B);
- Stroke patients with, or at risk of, pressure injuries can be repositioned on an individualized schedule. (Recommendation IIa-B);
- Hydrogels, hydrocolloids, and polymeric wound dressings for non-infected stage II PI can be considered. (Recommendation IIa-B);
- Wound dressing with calcium alginate for stages III and IV PI with moderate exudates can be considered. (Recommendation IIa-B);
- Hydrogel for stage III and IV non-infected PI with minimal exudate is recommended. (Recommendation IIa-B);
- Subjects at risk of PI may be encouraged to sit out of bed for limited periods. (Recommendation IIb-B);
- Offering high-calorie, high-protein fortified foods or nutritional supplements in addition to the usual diet might be considered for stroke individuals at risk of PI. (Recommendation IIb-C);
- The benefits of topical antiseptics that are active against biofilms are uncertain. (Recommendation IIb-C).

NUTRITIONAL SUPPORT

After a stroke, individuals are susceptible to nutritional changes due to a variety of symptoms and sequelae. The risk factors for nutritional changes after stroke are dysphagia, immobility, impaired cognition, as well as reduced food and macro- and micronutrient intake[66]. Approximately 50% of stroke patients suffer from malnutrition[67].

For individuals without dysphagia and who are not malnourished or at risk of malnutrition, the use of oral nutritional supplements is not indicated[66]. Oral supplements are indicated for individuals who are able to eat and have been diagnosed with malnutrition or were at risk of malnutrition during hospital admission[66].

Individuals with dysphagia who need food texture modification or fluid thickening should be referred to a dietitian to ensure adequate nutrition and water intake[66]. If oral feeding is not possible, feeding by a nasogastric/enteric tube is recommended[67]. Patients with severe dysphagia, probably lasting longer than seven days, should receive early enteral nutrition, preferably in the first 72 hours[67]. If enteral nutrition is needed for a period longer than three weeks, a percutaneous endoscopic gastrostomy is recommended[67].

Sarcopenia is a complication of malnutrition after stroke, and it is associated with an increased risk of falls, fractures, functional disability, rehabilitation difficulties, and mortality[68]. Sarcopenia is caused by increased inactivity, muscle atrophy, neural loss, and bed rest[69,70]. The most severe muscle loss occurs in the limb affected by the brain injury[71]. The instrument recommended for identifying the risk of developing sarcopenia is the SARC-F (sluggishness, requiring assistance in walking, rising from a chair, climbing stairs, falls) questionnaire[72]. It assesses muscle strength, muscle quantity/quality, and physical performance.

Recommendations

- Screening for the risk of malnutrition is highly recommended within the first 48 hours of hospital admission. (Recommendation I-C);
- If oral feeding is not possible, feeding by a nasogastric/enteric tube is recommended. (Recommendation I-A);
- Every patient with dysphagia who needs food texture modification or fluid thickening should be referred for nutritional assessment to ensure adequate nutrition and water intake. (Recommendation I-C);
- Percutaneous endoscopic gastrostomy is recommended when there has been a need for enteral nutrition for more than three weeks. (Recommendation I-A);
- Patients should be screened for the risk of sarcopenia using the SARC-F questionnaire. (Recommendation I-C);
- The use of oral nutritional supplements is probably recommended for individuals who are able to eat and have been diagnosed with malnutrition or were at risk of malnutrition during hospital admission. (Recommendation IIa-C);
- For patients with severe dysphagia lasting longer than seven days, early enteral nutrition is probably recommended. (Recommendation IIa-C);
- The use of oral nutritional supplements is not recommended for patients without dysphagia and those who are not malnourished or at risk of malnutrition. (Recommendation III-C).

MOOD DISORDERS

Post-stroke depressive disorder (PSDD) is defined by the presence of a significantly depressed mood or a marked decrease in interest or pleasure that occurs as a consequence of a stroke[73]. It occurs in approximately 30% of patients in the first five years after stroke[74]. The risk of developing PSDD is proportional to the severity of the stroke[75], and social, genetic, and epigenetic factors[76]. However, the association with the topography of the stroke is not clear[76]. The presence of PSDD increases the risk of death threefold over a 10-year period, particularly in patients with less social support[77]. PSDD is associated with fewer feelings of guilt and a high risk of suicide, and this should be specifically monitored in younger patients with a history of depressive episodes before the stroke[78].

Adequate social support is necessary to prevent PSDD[79,80]. A systematic review and meta-analysis of low quality showed that prophylactic use of selective serotonin reuptake inhibitors (SSRI) in nondepressed stroke patients for one year may reduce the odds for development of post stroke depression[81]. Non-pharmacological treatment of PSDD involves family support, cognitive behavioral therapy, and lifestyle interventions[79]. Patient education about stroke has a positive effect[79]. Physical exercise training is a potential treatment option for PSDD[79]. Transcranial magnetic stimulation is a promising treatment[82]. Pharmacological treatment with antidepressants, especially SSRIs, has been shown to be effective in improving post-stroke survival and in cases of emotional lability[79] (Table 1). Neuroleptics, anticonvulsants, and lithium have been used for post-stroke manic symptoms[79].

Recommendations

- Pharmacological treatment with antidepressants, such as SSRIs, can be recommended for the treatment of PSDD. (Recommendation IIa-A);
- Selective serotonin reuptake inhibitors may be used prophylactically after stroke. (Recommendation IIb-B);
- Family support, cognitive behavioral therapy, and lifestyle interventions can be considered. (Recommendation IIa-B);
- Exercise training may be used as a complementary treatment option in cases of PSDD. (Recommendation IIb-B);
- The combination of pharmacological and non-pharmacological treatments may be considered. (Recommendation IIb-B);
- Transcranial magnetic stimulation has unclear benefits. (Recommendation III-B).

DEEP VEIN THROMBOSIS

Acute stroke survivors are at high risk of deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), with incidence ranging from 10% to 75% in this population[83]. The main risk factors for post-stroke DVT are advanced age, atrial fibrillation, limb paresis, or plegia[84]. DVT may be present on the second day, with a peak incidence from the second to the seventh day and may persist during the rehabilitation phase in 30% of patients with severe paresis[83]. The main complications of DVT in post-stroke patients are post-thrombotic syndrome and PTE, which can occur in 15% of cases with proximal DVT and account for approximately 3% of post-stroke deaths[85].

Non-pharmacological interventions have been effective in preventing DVT and PTE. The randomized CLOTS 3 study showed that in patients with ischemic or hemorrhagic stroke, intermittent pneumatic compression was effective in reducing DVT and possibly improved survival[86].

For the prevention of DVT or PTE in patients with ischemic stroke, a meta-analysis[87] concluded that: 1) intermittent pneumatic compression should be used in immobilized patients; 2) elastic compression stockings are not indicated; 3) prophylactic anticoagulation with unfractionated heparin (UFH)* or low molecular weight heparin (LMWH)** or heparinoids should be considered in immobilized post-stroke patients for whom the benefits of reducing the risk of DVT outweigh the risk of intra- or extracranial bleeding; 4) if anticoagulation is chosen, LMWH or heparinoids should be prioritized over UFH due to the greater reduction in the risk of DVT, better ease of use, cost reduction, and patient comfort; and 5) LMWH is associated with a higher risk of extracranial bleeding, with the risk being higher in elderly patients with renal dysfunction.

A double-blind randomized study showed that in critically ill patients, including 15% of patients with ischemic stroke, after hospital discharge, rivaroxaban at a dose of 10 mg/day for 45 days reduced the combined risk of fatal and severe thromboembolism by approximately 28%, without a significant increase in bleeding tendencies[88].

Regarding hemorrhagic stroke, a prophylactic dose of heparin between the second or fourth day did not increase the risk of intracranial bleeding, despite the low quality of the evaluated studies[89-91].

In patients with ischemic stroke and DVT or PTE, the anticoagulation maintenance period will be three months, unless another overlapping medical condition increases the risk of recurrence[92].

Literature lacks studies using the inferior vena cava filter (IVCF) in cases of hemorrhagic stroke. However, considering its use in other conditions with contraindications for the use of anticoagulants, the use of inferior vena cava filters in patients with hemorrhagic stroke can be considered[93,94].

*Recommend dose of unfractionated heparin: < 15.000 UI/day. ** Recommended dose for low molecular weight heparin: 30 to 60 mg/day.

Recommendations

- Intermittent pneumatic compression is recommended in immobilized post-stroke patients to prevent DVT. (Recommendation I-A);
- In ischemic stroke, prophylactic doses of UFH or LMWH should be used during the hospital stay or even after discharge until the patient regains mobility. (Recommendation I-A);
- In ischemic stroke, a prophylactic dose of LMWH over UFH can be used to prevent DVT. (Recommendation IIa-A);
- Rivaroxaban at a dose of 10 mg/day for 45 days can be considered as prophylaxis for thromboembolism. (Recommendation IIa-B);

- IVCF can be considered in immobilized hemorrhagic stroke patients if anticoagulation is contraindicated. (Recommendation IIa-B);
- In hemorrhagic stroke, it may be reasonable to use a prophylactic dose of UFH or LMWH to start between the second and fourth days of hospitalization rather than no prophylaxis. (Recommendation IIb-C);
- The use of elastic compression stockings is not recommended. (Recommendation III-B).

SECONDARY STROKE PREVENTION

After an ischemic stroke or a transient ischemic attack (TIA), the risk of recurrence without treatment was 10% in the first week, 15% at one month, and 18% at three months[95]. In the long term, it was 10% in one year, 25% in five years, and 40% in ten years[96].

Meta-analysis of individuals with cardiovascular disease through long-term follow-up identified that a reduction of 1 g/d sodium (2.5 g/d salt) was associated with a decrease in cardiovascular events[97]. Another study established the efficacy of physical activity compared with usual care to reduce risk factors after stroke[98]. Some evidence suggests that smoking cessation and reduced alcohol consumption reduce recurrent events[99,100].

Antihypertensive therapy reduces the risk of ischemic or hemorrhagic stroke[101]. All classes of antihypertensive drugs have been shown to be equally effective, to the detriment of beta-blockers, due to their permissiveness in pressure variability[101]. The use of statins is recommended regardless of the initial LDL cholesterol level[102]. The target for maximum secondary prevention is an LDL< 70 mg/dl, preferably using high-potency statins, such as rosuvastatin or atorvastatin.

Prediabetes and diabetes are associated with increased risk of initial ischemic stroke[103]. The American Diabetes Association and European Association for the Study of Diabetes recommend metformin and lifestyle optimization as first-line therapies[104]. To prevent vascular events, including ischemic stroke, GLP-1 receptor agonists should be added[104].

Antiplatelet agents should be prescribed to patients with non-cardiac-embolic stroke or TIA. Short-term use of aspirin plus clopidogrel for up to 21 days is recommended in patients with acute minor stroke or high-risk TIA[105]. In the long term, agent selection must be individualized based on the risk profile, cost, and tolerance[105].

Patients with cardiac embolism, particularly those with atrial fibrillation, should be treated with anticoagulants[105]. Options include warfarin with an adjusted dose INR between 2 and 3 or direct oral anticoagulants (DOACs: apixaban, dabigatran, edoxaban, or rivaroxaban). The safety profile of DOACs is superior to that of warfarin, with equal or superior efficacy in preventing new events[105].

Patent foramen ovale (PFO) closure is recommended for patients with cryptogenic stroke aged < 60 years, large PFO, or pronounced right-to-left shunt, without other concomitant etiologies[105].

Severe symptomatic intracranial stenosis or occlusion should be treated with antiplatelet agents, and the combination of clopidogrel with aspirin for 90 days may be reasonable[105].

The approach to stroke rehabilitation does not differ in the presence of comorbidities.

Recommendations

- Antiplatelet agents are recommended in patients with non-cardioembolic stroke or TIA for secondary stroke prevention. (Recommendation I-A);
- Anticoagulation with warfarin or DOACs is recommended for stroke or TIA with a cardioembolic source, with a preference for DOACs over warfarin. (Recommendation I-A);
- Patients with diabetes should control their blood glucose with physical activity, lifestyle modifications, and glucose-lowering agents with proven effectiveness in reducing risk for major cardiovascular events. (Recommendation I-A);
- In severe symptomatic intracranial stenosis or occlusion, a combination of clopidogrel and aspirin should be used. (Recommendation I-A);
- An exercise program by a health care professional, in addition to routine rehabilitation, is beneficial for secondary stroke prevention. (Recommendation I-A);
- Blood pressure control with a goal of systolic pressure less than 140 mmHg and diastolic pressure less than 90 mmHg is recommended. (Recommendation I-A);
- It is recommended that LDL values be kept below 70 mg/dl. (Recommendation I-A);
- Quitting smoking and reducing alcohol consumption are recommended. (Recommendation I-B);
- Reducing sodium intake is recommended to reduce the risk of stroke. (Recommendation II-A);
- PFO closure is recommended for cryptogenic stroke patients aged < 60 years. (Recommendation IIa-B);
- For severe symptomatic intracranial stenosis or occlusion, the combination of clopidogrel and aspirin for 90 days should be considered. (Recommendation IIa-B).

SLEEP DISORDERS

Post-stroke patients experience insomnia, excessive daytime sleepiness, fatigue, non-restorative sleep, nocturia, and sleep fragmentation, often present even before the stroke[106]. It is important that conventional polysomnography be performed in this population, as stroke can cause respiratory changes that are undetectable by the screening devices available on the market[107].

Obstructive sleep apnea syndrome (OSAS) affects 50% of stroke patients, and there is a strong interrelationship between the two conditions[108-112]. OSAS exacerbates post-stroke deficits by impairing the consolidation of neuroplastic synaptic processes involving cognition and praxis[113].

Muscle relaxants, including benzodiazepines, are known to worsen OSAS[106]. Continuous positive airway pressure (CPAP) treatment of OSAS must be performed with a positive pressure sufficient to eliminate the apnea events. The device must be worn in an uninterrupted fashion during sleep, every day of the week, with an appropriate nosepiece[114]. A meta-analysis has shown that the use of CPAP can be beneficial for post-stroke neurological recovery[115]. Whether OSAS treatment also reduces the recurrence of stroke remains controversial[116].

Fully-fledged insomnia or symptoms of insomnia affect one-third to nearly half of all post-stroke patients[106]. Antidepressants should be taken in the morning, so avoiding the conditioning effect associated with the idea that night-time use of these drugs is intended to induce sleep[108]. Trazodone has been shown to improve sleep and blood pressure parameters in post-ischemic stroke patients[110]. (Table 1). Cognitive-behavioral therapy is beneficial and positively impacts neurofunctional outcomes[111].

Excessive daytime sleepiness is frequent in post-stroke patients and is associated with higher mortality and less successful rehabilitation[117]. Restless leg syndrome can have a negative impact on the prognosis of post-stroke patients[118].

Recommendations

- CPAP is recommended in individuals with post-stroke OSAS. (Recommendation I-A);
- Excessive daytime sleepiness and restless leg syndrome should be investigated and treated if present. (Recommendation I-B);
- Trazodone can be considered in individuals with ischemic stroke and OSAS. (Recommendation IIa-A);
- Conventional polysomnography is probably recommended in individuals with a history of stroke or TIA. (Recommendation IIa-B);
- Antidepressants should be taken in the morning. (Recommendation IIa-B);
- Cognitive behavioral therapy can be considered in individuals with post-stroke sleep disorders. (Recommendation IIa-B);
- Benzodiazepines and muscle relaxants should not be used in the management of post-stroke sleep disorders. (Recommendation III-C).

FALLS

Falls are one of the most common causes of post-stroke complications. They can occur in the acute or chronic phases[119,120]. Approximately 7% of falls occur in the first week after stroke, 25% to 37% between one and six months, and 40% to 50% at six to 12 months. After one year, falls continue to occur in 73% of patients[121]. Falls are most frequent in the first three weeks of rehabilitation[122].

Falls are associated with motor, sensory, or visual impairment, cognitive dysfunction, hemineglect, and stroke in the posterior circulation[123,124]. The causes of falls include cardiac arrhythmias; orthostatic hypotension; vasovagal syncope; psychological factors, such as depression and fear of falling; seizures; and some drugs, such as antihypertensives, diuretics, anticholinergics, antidepressants, and antiepileptics[124-128].

Prevention of falls can be achieved by supervision, strength training, improvement of balance and cognition, less use of sedative drugs and diuretics, and counseling to avoid risky situations[129,130]. Physical activity showed positive outcomes in long-term stroke patients, mainly with specific tasks to improve postural stability, walking in challenging situations, and agility training programs for effective fall prevention[131-133]. A systematic review with meta-analysis showed a reduction in falls in post-stroke patients with the practice of ancient tai chi[134].

Recommendations

- Exercises aimed at preventing falls, with training to improve balance, are recommended. (Recommendation I-B);
- Prevention of falls through patient supervision, reduction of the use of sedatives and diuretics, and restriction of activities with a risk of falling should be instituted. (Recommendation I-C);
- Tai chi can be considered for fall prevention. (Recommendation IIa-B);
- Agility training programs for fall prevention is reasonable. (Recommendation IIa-C).

OSTEOPOROSIS

Osteoporosis is a metabolic bone disease characterized by an imbalance between bone resorption and accumulation, leading to changes in the bone microarchitecture and a reduction in bone mineral density (BMD)[135,136]. In addition to spasticity, changes in geometric bone properties on the paretic side, increased skeletal fragility, and accelerated bone loss that occurs after a stroke, result in osteoporosis due to disuse[135]. This loss of bone mass as well as reduction in bone structure is greater on the paretic side than on the non-paretic side and affects the upper limbs more than the lower limbs[135]. The risk of fractures in stroke patients is seven times higher than that in the same population according to sex and age[136]. Eighty percent of fractures occur on the paretic side.

The evidence for drug treatment strategies for osteoporosis in stroke patients is limited[137]. It is not known who is eligible, the best timing, which drug is better, and the best duration of treatment[138]. Further studies are needed to recommend calcium

and vitamin D supplements[139,140]. However adequate supplementation of both can be used in all post-stroke patients[141,142]. Bisphosphonates such as zoledronic acid are a therapeutic option for both oral and intravenous administration[143,144]. Hormonal therapy, tibolone, and selective estrogen receptor modulators have cardiovascular risks[145].

Some medications, such as warfarin, pioglitazone, enzyme-inducing anticonvulsant drugs[146] and selective serotonin reuptake inhibitors, are associated with an increased risk of fracture[147]. There are clinical studies showing the potential benefits of statins in preventing osteoporosis and fractures[148].

Physical activity with gait training and resistance exercises may have some beneficial effects on BMD loss, but there is limited evidence[149].

Recommendations

- Vitamin D and calcium supplementation can be recommended for stroke patients. (Recommendation IIa-C);
- Bisphosphonates can be used. (Recommendation IIa-B);
- Statins can be beneficial in preventing osteoporosis after stroke. (Recommendation IIa-B);
- Physical activity with gait training and resistance exercises can be useful. (Recommendation IIa-C);
- Selective estrogen receptor modulators, warfarin, pioglitazone, enzyme-inducing anticonvulsants, and selective serotonin reuptake inhibitors can be used with caution. (Recommendation IIb-B);
- Tibolone should be avoided. (Recommendation III-B).

SEIZURE MANAGEMENT

Stroke is the leading cause of epilepsy among individuals over 60 years of age[150]. The incidence of post-stroke epileptic seizures is 7% and may be higher in cases with cortical involvement, greater severity of the vascular event, and hemorrhagic stroke[151]. Epilepsy is associated with increased mortality, prolonged hospitalization, and higher rates of disability[152]. In stroke patients, the risk of subsequent seizures after an unprovoked seizure is approximately 70%[153]. A single unprovoked seizure is sufficient for the diagnosis of epilepsy.

The risk of acute symptomatic seizures or unprovoked seizures is low. Even in patients with hemorrhagic stroke and cortical involvement, the risk does not exceed 35%. Therefore, the use of antiseizure medication (ASM) as primary prophylaxis is not justified[154]. Likewise, since the risk of seizure recurrence within seven days of stroke is less than 20%, initiation of ASM after a first symptomatic seizure is generally not recommended[155]. Nevertheless, no adequately powered randomized trial results are available, and this issue is still being debated[156]. In addition, there is a lack of data to determine the differences between ischemic and hemorrhagic stroke-related seizures in terms of risk factors and treatment approaches[150]. Therefore, the guidelines end with generalized Recommendations[155]. In practice, clinicians consider the risk of clinical worsening following seizure. It is therefore reasonable to base the decision on stroke severity, injury location, stroke subtypes (intracerebral hemorrhage/subarachnoid hemorrhage), and electroencephalogram findings[150,156]. If ASM is used for some reason, it should be limited to the acute phase[155].

Conversely, the risk of recurrence after an unprovoked seizure is approximately 70%, which defines epilepsy. In this situation, the use of ASM as secondary prophylaxis should be considered. The decision of a possible future suspension of ASM must be individualized since the risk of seizures after ASM withdrawal is high in patients with structural damage[155].

Most patients with post-stroke epilepsy have seizure control with monotherapy alone[156]. The drugs that have proved to be effective in controlling focal epilepsy are carbamazepine, levetiracetam, phenytoin, and zonisamide for adults, with lamotrigine and gabapentin for the elderly[157]. However, there is no current evidence for ASM choice in stroke patients. The newer ASMs seem to be better tolerated, with fewer drug interactions and better side effect profiles[150]. In a systematic review with network meta-analysis, levetiracetam and lamotrigine were better tolerated than controlled-release carbamazepine for post-stroke epilepsy, with no significant differences in seizure control[157] (Table 1).

Recommendations

- Long-term use of antiseizure medication after an unprovoked seizure is recommended. (Recommendation I-B);
- Recurrent post-stroke seizures must be treated, and the selection of antiseizure medication should consider the patient´s characteristics. (Recommendation I-B);
- Use of antiseizure medication after an acute symptomatic seizure is generally not recommended, but it can be considered during the acute phase. (Recommendation IIa-B);
- Use of antiseizure medication as primary prophylaxis of post-stroke seizures is not recommended. (Recommendation III-B).

NEUROGENIC LOWER URINARY TRACT DYSFUNCTION AND FECAL INCONTINENCE

Post-stroke neurogenic lower urinary tract dysfunction (NLUTD) is defined as a dysfunctional condition of the muscles of the bladder, urethra, urethral sphincter, and pelvic floor, and is related to the topography of the damage caused by the stroke, leading to abnormal or difficult control in voluntary and/or involuntary muscle contraction and/or relaxation during the storage and voiding phases of the bladder[158].

Approximately one-third of adult stroke survivors have symptoms related to NLUTD[159] with a prevalence ranging from 11.1% to 70%. Detrusor hyperactivity is the most prevalent

symptom (64.7%)[160] and urinary incontinence is associated with a high risk of death after a new stroke[161].

Fecal incontinence (FI) is the inability to control bowel movements, causing stool to unexpectedly leak from the rectum. The prevalence of FI is approximately 40% in the post-stroke acute phase and 20% during rehabilitation. The risk factors are age and functional limitations[162].

Due to the low quality of the studies, no significant effects on NLUTD in post-stroke individuals have been shown by behavioral interventions, assistance from specialized professionals, complementary therapies such as acupuncture (electroacupuncture and moxibustion), transcutaneous electrical stimulation, physical therapy techniques, pharmacotherapy with oxybutynin or estrogen, and a combination of interventions[163].

There are few studies in the literature on interventions for FI in post-stroke individuals, and they show that educational actions and dietary control have inconclusive effects[164].

Recommendations

- For post-stroke NLUTD, behavioral interventions, specialized professional care, complementary therapies such as acupuncture (electroacupuncture and moxibustion), transcutaneous electrical stimulation, physical therapy techniques, pharmacotherapy, and a combination of interventions have uncertain benefits. (Recommendation IIb-B);
- For post-stroke FI, educational actions and dietary control have inconclusive effects. (Recommendation IIb-B).

SEXUAL DYSFUNCTION

Sexual dysfunction after stroke is underrecognized. It affects over half of stroke survivors and it is not solely attributed to the physical effects of stroke[165]. Fewer than 10% of patients receive any advice, despite 90% of patients hoping for advice relating to sexual dysfunction in stroke. Symptoms are characterized by changes in sexual activity, sexual dissatisfaction, decreased libido, problems in achieving orgasm, and erectile dysfunction (ED)[166].

Sexual dysfunction is associated with depression, fear of recurrence of a new stroke, and self-perception of impaired motor function[167]. Antihypertensive drugs, depression, and anxiety are associated with ED168.

Sexual rehabilitation involves counseling and non-pharmacological and pharmacological interventions[169,170]. Counseling may address sexual performance related to medication issues and comorbid conditions that may affect sexual function. Orientation to reduce anxiety related to sexual problems involves discussions regarding the ideal timing for sexual activity (in the morning when the person is not tired), dealing with bladder and bowel issues, and working around the weakness (physical support with pillows), thus helping stroke survivors and their partners. Pharmacological interventions include phosphodiesterase-5 inhibitors, intracavernosal injections, and intraurethral suppositories to assist erectile function. Non-pharmacological interventions, such as mechanical devices, lubricating gels, and psycho-educational interventions, are also components of sexual rehabilitation[169,170].

The effectiveness of interventions to treat sexual dysfunction is limited. According to a recent meta-analysis, data indicating the benefits or risks of using sertraline to treat premature ejaculation, pelvic floor physiotherapy and sexual rehabilitation to treat sexual dysfunction after stroke are insufficient[171].

Recommendations

- It is recommended that stroke subjects be asked about their sexual function. (Recommendation I-C);
- Mood disorders and fears should be addressed in sexual dysfunction after stroke.
- If ED is present in men after stroke, antihypertensive drug use, anxiety, and depression should be investigated. (Recommendation I-B);
- The benefits of sertraline in treating premature ejaculation are uncertain. Recommendation IIb-B);
- The effects of sexual rehabilitation for treating sexual dysfunction after stroke are not well established. (Recommendation IIb-B).

CONCLUSION

The Brazilian Guideline for Stroke Rehabilitation – Part I presents Recommendations on interventions to manage and prevent complications and comorbidities after stroke. However, this guideline is open to criticism for potential issues in the Recommendations: 1) the variety of topics covered; 2) the diverse effects of a single intervention in recovery from neurological deficits and disabilities; 3) the low methodological quality of the studies evaluated in systematic reviews and meta-analyses; 4) the personal experience of each professional; and 5) the complexity of the theme of stroke rehabilitation. We hope that Part I of this guideline helps the multidisciplinary team in offering the best care of the most frequent clinical conditions after stroke.

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Ivan Petrovich Pavlov and Santiago Ramón y Cajal, scientists and Nobel laureates of a new century

Iván Petrovich Pavlov y Santiago Ramón y Cajal, científicos y premios Nobel de un nuevo siglo

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ABSTRACT

Pavlov and Cajal were two influential scientists who developed their work in the late nineteenth and early twentieth centuries. Both won the Nobel Prize in Physiology or Medicine. The authors analyze the similarities between their life and work, delving into a single aspect: the Nobel prize obtained by both with only two years of difference: Pavlov in 1904 and Cajal in 1906, shared with Camilo Golgi. Both belonged to two declining empires when nationalism was still of some importance. The theories proposed by them more than 115 years ago are still valid in much of what they contributed in their respective disciplines.

Keywords: History of Medicine; Biography; Classical Conditioning; Neurosciences; Nobel Prize.

RESUMEN

Pavlov y Cajal fueron dos científicos influyentes que desarrollaron su trabajo a finales del siglo XIX y principios del XX. Ambos ganaron el premio Nobel de Fisiología o Medicina. Los autores analizan las similitudes entre su vida y obra, profundizando en un solo aspecto: el premio Nobel obtenido por ambos con tan solo dos años de diferencia: Pavlov en 1904 y Cajal en 1906, compartido con Camilo Golgi. Ambos pertenecían a dos imperios en decadencia, en un momento en que el nacionalismo todavía tenía cierta importancia. Las teorías propuestas por ellos, hace más de 115 años, siguen vigentes en lo fundamental de lo que aportaron en sus respectivas disciplinas.

Palabras clave: Historia de la Medicina; Biografía; Condicionamiento Clásico; Neurociencias; Premio Nobel.

Iván Petrovich Pavlov (1849-1936) and Santiago Ramón y Cajal (1852-1934) were two major scientists who developed their work in the late 19th and early 20th centuries. Both won the Nobel Prize in Physiology or Medicine with a short chronological difference: Pavlov in 1904 and Cajal (shared with Camilo Golgi) in 1906[1-4].

There are similarities between their life and work. Since it is impossible to cover the work of both, the authors have decided to delve into only one aspect: the Nobel Prize won by both with only two years of difference, Pavlov: 1904, and Cajal: 1906[5,6].

The historical context of these two characters was marked by a strong nationalism in Europe, both in the second half of the 19th century and in the first half of the 20th century, which tragically unleashed the First and Second World Wars. Nationalism impacted on the scientific field, as a source of competition in achievements between countries, for example, the Nobel prizes in science: Physiology or Medicine, Physics, Chemistry, to their credit[7].

Pavlov and Cajal both belonged to empires in decline; Russia, the home country of Pavlov, and Spain of Cajal. These two scientists, their Nobel prizes, and other distinctions obtained by them, were also of the most significant importance[8,9].

Cajal published in 1899 the first edition of his masterpiece "Texture of the nervous system of man and vertebrates" only a year before the "Disaster of 98" occurred, caused by the war between the United States of America and Spain. After a few naval battles, all lost by Spain, the decadent empire asked to sign a peace treaty, yielding independence to Cuba, and the cession of Puerto Rico, the Philippines, and Guam to the United States, which became a colonial power[9].

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Ivan Pavlov's extensive and productive investigative career took place in Tsarist Russia and post-October 1917 Soviet Russia[8]. It was under the last two tsars, Alexander III and his son Nicholas II, that Pavlov obtained his greatest glories, such as getting the seat of the Institute of Experimental Medicine in Saint Petersburg, the honorable invitation to the conference in Madrid in 1903 (where he probably met Cajal in person), and the summit: the Nobel Prize in Medicine or Physiology, in 1904[3]. Before the fall of the Winter Palace, and although he did not agree so much with Lenin's ideals, to his fortune, revolutionary support for his prestigious investigative company was assured until he died in 1936. Thus, the famous and unstoppable Tower of Silence continued to produce scientific research beyond the radical social and economic changes that occurred due to the creation of the Soviet Union[10].

Regarding the Nobel Prize, the juries had difficulties awarding it to Pavlov in 1904, his main competitor being Cajal[3], who, in turn, had managed to see very precisely the "butterflies of the soul," a name he chose for the cells of the nervous system, which the German pathologist Heinrich Waldeyer (1836-1921) called neurons in 1901[11].

The controversy also had another ingredient. Many researchers worked alone, and Pavlov was the first to research with his Ph.D. students at the St. Petersburg Institute of Experimental Medicine. Some jurors had doubts about the originality of his work[8,10]. However, once his way of working was thoroughly reviewed, they did not hesitate to designate him as the winner in 1904: "in recognition of his work in the physiology of digestion, through which knowledge on vital aspects of the matter have been transformed and increased"[5]. The speech given by Pavlov on December 12th of that year was titled: "Physiology of digestion"[4].

Pavlov went to Stockholm to receive the award, becoming the first Russian scientist to obtain it. At 55, the scientist peaked his career: international recognition for his work and financial compensation of 73,000 gold rubles (about $ 36,000 at the time). He assigned it to his laboratory and future research[12,13]. However, curiously, Pavlov seemed not to attach much importance to such recognition. He never referred to it during the rest of his life, not even in his short autobiography. But it was an important recognition for him, his collaborators, and the nation to which he belonged[3].

Cajal, in turn, had become the leading exponent of the "neuronal doctrine," in opposition to the "reticularists," who did not accept the existence of unicellular structures in the nervous system[14]. Camilo Golgi, who in 1880 had discovered silver staining to visualize nerve cells, was, paradoxically, a vigorous defender of the reticular theory. Cajal began to use this modified stain (double silver impregnation) in 1887. Thus, the juries also had difficulties and decided to award the prize in a shared way. The winners received the award "in recognition of their work on the structure of the nervous system." The speech delivered in French by Cajal on December 12th of that year was entitled "Structure and connections of neurons"[6,15,16]. The wise Aragonese would be the first Spaniard to receive the specific award in Physiology or Medicine[17].

Jones (1998), cited by Grant[18], points out that Golgi may have thought there would be a struggle between his conference and Cajal's. Having the opportunity to speak first, he misjudged the Spanish scientist's position and would have ended up attacking him. This situation would explain the controversy of his presentation. Nieto[19] points out that Golgi was so tense that he wanted to get to the Stockholm station incognito. However, upon his arrival, a large group of people was waiting for him on the platform, including Cajal. Golgi was very nervous; he avoided any gesture of kindness with this one. According to Nieto, Golgi's attitude was because he was fully aware of the lack of updating in the bibliography on histology of the nervous system and was also concerned about a direct reply from Cajal to his speech. His state of mind is reflected in a letter from his wife, Lina Golgi, to his mother: "Camilo would run home like a runaway horse."

Finally, it would be the neural doctrine that ended up being accepted and the one that prevails, in almost all its aspects, to this day.

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Simultaneous mixed phenotype and neuroimaging of progressive supranuclear palsy, progressive ataxia and palatal tremor: two different faces of tauopathies

Fenótipo misto simultâneo e neuroimagem de paralisia supranuclear progressiva, ataxia progressiva e tremor palatal: duas faces diferentes das tauopatias

Leonardo Furtado FREITAS[1], Victor Moreira de CARVALHO[2], José Luiz PEDROSO[3], Márcio Luís DUARTE[4], Rodrigo Meirelles MASSAUD[5]

A 74-year-old woman was referred with a six-month history of progressive gait disturbance and falls. Physical examination showed bradykinesia, rigidity, postural instability, palatal tremor, and vertical gaze palsy (Video). There was no improvement with levodopa. Brain magnetic resonance demonstrated midbrain atrophy and hyperintense signal in the inferior olivary nuclei (Figure 1). The patient was diagnosed simultaneously with progressive supranuclear palsy (PSP), progressive ataxia and palatal tremor (PAPT).

PSP is a well-known form of tauopathy. Recent reports have described tau-positive neuronal inclusions in PAPT[1]. The unusual syndrome characterized simultaneously by PSP and PAPT may suggest a unique phenotype of tau pathology[2].

Video. Patient with mixed phenotype: progressive supranuclear palsy, progressive ataxia and palatal tremor. Note gait instability, ataxia, bradykinesia, tremor, vertical gaze palsy and palatal tremor.
https://www.arquivosdeneuropsiquiatria.org/wp-content/uploads/2022/02/ANP-2021.0442-Video.mp4

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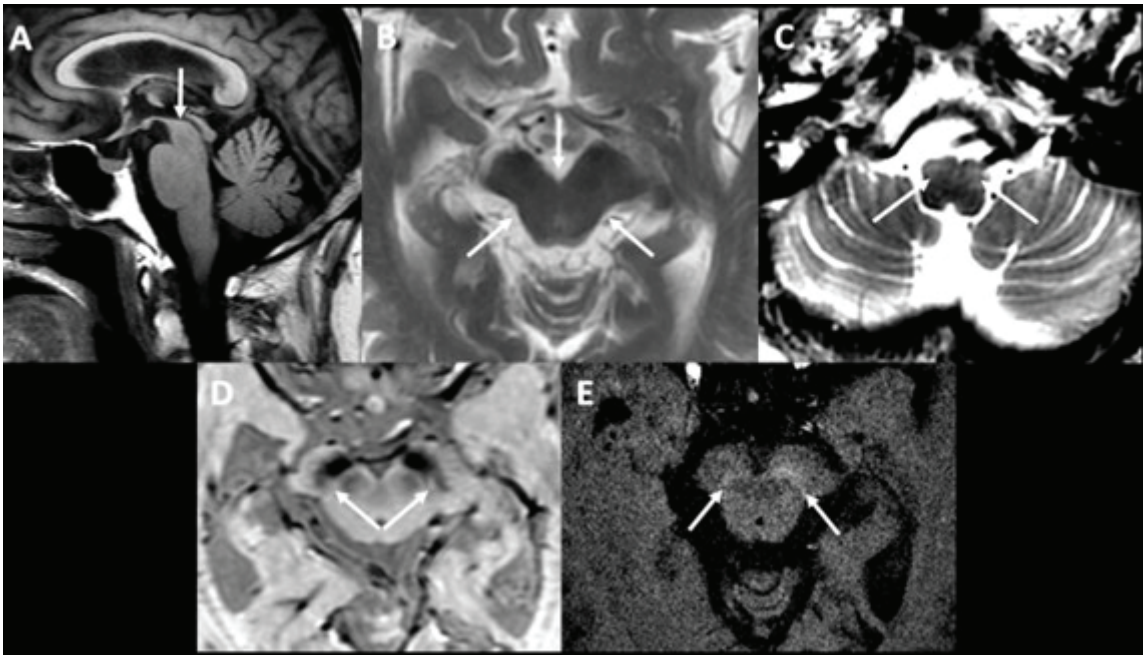

Figure 1. 3.0 Tesla magnetic resonance imaging shows volumetric reduction of the midbrain in the sagittal T1 sequences (A), with rectification of the upper contour of the tegment (arrow) and axial T2 (B) showing prominence of the interpeduncular cistern and greater concavity of the tegment (morning glory sign – arrows) described in progressive supranuclear palsy (PSP). The T2 axial sequence of the medulla oblongata (C) shows hypersignal and hypertrophy of bilateral inferior olivary nuclei (arrows), which can be associated to progressive ataxia and palatal tremor (PAPT). Axial thin slices of the midbrain in SWI (D) and T1 (E) sequences with reduction of nigrosome1 and neuromelanin in the substantia nigra (arrows), respectively, mainly on the right, a structural biomarker of transaxonal degeneration of the striatonigral dopaminergic pathway, not specific for this entity, which can found in other parkinsonian syndromes, such as Parkinson's disease.

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Rucksack palsy after military boot camp

Paralisia do mochileiro após treinamento militar

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A 18-year-old soldier reported weakness on the abduction of right arm and mild right shoulder pain five days after wearing a rucksack during a 3-day boot camp training (Figure 1-A). After six weeks, he presented hypotrophy of shoulder girdle muscles and winged scapula (Figure 1-B). An electroneuromyography performed at this moment revealed signs of progressive subacute neurogenic motor unit potentials of right deltoid, biceps brachii and anterior serratus (Figure 1-C).

Right brachial plexus, shoulder MRI and a viral serum panel were unremarkable. Rucksack palsy is most described in the military population[1]. It is associated with damage to the brachial plexus as a result of wearing a heavy rucksack[2].

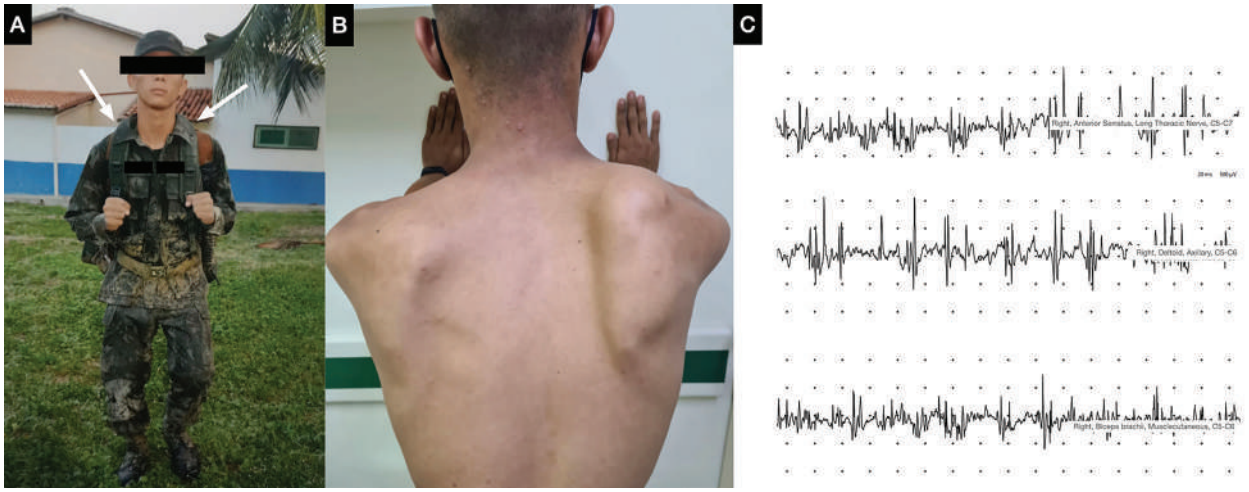

Figure 1. Rucksack palsy. (A) Military rucksack carries a load of approximately 15 kilograms; superior armpit is a point of compression (white arrows). It is the result of traction of brachial nerves on scalene muscles caused by the shoulder straps of a heavy rucksack. (B) Hypotrophy of right shoulder girdle muscles, more prominent deltoid, supraspinatus, biceps brachii muscles, and winged scapula. (C) Electroneuromyography signs of progressive subacute neurogenic motor unit potentials of right deltoid, biceps brachii, anterior serratus suggesting pathology of the brachial plexus.

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Authors' contributions: PHAF, FTA: analysis and interpretation of data, writing and drafting the manuscript; IMDP, BMF: analysis and interpretation of data; CGJ: critical revision of the manuscript for intellectual content.

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Professor Paulo Norberto Discher de Sá (1939-2022)

Professor Paulo Norberto Discher de Sá (1939-2022)

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Professor Paulo Norberto Discher de Sá (Figure 1) was born in October 11th, 1939, in Lages, a small city in the highlands of Santa Catarina State, Brazil. When he was still young his family moved to the coastal city of Florianópolis, State's capital. The interest in Medicine came from reading Ambroise Paré and William Osler biographies and Cronin's Citadel in childhood. Professor Sá studied Medicine at the Federal University of Paraná, Curitiba, from 1958 to 1963, becoming a disciple of Professor Lysandro de Santos Lima, a well-known inspiring clinician. Between 1964 and 1965 he studied Neurology at the Guanabara State Public Servers Hospital, an important centre on Neurology training in Rio de Janeiro[1,2,3]. Back to Florianópolis Professor Sá worked at the Charity Hospital, whose Neurology service he would became chief. In 1968 he became the first neurologist to teach Neurology at Federal University of Santa Catarina. When the University Hospital was inaugurated in 1980, he assumed the Neurology service and later created the hospital Neurology Residence Program. Professor Sá also taught Neurology at UNISUL, a university in the nearby cities of Tubarão and Palhoça. Admired teacher, Professor Sá knew how to summarize complex matters on lectures and how to instigate the mystery of neurological examination on clinical rounds. Always cordial with his students, Professor Sá inspired the study of Neurology in many of them. Respected by his patients, he carefully paid visit daily to them on Charity and University Hospital, including on weekends and holidays. At the State Medical Ethics Council, he was known by his sharp and wise analysis. At the Brazilian Academy of Neurology, Professor Sá acted many years at the Teaching Commission and presided the Brazilian Congress of Neurology, at 2002 in Florianópolis. Professor Sá died on March 15th, 2022, after a long neurodegenerative disease, leaving his wife Regina, his son Daniel, neurologist established in the USA, his daughter Paula, architect, and grandchildren.

Figure 1. Professor Paulo Norberto Discher de Sá (1939-2022).

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Erratum

In the article "Neuromuscular choristoma: a rare cause of congenital non-progressive lower limb amyotrophy", with DOI code number https://doi.org/10.1590/0004-282X-ANP-2020-0370, published in the Arq Neuropsiquiatr. 2021;79(5):465-6, page 465:

Where it was written:

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Should read:

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Keppra®
levetiracetam

NOVO
KEPPRA XR™
levetiracetam
O PRIMEIRO.[1]
O ÚNICO.*

O ÚNICO LEVETIRACETAM DISPONÍVEL EM AMPLA GAMA DE OPÇÕES TERAPÊUTICAS.[2,3]

M.S. 1.2361.0083.007-1 M.S. 1.2361.0083.004-7 M.S. 1.2361.0083.005-5 M.S. 1.2361.0093.001-7 M.S. 1.2361.0093.002-5

CONFIANÇA:
mais de 20 anos de experiência clínica[4]

COMODIDADE:
ampla gama de apresentações[2,3]

ADESÃO:
apresentação XR **(1X ao dia).[2]**

*Único no Brasil.

Referências bibliográficas: 1. Diário Oficial da União. Nº 61, segunda-feira, 30 de março de 2020. RESOLUÇÃO-RE Nº 871 **2.** Bula de Keppra XR®. **3.** Bula de Keppra®. **4.** Shorvon, S. D. et al. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. *Epilepsia*. 2000 Sep; 41(9):1179-86.

Keppra XR (levetiracetam). **Apresentações:** comprimidos revestidos de liberação prolongada de 500 mg ou 750 mg em embalagens com 60 comprimidos. **Indicações: é indicado como monoterapia** para o tratamento de crises focais/parciais em pacientes a partir dos 16 anos com epilepsia. **Keppra XR** também é indicado como terapia adjuvante no tratamento de: crises focais/parciais em pacientes com idade superior a 12 anos, com epilepsia refratária; crises mioclônicas em adultos, adolescentes e crianças com idade superior a 12 anos, com epilepsia mioclônica juvenil; crises tônico-clônicas primárias generalizadas em adultos, adolescentes e crianças com mais de 12 anos de idade, com epilepsia idiopática generalizada. **Contraindicações:** hipersensibilidade ao princípio ativo ou a outros derivados da pirrolidona ou a qualquer um dos excipientes. **Cuidados e Advertências:** para informações completas de advertências, vide bula do produto. A administração de **Keppra XR** em pacientes com comprometimento renal poderá necessitar de um ajuste da dose. Foram notificados suicídio, tentativa de suicídio e ideias e comportamento suicida, além de alterações no comportamento como agressividade, agitação, raiva, ansiedade, apatia, depressão, hostilidade e irritabilidade e sintomas psicóticos em pacientes tratados com levetiracetam. Casos de diminuição na contagem de células sanguíneas (neutropenia, agranulocitose, leucopenia, trombocitopenia e pancitopenia) foram descritos em associação à administração de levetiracetam. *Gravidez* categoria C de risco de gravidez. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica. Levetiracetam é excretado no leite humano materno. **Keppra XR** é um medicamento e durante seu uso, recomenda-se precaução nos pacientes que executam tarefas especializadas, como condução de veículos ou utilização de máquinas. **Interações Medicamentosas** (vide bula completa do produto): Dados indicam que levetiracetam não influencia as concentrações séricas de medicamentos antiepilépticos existentes (fenitoína, carbamazepina, ácido valpróico, fenobarbital, lamotrigina, gabapentina e primidona) e que estes medicamentos antiepilépticos não influenciam a farmacocinética de levetiracetam. A probenecida (500 mg quatro vezes ao dia), um agente bloqueador da secreção tubular renal, mostrou inibir a depuração renal do metabólito primário, mas não a do levetiracetam. Contudo, a concentração deste metabólito permanece baixa. Levetiracetam 1000 mg por dia não influenciou a farmacocinética dos contraceptivos orais (etinilestradiol e levonorgestrel). Foram observados relatos isolados de diminuição de eficácia quando o laxante osmótico macrogol foi administrado concomitantemente a levetiracetam oral. Assim, a administração oral de macrogol não deve ser realizada dentro de 1 hora (antes ou após) da administração de levetiracetam. A extensão de absorção do levetiracetam não sofreu qualquer alteração com a ingestão de alimentos, mas a taxa de absorção diminuiu ligeiramente. Não estão disponíveis dados sobre a interação do levetiracetam com o álcool. **Reações Adversas:** para informações completas de reações adversas, vide bula do produto. Os eventos adversos mais comumente reportados nos estudos clínicos foram astenia, fadiga, dor de cabeça e sonolência. Adicionalmente às reações adversas relatadas durante os estudos clínicos as seguintes reações adversas foram reportadas na experiência pós-comercialização, além de outras mencionadas na bula completa do produto: comportamento anormal, raiva, delírio, ataque de pânico, ansiedade, estado de confusão, alucinação, distúrbios psicóticos, suicídio, tentativa de suicídio e ideação suicida, parestesia, coreoatetose, discinesia, letargia, distúrbio de marcha, agravamento das crises epilépticas, dano renal agudo, reações anafiláticas, angioedema. Casos raros de prolongamento do intervalo QT foram observados na vigilância pós-comercialização. Evidências também sugerem uma possível predisposição da população japonesa à síndrome neuroléptica maligna (SNM). **Posologia:** A dose inicial recomendada para monoterapia no tratamento de crises focais/parciais em pacientes a partir dos 16 anos com epilepsia, é de 500 mg ao dia, a qual poderá ser aumentada para uma dose terapêutica inicial de 1000 mg ao dia, após duas semanas. A dose máxima é de 3000 mg ao dia. Nos casos de terapia adjuvante, para adultos e adolescentes acima de 12 anos e com mais de 50 kg, a dose terapêutica inicial é de 1000 mg ao dia. Esta dose poderá ser iniciada no primeiro dia de tratamento, a dose diária poderá ser aumentada até o máximo de 3000 mg ao dia. Ainda nos casos de terapia adjuvante, para adolescentes (dos 12 aos 17 anos) com peso inferior a 50 kg a dose terapêutica inicial é de 20 mg/kg ao dia, a dose pode ser aumentada até 60 mg/kg ao dia. A alteração das doses não deve exceder aumentos ou reduções de 20 mg/kg ao dia, a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A posologia em crianças com peso igual ou superior a 50 kg é igual à dos adultos. Além disso, as concentrações disponíveis de **Keppra XR** não são apropriadas para o tratamento inicial em crianças com menos de 25 kg, para pacientes incapazes de deglutir comprimidos ou para administração de doses menores que 500 mg. Em todas estas situações deve ser utilizada a solução oral de **Keppra. USO ADULTO E PEDIÁTRICO ACIMA DE 12 ANOS. USO ORAL. VENDA SOB PRESCRIÇÃO MÉDICA. SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA.** Para maiores informações, consulte a bula completa do produto. (030204014 R4 Rev. Março 2021). www.ucb-biopharma.com.br **Reg. MS - 1.2361.0093**. **Levetiracetam (lista C1 Port. 344/98).**

Keppra® (levetiracetam). **Apresentação**: comprimidos revestidos de 250 mg em embalagens com 30 ou 60 comprimidos ou comprimidos de 750 mg também em embalagens com 30 ou 60 comprimidos. **Indicações:** é indicado como monoterapia para o tratamento de crises focais/parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia. **Keppra®** também é indicado como terapia adjuvante no tratamento de: crises focais/parciais com ou sem generalização secundária em adultos, adolescentes e crianças com idade superior a 6 anos, com epilepsia; crises mioclônicas em adultos, adolescentes e crianças com idade superior a 12 anos, com epilepsia mioclônica juvenil; crises tônico-clônicas primárias generalizadas em adultos, adolescentes e crianças com mais de 6 anos de idade, com epilepsia idiopática generalizada. **Contraindicações**: Hipersensibilidade ao princípio ativo ou a outros derivados da pirrolidona ou a qualquer um dos excipientes. **Cuidados e Advertências:** para informações completas de advertências, vide bula do produto. A administração de **Keppra®** em pacientes com comprometimento renal poderá necessitar de um ajuste da dose. Foram notificados suicídio, tentativa de suicídio e ideias e comportamento suicida, além de alterações no comportamento como agressividade, agitação, raiva, ansiedade, apatia, depressão, hostilidade e irritabilidade e sintomas psicóticos em pacientes tratados com levetiracetam. Casos de diminuição na contagem de células sanguíneas (neutropenia, agranulocitose, leucopenia, trombocitopenia e pancitopenia) foram descritos em associação à administração de levetiracetam. *Gravidez* categoria C de risco de gravidez. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica. Levetiracetam é excretado no leite humano materno**. Keppra®** é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas. *Interações medicamentosas: (vide bula completa do produto)*: Dados indicam que levetiracetam não influencia as concentrações séricas de medicamentos antiepilépticos existentes (fenitoína, carbamazepina, ácido valpróico, fenobarbital, lamotrigina, gabapentina e primidona) e que estes medicamentos antiepilépticos não influenciam a farmacocinética de levetiracetam. A probenecida (500 mg quatro vezes ao dia), um agente bloqueador da secreção tubular renal, mostrou inibir a depuração renal do metabólito primário, mas não a do levetiracetam. Contudo, a concentração deste metabólito permanece baixa. Levetiracetam 1000 mg por dia não influenciou a farmacocinética dos contraceptivos orais (etinilestradiol e levonorgestrel). Foram observados relatos isolados de diminuição de eficácia quando o laxante osmótico macrogol foi administrado concomitantemente a levetiracetam oral. Assim, a administração oral de macrogol não deve ser realizada dentro de 1 hora (antes ou após) da administração de levetiracetam. A extensão de absorção do levetiracetam não sofreu qualquer alteração com a ingestão de alimentos, mas a taxa de absorção diminuiu ligeiramente. Não estão disponíveis dados sobre a interação do levetiracetam com o álcool. *Reações Adversas:* para informações completas de reações adversas, vide bula do produto. Os eventos adversos mais comumente reportados nos estudos clínicos foram astenia, fadiga, dor de cabeça e sonolência. Adicionalmente às reações adversas relatadas durante os estudos clínicos as seguintes reações adversas foram reportadas na experiência pós-comercialização, além de outras mencionadas na bula completa do produto: comportamento anormal, raiva, delírio, ataque de pânico, ansiedade, estado de confusão, alucinação, distúrbios psicóticos, suicídio, tentativa de suicídio e ideação suicida, parestesia, coreoatetose, discinesia, letargia, distúrbio de marcha, agravamento das crises epilépticas, dano renal agudo, reações anafiláticas, angioedema. Casos raros de prolongamento do intervalo QT foram observados na vigilância pós-comercialização. Evidências também sugerem uma possível predisposição da população japonesa à síndrome neuroléptica maligna (SNM). **Posologia**: A dose inicial recomendada para monoterapia no tratamento de crises focais/parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia, é de 250 mg duas vezes ao dia, a qual poderá ser aumentada para uma dose terapêutica de 500 mg duas vezes ao dia, após duas semanas. A dose máxima é de 1500 mg duas vezes ao dia. Nos casos de terapia adjuvante, para adultos e crianças acima de 12 anos e com mais de 50 kg, a dose terapêutica inicial é de 500 mg duas vezes ao dia. Esta dose poderá ser iniciada no primeiro dia de tratamento, a dose diária poderá ser aumentada até o máximo de 1500 mg/duas vezes ao dia. Ainda nos casos de terapia adjuvante, para crianças (dos 6 aos 11 anos) e adolescentes com peso inferior a 50 kg a dose terapêutica inicial é de 10 mg/kg duas vezes ao dia, a dose pode ser aumentada até 30 mg/kg duas vezes ao dia. A alteração das doses não deve exceder aumentos ou reduções de 10 mg/kg duas vezes ao dia, a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A posologia em crianças com peso igual ou superior a 50 kg é igual à dos adultos. A forma farmacêutica comprimido revestido não é adaptada para bebês e crianças com menos de 6 anos. **Keppra®** solução oral é a forma farmacêutica ideal para uso nesta população. **USO ADULTO E PEDIÁTRICO ACIMA DE 06 ANOS DE IDADE. USO ORAL. VENDA SOB PRESCRIÇÃO MÉDICA. SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA**. Para maiores informações, consulte a bula completa do produto. (030204013 R26 Rev. Junho/2021). www.ucbbiopharma.com.br **Reg. MS - 1.2361.0083**. **Levetiracetam (lista C1 Port. 344/98)**.

Keppra® (levetiracetam). **Apresentação**: Frasco de vidro âmbar contendo 150 mL de solução oral (100 mg/mL), acompanhado de uma seringa de 3 mL para administração. **Indicações:** é indicado como monoterapia para o tratamento de crises focais/parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia. **Keppra®** também é indicado como terapia adjuvante no tratamento de: crises focais/parciais em adultos, crianças e bebês a partir de 1 mês de idade, com epilepsia; crises mioclônicas em adultos e adolescentes a partir dos 12 anos, com epilepsia mioclônica juvenil; crises tônico-clônicas primárias generalizadas em adultos e crianças com mais de 6 anos de idade, com epilepsia idiopática generalizada. **Contraindicações**: Hipersensibilidade ao princípio ativo ou a outros derivados da pirrolidona ou a qualquer um dos excipientes. **Cuidados e Advertências:** para informações completas de advertências, vide bula do produto. A administração de **Keppra®** em pacientes com comprometimento renal poderá necessitar de um ajuste da dose. Foram notificados suicídio, tentativa de suicídio e ideias e comportamento suicida, além de alterações no comportamento como agressividade, agitação, raiva, ansiedade, apatia, depressão, hostilidade e irritabilidade e sintomas psicóticos em pacientes tratados com levetiracetam. Casos de diminuição na contagem de células sanguíneas (neutropenia, agranulocitose, leucopenia, trombocitopenia e pancitopenia) foram descritos em associação à administração de levetiracetam. *Gravidez* categoria C de risco de gravidez. Este medicamento não deve ser utilizado por mulheres grávidas sem orientação médica. Levetiracetam é excretado no leite humano materno. **Keppra®** é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas. *Interações medicamentosas (vide bula completa do produto)*: Dados indicam que levetiracetam não influencia as concentrações séricas de medicamentos antiepilépticos existentes (fenitoína, carbamazepina, ácido valpróico, fenobarbital, lamotrigina, gabapentina e primidona) e que estes medicamentos antiepilépticos não influenciam a farmacocinética de levetiracetam. A probenecida (500 mg quatro vezes ao dia), um agente bloqueador da secreção tubular renal, mostrou inibir a depuração renal do metabólito primário, mas não a do levetiracetam. Contudo, a concentração deste metabólito permanece baixa. Levetiracetam 1000 mg por dia não influenciou a farmacocinética dos contraceptivos orais (etinilestradiol e levonorgestrel). Foram observados relatos isolados de diminuição de eficácia quando o laxante osmótico macrogol foi administrado concomitantemente a levetiracetam oral. Assim, a administração oral de macrogol não deve ser realizada dentro de 1 hora (antes ou após) da administração de levetiracetam. A extensão de absorção do levetiracetam não sofreu qualquer alteração com a ingestão de alimentos, mas a taxa de absorção diminuiu ligeiramente. Não estão disponíveis dados sobre a interação do levetiracetam com o álcool. *Reações Adversas:* para informações completas de reações adversas, vide bula do produto. Os eventos adversos mais comumente reportados nos estudos clínicos foram astenia, fadiga, dor de cabeça e sonolência. Adicionalmente às reações adversas relatadas durante os estudos clínicos as seguintes reações adversas foram reportadas na experiência pós-comercialização, além de outras mencionadas na bula completa do produto: comportamento anormal, raiva, delírio, ataque de pânico, ansiedade, estado de confusão, alucinação, distúrbios psicóticos, suicídio, tentativa de suicídio e ideação suicida, parestesia, coreoatetose, discinesia, letargia, distúrbio de marcha, agravamento das crises epilépticas, dano renal agudo, reações anafiláticas, angioedema. Casos raros de prolongamento do intervalo QT foram observados na vigilância pós-comercialização. Evidências também sugerem uma possível predisposição da população japonesa à síndrome neuroléptica maligna (SNM). **Posologia**: A dose inicial recomendada para monoterapia no tratamento de crises focais/parciais, com ou sem generalização secundária em pacientes a partir dos 16 anos com diagnóstico recente de epilepsia, é de 250 mg (2,5 mL) duas vezes ao dia, a qual poderá ser aumentada para uma dose terapêutica inicial de 500 mg (5 mL) duas vezes ao dia, após duas semanas. A dose máxima é de 1500 mg (15 mL) duas vezes ao dia. Nos casos de terapia adjuvante, para adultos e crianças acima de 12 anos e com peso igual ou superior a 50 kg, a dose terapêutica inicial é de 500 mg/duas vezes ao dia (5 mL/duas vezes ao dia). Esta dose poderá ser iniciada no primeiro dia de tratamento, a dose diária poderá ser aumentada até o máximo de 1500 mg/duas vezes ao dia (15 mL/duas vezes ao dia). Ainda nos casos de terapia adjuvante, para adolescentes, crianças e bebês a partir dos 6 meses com peso inferior a 50 kg a dose terapêutica inicial é de 10 mg/kg (0,1 mL/kg) duas vezes ao dia, a dose pode ser aumentada até 30 mg/kg (0,3mL/kg) duas vezes ao dia. A alteração das doses não deve exceder aumentos ou reduções de 10 mg/kg (0,1 mL/kg) duas vezes ao dia, a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A posologia em crianças com peso igual ou superior a 50 kg é igual à dos adultos. Nos casos de terapia adjuvante para bebês com mais de 1 mês e menos de 6 meses de idade a dose terapêutica inicial é de 7mg/kg (0,07 mL/kg) duas vezes ao dia, a dose pode ser aumentada para um máximo de 21 mg/kg (0,21 mL/kg) duas vezes ao dia. A alteração das doses não deve exceder aumentos ou reduções de 7 mg/kg (0,07 mL/kg) duas vezes ao dia a cada duas semanas. Deve ser utilizada a dose eficaz mais baixa. A solução oral é a forma farmacêutica ideal para uso em bebês. **USO ADULTO E PEDIÁTRICO ACIMA DE 01 MÊS DE IDADE. USO ORAL. VENDA SOB PRESCRIÇÃO MÉDICA. SÓ PODE SER VENDIDO COM RETENÇÃO DA RECEITA.** Para maiores informações, consulte a bula completa do produto. (030204021 R22 Rev. Março/2021). www.ucb-biopharma.com.br. **Reg. MS - 1.2361.0083**. **Levetiracetam (lista C1 Port 344/98)**.

CONTRAINDICAÇÃO: HIPERSENSIBILIDADE AO PRINCÍPIO ATIVO OU A OUTROS DERIVADOS DA PIRROLIDONA OU A QUALQUER UM DOS EXCIPIENTES. **INTERAÇÃO MEDICAMENTOSA:** FORAM OBSERVADOS RELATOS ISOLADOS DE DIMINUIÇÃO DE EFICÁCIA QUANDO O LAXANTE OSMÓTICO MACROGOL FOI ADMINISTRADO CONCOMITANTEMENTE A LEVETIRACETAM ORAL. ASSIM, A ADMINISTRAÇÃO ORAL DE MACROGOL NÃO DEVE SER REALIZADA DENTRO DE 1 HORA (ANTES OU APÓS) DA ADMINISTRAÇÃO DE LEVETIRACETAM.

BR-P-KP-EPI-2100055- Dezembro/2021 - Material de uso exclusivo da classe médica.
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