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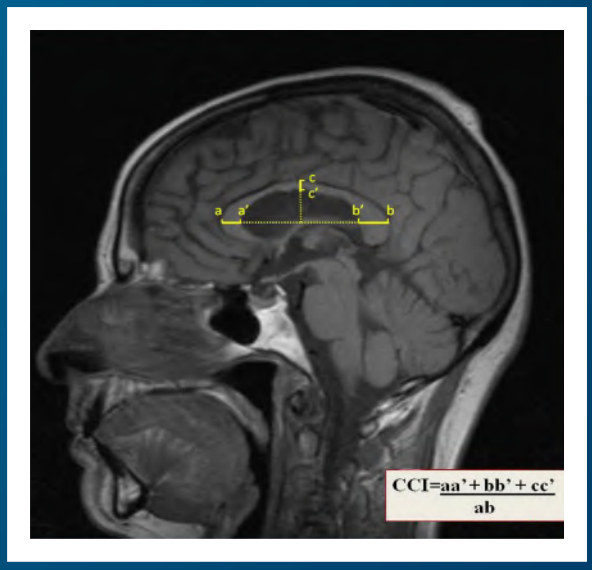

ACADEMIA BRASILEIRA DE NEUROLOGIA

Congresso Brasileiro de Neurologia 2022
Fortaleza.CE

Caros Amigos,

É com muito prazer que convidamos a todos para o Neuro 2022, o XXX Congresso da Academia Brasileira de Neurologia, que será realizado aqui em Fortaleza entre os dias 21 a 24 de setembro do próximo ano.

Nós da Comissão Organizadora, atentos às condições epidemiológicas e sanitárias, planejamos um evento híbrido. Teremos o retorno de atividades presenciais para o número de participantes permitido pelas normas vigentes e faremos transmissão ao vivo para os que preferirem participar de forma virtual.

Esperamos vocês no Neuro 2022 para refletirmos a neurologia do Futuro através de estratégias inovadoras, abrindo o espaço de reconhecimento de toda a produção em neurociências de nosso país, a qual nos guiará pelos melhores caminhos futuros. Faremos isso a partir de quatro eixos principais: **Discutir, Rever, Abordar e Inovar**.

Iremos **Discutir** os dilemas éticos e os desafios como neurologistas; **Rever** temas importantes para a prática neurológica e seu ensino; **Abordar** os avanços dos últimos anos; e **Inovar** na maneira de agir, diagnosticar e tratar.

Com a participação de todos o debate em torno destes tópicos terá a consistência e a força necessária para melhorar o nosso exercício profissional e, por consequência, a neurologia em nosso País.

Além das belezas naturais de Fortaleza, queremos fazer do Neuro 2022 uma oportunidade ímpar para o tão desejado reencontro, seja de forma presencial ou virtual, e uma experiência transformadora inesquecível.

Acessem nosso site, www.neuro2022.com.br e contribuam com sugestões de temas.

Até lá.

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Figueira GMA, Soares PV, Silveira RC, Figueira FFA. “Stable” vs. “silent progressive multiple sclerosis”: a real-world retrospective clinical imaging Brazilian study. Arq Neuropsiquiatr 2022;80(4):405-409. https://doi.org/10.1590/0004-282X-ANP-2020-0234. Page: 408. Figure 3.

Apoio:

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ACADEMIA BRASILEIRA DE NEUROLOGIA

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EDITORIAL

ARTICLE

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Carotid artery stenosis: to infinity and beyond

Estenose carotídea: para o infinito e além

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Thrombosis or embolism originating from large artery atherosclerosis causes 15% of the ischemic strokes with a transient or permanent functional deficit. Primary stroke prevention is based on the control of lifestyle-related risk factors and optimal medical therapy. Patients with a significant atherosclerotic narrowing in their carotid artery can also benefit from an additional surgical or endovascular intervention to reduce the risk, having in mind that atherosclerosis is a systemic disease. We all know that the degree of stenosis is a relevant risk factor of ipsilateral ischemic stroke, and this criterion has been used to select patients in randomized clinical trials. Several clinical trials have been performed to find a cut-off for stenosis and classify the risk of symptomatic and asymptomatic carotid artery disease. However, after the introduction of the so-called 'aggressive medical treatment', there is a lack of long-term results regarding this new medical approach. On the other hand, some ischemic strokes associated with carotid artery disease result from hypoperfusion, in addition to a vulnerable atherosclerotic plaque embolization in which no clinical treatment can solve the issue. We also know that these two mechanisms may act synergistically, and a more profound investigation can make the difference in treating this setting. Routine and more advanced imaging modalities may provide information on the underlying mechanism involved in the ipsilateral ischemic stroke. New concepts about intracranial hemodynamic status and the morphology of the plaque have been discussed, in addition to many neuroimaging modalities to better understand the pathophysiology involved in each situation. Management is an ongoing debate and, most of the time, treatment to prevent an ischemic or recurrent stroke involves some individualized decisions[1,2].

Cerebral ischemia will arise due to reduced oxygen being delivered to the tissue and can occur because of reduced oxygen delivery with or without arterial steno-occlusion. Compromised cerebral perfusion pressure (CPP) occurs in phases, where compensatory mechanisms can be evaluated. When reduced oxygen delivery starts, vasodilation of pial arterioles will ensue, resulting in decreased vascular resistance and increased inflow. In some cases, these tissue-level compensations may be sufficient to ensure the necessary supply of oxygen, but chronic and increased reductions may cause these vessels to approach their dilation limit or exhaust the cerebrovascular reserve capacity. The term cerebrovascular reactivity (CVR) reflects the ability of the blood vessels to dilate to match tissue blood supply to the increased demand and can be investigated by measuring the change in cerebral blood flow (CBF) or cerebral blood volume (CBV) induced by vasodilation. This is obviously not new, and several imaging methods can assess hemodynamic changes to better understand in which stage brain perfusion is facing extracranial stenosis[3,4]. In 1998, Grub and colleagues already demonstrated in the St. Louis Carotid Occlusion study that elevated OEF (oxygen extract fraction) is an independent predictor of stroke in patients with carotid occlusion with an ipsilateral ischemic stroke rate at two years of 5.3% in 42 patients with normal OEF and 26.5% in 39 patients with increased OEF (p=0.004)[5]. Since then, this result has been reproduced in many studies, with several methodologies and neuroimaging modalities. Nevertheless, although these data are recognized as important, this approach could not be established in guidelines mainly because of the unavailability of methods and because of the high cost to screen all patients with carotid stenosis. More recently, neurovascular coupling has been studied following the same principle of hemodynamic response after metabolic demand. The relationship between local activity and subsequent changes in cerebral blood flow can be considered impaired or not[6].

The article published in the April 2022 issue of *Arquivos de Neuropsiquiatria* shows the response to a motor task protocol as a provocative vasodilatory/vasoreactivity TCD test

comparing patients with unilateral symptomatic carotid stenosis (three groups according to the stenosis degree) and health subjects[7]. The study was analyzed considering the degree of stenosis and the asymptomatic and symptomatic sides. They showed an association between impaired CVR and carotid occlusion when compared with the healthy population, and some additional findings concerning the pulsatility index and the sides of stenosis. Although the study design included a small number of patients and did not perform micro embolus monitoring, the authors offer us a simple and accessible tool to access hemodynamic information that can improve our decision-making. Despite the completion of several multi-center trials, the management of carotid stenosis remains in flux and any additional information can help make more reliable individual decisions. Dr. Aysel Milanlioglu et al.[7] demonstrated that TCD can provide information about cerebral hemodynamic status in real-time through an easy and affordable process. TCD with stimulus represented by motor tasks can inform a 'valid number' to explore cerebral autoregulation through the compensatory mechanisms, including vasoreactivity and functional reserve. They argue that it is possible to more effectively determine who the high-risk patients are. The authors found a good correlation between a low reserve and a high degree of stenosis reinforcing this concept. Considering that stenosis is dynamic and includes other variables, individual hemodynamic status data should be guaranteed when monitoring in real-time and should be repeated several times during follow-up. An association with neuroimage markers, like watershed or border zone, can also provide a full understanding of its relationship in symptomatic patients.

Future validation of these method findings could lead to powerful biomarkers of cerebrovascular health and create a different way of thinking in a setting of cerebrovascular disease.

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ARTICLE

Evaluation of cerebral hemodynamic status in patients with unilateral symptomatic carotid artery stenosis during motor tasks, through use of transcranial Doppler sonography

Avaliação do estado hemodinâmico cerebral em pacientes com estenose sintomática unilateral da artéria carótida durante tarefas motoras, por meio de ultrassonografia Doppler transcraniana

Aysel MILANLIOGLU[1], Aslı YAMAN[2], Mehmet KOLUKISA[2], Talip ASIL[2]

ABSTRACT

Background: Carotid artery stenosis increases cerebral ischemic event risk through changing different cerebral hemodynamic parameters. **Objective:** To investigate how cerebral hemodynamics in the M1 segment of middle cerebral artery change in patients with carotid artery stenosis, after motor tasks using transcranial Doppler sonography (TCD). **Methods:** Thirty-two healthy subjects and 30 patients with unilateral symptomatic carotid artery stenosis were recruited. The patient population was divided into three groups according to the degree of stenosis (group 1: ≥50 to 69%, group 2: 70 to 89% and group 3: ≥90 to 99%). TCD was used to measure the pulsatility index (PI) and cerebral vasomotor reactivity (CVR). **Results:** In the patient group, significant differences for symptomatic side PI values (p=0.01) and mean CVR increases (p=0.05) were observed, compared with the healthy controls. However, the difference was not statistically significant for asymptomatic side PI values and mean CVR increases. The results from the intergroup comparison showed significantly higher percentages of symptomatic and asymptomatic side CVR increases in group 1, compared with groups 2 and 3 (p=0.001 and p=0.002, respectively). **Conclusions:** Our study showed that cerebral autoregulation and hemodynamic mechanisms are impaired in patients with carotid artery stenosis. Furthermore, the impairment of PI and CVR tends to get worse with increasing degrees of stenosis. In addition, this study demonstrated that assessment of these two hemodynamic parameters in clinical practice might be helpful for monitoring the progress of carotid artery stenosis.

Keywords: Carotid Stenosis; Vasomotor System; Ultrasonography, Doppler, Transcranial.

RESUMO

Antecedentes: A estenose da artéria carótida aumenta o risco de evento isquêmico cerebral por meio da alteração de diferentes parâmetros hemodinâmicos cerebrais. **Objetivo:** Investigar como a hemodinâmica cerebral no segmento M1 da artéria cerebral média se altera em pacientes com estenose da artéria carótida, após tarefas motoras com ultrassonografia Doppler transcraniana (DTC). **Métodos:** Foram recrutados trinta e dois indivíduos saudáveis e 30 pacientes com estenose da artéria carótida sintomática unilateral. A população de pacientes foi dividida em três grupos de acordo com o grau de estenose (grupo 1: ≥50 a 69%, grupo 2: 70 a 89% e grupo 3: ≥90 a 99%). A DTC foi usada para medir o índice de pulsatilidade (IP) e a reatividade vasomotora cerebral (RVC). **Resultados:** No grupo de pacientes, foram observadas diferenças significativas para os valores de IP do lado sintomático (p=0,01) e aumentos médios da RVC (p=0,05), em comparação com os controles saudáveis. No entanto, a diferença não foi estatisticamente significativa para os valores de IP laterais assintomáticos e aumentos médios de RVC. Os resultados da comparação intergrupos mostraram percentagens significativamente maiores de aumentos da RVC do lado sintomático e assintomático no grupo 1, em comparação com os grupos 2 e 3 (p=0,001 e p=0,002, respectivamente). **Conclusões:** Nosso estudo mostrou que a autorregulação cerebral e os mecanismos hemodinâmicos estão prejudicados em pacientes com estenose da artéria carótida. Além disso, o comprometimento do IP e da RVC tende a piorar com o aumento dos graus de estenose. Além disso, este estudo demonstrou que a avaliação desses dois parâmetros hemodinâmicos na prática clínica pode ser útil para monitorar a evolução da estenose da artéria carótida.

Palavras-chave: Estenose das Carótidas; Sistema Vasomotor; Ultrassonografia Doppler Transcraniana.

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Authors' contributions: TA: supervision, project administration, conceptualization, resources, funding acquisition; AM: writing original draft, writing-review, editing, methodology, investigation; MK: validation, visualization, software, investigation; AY: formal analysis, data curation, resources, software.

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INTRODUCTION

The relationship between internal carotid artery stenosis and stroke has been widely examined in the medical literature. This disease is reported in approximately 15–20% of stroke patients[1], and older age definitely increases the risk. It has been reported that 7% of women and 9% of men have more than 50% carotid artery stenosis above age 75 years[2].

There are many studies demonstrating that carotid artery stenosis increases the cerebral ischemic event risk through changing different cerebral hemodynamic parameters[3,4]. However, how these cerebral hemodynamic parameters alter in relation to the degree of stenosis in the carotid artery remains unexplored. It would be expected that these two physiological mechanisms affect each other, given that stenosis is likely to cause a reduction in cerebral blood flow and it also decreases the effectiveness of autoregulation[5]. A full understanding of their relationship can aid in clinical practice and in monitoring the progress of stenosis in the carotid artery.

Neurovascular coupling refers to the relationship between local neural activity and subsequent changes in cerebral blood flow. Understanding which aspects of neural activity drive the vascular response is important. Up to now, numerous vascular-based functional brain imaging modalities, like functional magnetic resonance imaging (fMRI), have been used. However, these may not always be feasible, due to their high costs and logistic issues.

Transcranial doppler sonography (TCD) is a relatively cheaper and more accessible method. TCD is a noninvasive technique that detects flow velocities in the cerebral arterioles and hemodynamic changes during specific activation stimuli that are capable of producing changes in cerebral activity and metabolism. This method has been used as an alternative measurement of cerebral blood flow responses to neural activity[6].

TCD can measure several parameters, including cerebral vasomotor reactivity (CVR). CVR demonstrates the compensatory vasodilatation capacity of cerebral arterioles in response to various specific vasomotor stimuli, such as reduction in systemic blood pressure, changes in oxygen extraction or partial carbon-dioxide pressure, breath-holding, application of vasoactive substances such as acetazolamide, or motor stimulus. Briefly, this parameter gives an idea about individuals' functional cerebral hemodynamic reserves[7]. Previous studies have indicated that impairment of CVR might be related to various conditions including hypertension[8], cognitive disorder[9], diabetes mellitus[10] and sleep apnea syndrome[11].

One of the other major factors influencing cerebral hemodynamics is the pulsatility index (PI), which was originally designed to measure vascular resistance. Thus, an increased PI represents probably enhanced cerebrovascular resistance in the cerebral circulation and reduced CVR[12].

The association between neural activation and enhanced regional cerebral blood flow, due to increased metabolism of the cerebral cortex caused by external stimuli, has now been investigated in many studies[13-16]. However, none of the previous studies used a motor evoked response as a stimulus. Therefore, we aimed here to monitor changes in blood flow velocity in the middle cerebral artery (MCA) through using TCD in response to a repetitive motor stimulus, in patients with varying degrees of unilateral symptomatic carotid artery stenosis.

METHODS

Subjects

Patients with internal carotid artery stenosis of 50 to 99% were selected as participants for the current study. These carotid artery stenosis values were determined through using carotid duplex ultrasound and were measured in accordance with the criteria of the North American Symptomatic Carotid Endarterectomy Trial (NASCET).

Right-handed patients of 18-70 years of age, with unilateral symptomatic internal carotid artery stenosis of ≥50%, and with a history of ischemic stroke or transient ischemic attack (TIA) in the ipsilateral arterial region, were included in this study. Imaging of the patients' carotid artery was examined by using continuous-wave Doppler and color-flow B mode Doppler ultrasound (Esaote MyLab 30 CV Color Doppler Ultrasound System). In patients with steno-occlusive lesions of ≥70% that were observed via carotid duplex ultrasound, the degree of stenosis was confirmed by means of cervical CT angiography or magnetic resonance angiography.

A detailed medical history, including all major vascular risk factors (hypertension, diabetes mellitus, dyslipidemia and smoking), was established for all participants. Routine blood analyses and neurological examinations were also performed. In addition to antiplatelet drugs, other drugs (insulin, oral antidiabetic treatment, statins and different classes of antihypertensive drugs) were also given as medical treatments to manage vascular risk factors.

Patients with the following were not included as participants in this study: a history of stroke or transient ischemic attack (TIA) during the last 3 months; motor weakness in upper extremities; poor insonation of cranial window; intracranial and/or extra-cranial tandem stenosis; bilateral carotid artery stenosis (greater than 40% shown on the side contralateral to the occlusion); significant alteration in vertebral arteries in a simultaneous vertebra-basilar artery examination; anemia (hematocrit ≤30%) or polycythemia (hematocrit ≥50%) affecting cerebral blood flow; or cognitive disorders. Patients with possible or probable embolizing cardiopathy (atrial fibrillation, mitral valve stenosis, mechanical cardiac valves, recent myocardial infarction, left ventricular thrombus, dilated cardio-myopathies or patent foramen ovale) were also excluded.

Based on these criteria, 30 patients (21 males and 9 females; mean age 67.5 years) and 32 healthy subjects (24 males and 8 females; mean age 65.03 years) were recruited. Moreover, the patient population was divided into three groups: group 1

included 10 patients diagnosed with carotid stenosis of ≥50 to 69% (5 males and 5 females; mean age 69.40±11.34 years); group 2 included 10 patients with stenosis of 70 to 89% (8 males and 2 females; mean age 73.70±5.35 years); and group 3 included 10 patients with stenosis of ≥90 to 99% (8 males and 2 females; mean age 67.50±7.76 years). A population of 32 right-handed, age and gender-matched healthy subjects without carotid stenosis or any neurological abnormality in their history were also enrolled and underwent the same exploration procedures using TCD.

This study was conducted ethically in accordance with the World Medical Association's Declaration of Helsinki and ethical clearance was obtained from the regional ethics committee. Written and oral informed consent was obtained from the study participants.

Transcranial doppler sonography procedure

Prior to the TCD procedure, the patients' systolic and diastolic arterial blood pressures and heart rate were measured following a resting period of 10 minutes in a quiet and calm room. After this process, the patients were asked to lie down comfortably in a supine position. The Sonora TCD system (CareFusion, San Diego, CA, USA) was used for the standard TCD recording protocol. During TCD recording, a 2 MHz pulse doppler transducer probe was placed in a temporal window, and the middle cerebral artery blood flow velocity (MCAv) was measured at depths of between 50 and 60 mm. Systolic blood flow velocity (SBFV), diastolic blood flow velocity (DBFV) and PI were recorded in the M1 segment of the MCA. However, only PI results were analyzed without evaluating SBFV and DBFV separately. Moreover, the Gosling PI formulation was calculated automatically as (systolic velocity-diastolic velocity)/(mean velocity)[9].

MCAv is a marker of cerebral blood flow in the ipsilateral carotid artery. A baseline recording of MCAv was performed with the subject under baseline conditions (resting and breathing room air). One of the vasodilatory stimuli, a motor task, was then administered in accordance with the motor task protocol mentioned below. MCAv values were separately calculated for each group under the baseline conditions and during the motor task. The relative increase from baseline to motor activation was calculated based on the following equation: [(MCAv activation-MCAv baseline)/(MCAv baseline)]*100 and was expressed as the CVR value. Among the healthy subjects, measurements of PI and CVR were exclusively obtained from the left M1 branch of the MCA. At least three measurements of PI and CVR were performed at a similar depth, and the median value was selected and used in this study.

Motor task protocol

During the entire procedure, the subjects were tested with closed eyes in a comfortable supine position. For finger movements, the arm was positioned in a guide hinge that allowed movements in only one plane, coinciding with flexion and extension of the fingers. Flexion and extension movements of the fingers were performed every two seconds at the same rate, and this phase was terminated after 30 seconds. The rest condition was 1 minute period preceding each motor task after verification of the absence of oscillation of flow velocity. The subjects were instructed to move fingers in synchrony during the active periods and then to remain in a resting position. The TCD assessment was repeated three times and the mean value was calculated for each subject. Before proceeding to the definitive recording, the subjects were trained to perform the procedure correctly.

All the subjects abstained from drinking alcohol and beverages containing caffeine, and from smoking, for at least 24 hours prior to the examination. All recordings and calculations of CVR and PI were performed in the early morning by the same two operators, who were blinded to clinical and other TCD data.

Statistical analyses were performed by means of a computerized program, the *Statistical Package for the Social Sciences* software (version 13.0). The Pearson's chi-square test was performed to compare categorical variables among the groups. The age distribution between groups was assessed using Student's *t* test. The ANOVA test was used to assess the significance of differences among the three subject groups. Correlations between variables were measured and evaluated using Pearson's correlation coefficient. The statistical significance level was taken to be $p \leq 0.05$.

RESULTS

Among the subject groups, there were no significant differences when the distribution of age, sex and vascular risk factors was taken into consideration. The demographic data and vascular risk factors are presented in Table 1.

The comparison of mean CVR increases and PI values on the symptomatic and asymptomatic sides is summarized in Table 2. Although the CVR values were found to be negatively correlated with age and PI values ($p<0.01$), the PI values were found to be positively correlated with age ($p<0.05$).

From the subgroup analysis, the mean CVR increases on the symptomatic side were 34.78% in group 1, 27.74% in group 2 and 24.44% in group 3. However, the mean CVR increases on the asymptomatic side were 36.09, 30.02 and 26.75%, respectively. The CVR increases on the symptomatic and asymptomatic sides of group 1 were statistically significantly different from those of group 2 ($p=0.001$) and group 3 ($p=0.002$). On the other hand, the mean PI values on the symptomatic side were calculated as 0.78 in group 1, 1.43 in group 2 and 1.55 in group 3 while the mean PI values on the asymptomatic side were 0.76, 1.26 and 1.25, respectively. Intergroup comparisons showed that the PI values on the symptomatic and asymptomatic sides in group 1 were statistically significantly lower than those in group 2 ($p=0.001$) and group 3 ($p=0.002$).

Table 1. Demographic data and vascular risk factors in carotid stenosis patients and control group.

	Patients (n=30)	Controls (n=32)	p-value
Sex (male/female)	21/9	24/8	NS
Mean age (years)	67.5	65.03	NS
Smoking	6	8	NS
Hypertension	24	20	NS
Hyperlipidemia	27	25	NS
Diabetes mellitus	8	10	NS

NS: non-significant.

Table 2. Comparison of cerebral vasomotor reactivity increase and pulsatility index between carotid stenosis patients and control group.

	Patients		Controls	p-value
CVR increase	Symptomatic side	28.98%	32.37%	0.05
	Asymptomatic side	30.95%		0.40
PI	Symptomatic side	1.25	0.97	0.01
	Asymptomatic side	1.09		0.20

PI: pulsatility index; CVR: cerebral vasomotor reactivity.

In addition, the mean CVR increases on the symptomatic side were negatively associated with the degree of stenosis in the carotid artery ($p<0.01$), while the mean CVR increases on the asymptomatic side were negatively associated with the degree of stenosis in the carotid artery and were positively associated with the mean CVR increases on the symptomatic side ($p<0.01$). Correlation analysis on the data revealed that the mean PI values on the symptomatic side were negatively correlated with the mean CVR increases on the symptomatic and asymptomatic sides, and were positively correlated with the degree of stenosis in the carotid artery ($p<0.01$). Moreover, the mean PI values on the asymptomatic side were positively associated with the mean PI values on the symptomatic side, in addition to the abovementioned parameters ($p<0.01$).

From the analyses performed in both the patient and the control group, we were unable to observe any significant relationship between the risk factors, CVR increases and PI values.

DISCUSSION

Assessments of CVR by means of TCD and provocative vasodilatory tests are among the most commonly used tests for evaluating cerebral hemodynamic status in patients with carotid artery disease. Although several methods such as breath-holding, hyperventilation, CO_2 challenge and the acetazolamide provocation test[17] are widely used, we preferred to use active voluntary repetitive motor activity for the provocation test modality because of the evidence that such activity induces CVR improvements among stroke survivors[18].

The mechanism postulated for this active motor movement of the fingers is associated with neuronal activation, dilatation of cerebral arterioles and increased regional cerebral blood flow caused by increased metabolism of the contralateral primary sensory-motor cortex, with the maximum increase of blood flow velocity on the posterior margin of the central sulcus[19]. Although TCD findings cannot provide any information about the mechanism of activation or the exact localization of changes in cerebral activity after these motor movements, they are widely used to assess cerebral autoregulation and collateral circulation.

Previous studies demonstrated that patients showed an association between impaired CVR and carotid occlusion[3,20,21]. The recent findings are also supported by the results from fMRI and TCD, which display slowed and reduced cortical hemodynamic responses to the different stimuli in the hemisphere ipsilateral to carotid stenosis[22]. Despite the absence of asymptomatic side difference, we demonstrated that the symptomatic side showed decreased CVR in all patients, in relation to the healthy subjects. However, there were some modifications to the methodology of our study, regarding the evaluation of PI values, such that the asymptomatic side was analyzed and patients were grouped according to the degree of stenosis.

King et al.[4] described an association between CVR and the number of embolic signals in patients with asymptomatic carotid stenosis. This interesting result, which suggests that an interaction between hypoperfusion and embolism exists, can also guide us to an explanation for our findings about increased CVR and decreased PI values in group 1, compared with groups 2 and 3. Briefly, our study showed that both PI and CVR were impaired in patients with moderate to severe carotid artery stenosis.

Senescence causes atherosclerosis, decreased neuronal plasticity and greater rigidity of the vessel system, thus giving rise to constant vascular diameters. Therefore, patients of a given age might respond differently and show impaired reaction patterns to vasoactive stimuli. Schreiber et al.[23] proved that there was no change in the diameter of the MCA after acetazolamide provocation testing, seen through high-resolution MRI on patients with occlusive extracranial carotid artery disease. In our study, the positive impact of age on the PI values and negative impact of age on the CVR was clearly observed. Indeed, the adverse interaction between CVR and PI entirely reflected the accuracy of this information.

Regarding the positive association of PI and CVR values on the symptomatic and the asymptomatic sides, we speculate that the parameters causing changes to cerebral autoregulation actually affect the entire brain, regardless of the side. However, better understanding of this association and the changes in the cerebral autoregulation is needed.

Lastly, some limitations to this study should be noted. These include the small number of patients, the lack of a standardized examination protocol for motor task administration due to absence of a device and the lack of any evaluation of compensatory mechanisms, including collateral blood flow through the ophthalmic artery, anterior communicating artery and posterior communicating artery. Nonetheless, despite these limitations, we believe that our study provides new insights.

In conclusion, the present study demonstrated that cerebral autoregulation and hemodynamic mechanisms are impaired in patients with carotid artery stenosis. Furthermore, with increasing degrees of stenosis, impairment of PI and CVR tends to become worse. Assessment of these two hemodynamic parameters in clinical practice might be helpful for monitoring the progress of carotid artery stenosis.

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ARTICLE

Evaluation of cerebral hemodynamics by transcranial Doppler ultrasonography and its correlation with intracranial pressure in an animal model of intracranial hypertension

Avaliação da hemodinâmica encefálica utilizando Doppler transcraniano e sua correlação com a pressão intracraniana em um modelo animal de hipertensão intracraniana

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ABSTRACT

Background: Transcranial Doppler has been tested in the evaluation of cerebral hemodynamics as a non-invasive assessment of intracranial pressure (ICP), but there is controversy in the literature about its actual benefit and usefulness in this situation. **Objective:** To investigate cerebral blood flow assessed by Doppler technique and correlate with the variations of the ICP in the acute phase of intracranial hypertension in an animal model. **Methods:** An experimental animal model of intracranial hypertension was used. The experiment consisted of two groups of animals in which intracranial balloons were implanted and inflated with 4 mL (A) and 7 mL (B) for controlled simulation of different volumes of hematoma. The values of ICP and Doppler parameters (systolic [FVs], diastolic [FVd], and mean [FVm] cerebral blood flow velocities and pulsatility index [PI]) were collected during the entire procedure (before and during hematoma simulations and venous hypertonic saline infusion intervention). Comparisons between Doppler parameters and ICP monitoring were performed. **Results:** Twenty pigs were studied, 10 in group A and 10 in group B. A significant correlation between PI and ICP was obtained, especially shortly after abrupt elevation of ICP. There was no correlation between ICP and FVs, FVd or FVm separately. There was also no significant change in ICP after intravenous infusion of hypertonic saline solution. **Conclusions:** These results demonstrate the potential of PI as a parameter for the evaluation of patients with suspected ICP elevation.

Keywords: Intracranial Pressure; Intracranial Hypertension; Ultrasonography, Doppler, Transcranial; Models, Animal.

RESUMO

Antecedentes: O Doppler transcraniano (DTC) é uma técnica não invasiva para a avaliação da hemodinâmica cerebral, porém existem controvérsias na literatura sobre sua aplicabilidade preditiva em situações de elevada pressão intracraniana (PIC). **Objetivo:** Investigar o fluxo sanguíneo cerebral pelo DTC e correlacioná-lo com as variações da PIC na fase aguda da hipertensão intracraniana em modelo animal. **Métodos:** Dois grupos de animais (suínos) foram submetidos a hipertensão intracraniana secundária à indução de diferentes volumes de hematoma, por meio da insuflação de balão intracraniano controlado com 4 e 7 mL de solução salina fisiológica (grupos A e B, respectivamente). Em seguida, administrou-se infusão venosa de solução salina hipertônica (SSH 3%). Foram coletados os valores dos parâmetros de PIC e DTC (velocidade sistólica [FVs], diastólica [FVd] e média [FVm] do fluxo sanguíneo cerebral), bem como o índice de pulsatilidade (IP). Comparações entre os parâmetros do DTC e o monitoramento da PIC foram realizadas. **Resultados:** Vinte porcos foram estudados, dez no grupo A e dez no grupo B. Correlação significativa entre IP e PIC foi obtida, principalmente logo após a elevação abrupta da PIC. Não houve correlação entre PIC e FVs, FVd ou FVm separadamente. Também não houve alteração significativa na PIC após a infusão de SSH. **Conclusões:** Esses resultados demonstram o potencial do IP como um bom parâmetro para a avaliação de pacientes com suspeita de elevação da PIC.

Palavras-chave: Pressão Intracraniana; Hipertensão Intracraniana; Ultrassonografia Doppler Transcraniana; Modelos Animais.

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INTRODUCTION

Intracranial hypertension (ICH) is a challenging clinical condition in the management of patients with acute intracranial lesions. Many conditions can lead to an abrupt increase in intracranial pressure (ICP), such as traumatic brain injury (TBI), stroke, spontaneous intracerebral hemorrhage (SICH), hydrocephalus, infections, brain tumors, etc[1-4].

Invasive ICP monitoring is an important adjunct in the clinical management of ICH, although there are no studies with strong evidence of its benefits[5]. In a trial published in 2012, invasive ICP monitoring was not associated with better patient outcome compared to clinical and tomographic evaluations[6]. Nonetheless, this technique remains the gold standard method for ICP assessment according to the current Brain Trauma Foundation (BTF) guidelines[5].

With this in mind, techniques based on transcranial Doppler (TCD), a non-invasive method easily accessible at bedside, have been studied. Elevation of ICP leads to changes in the cerebral wave pattern and blood flow velocities obtained by TCD[7-9].

While TCD is a promising method for bedside evaluation, studies that investigated it as a surrogate of ICP have controversial results, especially because of influences of systemic factors on flow velocities and debate concerning pulsatility index (PI) as an indicator of whether ICP or cerebral perfusion pressure. Further studies are needed to confirm this hypothesis[10-12]. Thus, in this experimental study, we aimed to correlate cerebral blood flow assessed using Doppler technique with the variations of the ICP in acute phase of intracranial hypertension in an animal model.

METHODS

This experimental study was previously approved by the Ethics Committee for Research Projects of the University of São Paulo Medical School. All applicable institutional and national guidelines for the care and use of animals were followed.

Animals

Hybrid pigs of the Landrace, Duroc, and Pietrain breeds were used. These were brought into the laboratory on the day of the experiment.

Anesthesia protocol

The animals were pre-anesthetized with ketamine (Ketamin-S®, Cristália) at a dose of 5 mg/kg and midazolam (Dormire®, Cristália) at a dose of 0.25 mg/kg, both placed in the same syringe and administered intramuscularly. These drugs were selected because they have no significant influence on ICP and cerebral blood flow[13,14]. After 15 minutes, the marginal ear vein was punctured with a 20- or 22-gauge vascular catheter (BD Insyte®). Intravenous anesthetic induction with propofol (Provine® 1% — Cláris) was performed at a dose of 5 mg/kg. The animals were submitted to orotracheal intubation with an endotracheal tube of 6 mm diameter (Portex®), and anesthetic maintenance was performed with propofol (Provine® 1% — Cláris) at a dose of 3 mg/kg/h and analgesia was maintained with fentanyl (Fentanest® — Cristália) at an initial dose of 5 μg/kg followed by continuous intravenous (IV) infusion of 0.4 μg/kg/min. Neuromuscular blockade was obtained with pancuronium (Pancuron®, Cristalia) bolus at 0.1 mg/kg IV followed by continuous infusion of this agent at a dose of 0.02 mg/kg/h.

After intubation, the animals were submitted to volume-controlled mechanical ventilation (Dixtal® 5010 Ventilator). Through an abdominal medial incision, cystostomy was performed under direct vision to control diuresis of the animal. The right femoral artery was punctured and connected to a pressure transducer in all animals for monitoring of invasive mean arterial pressure. Arterial blood gas analysis was performed with samples of 0.3 mL at the beginning of the procedure (in order to establish ventilatory parameters), and after interventions, to evaluate maintenance of the physiological parameters.

Experimental procedure

The ICH animal model developed and previously validated by this research group was used in the present study[15], inclusive for TCD assessment in swine[16,17]. The model simulates a right frontal intracerebral hemorrhage, performed in a controlled manner. An L-shaped fronto-temporal incision was performed on the head of each animal, at the midline and temporal region just in front of the ear to expose the coronary and sagittal sutures. Then, a bone trepanation 1 cm lateral to the sagittal suture and 1 cm anterior to the coronal suture was made in the right hemicranium, through which the intraparenchymal catheter (Neurovent-P®, Raumedic®, Munchberg, Germany) was inserted for invasive ICP monitoring in the frontal lobe white matter. A bone trepanation located 1 cm lateral to the sagittal suture and 1 cm posterior to the coronary suture allowed the introduction of an 8-French pediatric vesical catheter, reaching the subcortical white matter. Then, infusion of 0.9% NaCl solution (PS) was performed for 15 minutes, controlled with infusion pump (Infusomat® compact, B Braun®, Melsungen, Germany). A small ipsilateral temporal trepanation was also performed to allow the accomplishment of cerebral Doppler ultrasound with a 5-8 MHz transducer (SonoSite - Micromax, FUJIFILM SonoSite, Washington, DC, United States). This allowed to analyze the cerebral blood flow velocity, establishing the systolic blood flow velocity (FVs), the diastolic velocity (FVd), and from these, the derived parameters were obtained: mean blood flow velocity (FVm=FVs+2xFVd/3) and the pulsatility index (PI) (FVs-FVd/FVm).

The animals were divided into two groups (A and B), in which intracranial hypertension was induced by the inflation of the intraparenchymal balloon with two different volumes, as described below (Table 1). Normal parameters were calibrated in both groups in the first hour.

In group A, the balloon already implanted in the frontal white matter was infused with 4 mL of PS, and soon after, the multiparametric data were collected, which included ICP and the evaluation by TCD. This hematoma is equivalent to an expansion of approximately 80 ml in a human adult brain. This equation is based on the proportion of the brain weight of the animal of 2 months and 18 kg (average of 75 g) relative to normal adult brain weight (1500 g), with a 5% relation. In group B, a 7 mL infusion of PS was performed, equivalent to a volume of approximately 140 mL in a human adult brain[15].

In both groups, one hour and 30 minutes after onset of balloon inflation, intravenous infusion of hypertonic saline solution (HS; 3% NaCl solution at the dose of 5.3 mL/kg) was performed. After another 30 minutes, we proceeded with balloon deflation, corresponding to the simulation of a surgical procedure.

During the experiment, several parameters were monitored including clinical parameters (pupils), invasive mean arterial pressure (MAP), parenchymal ICP, and TCD measurements (FVs, FVd, FVm, PI) obtained bilaterally from the middle cerebral arteries. These data were collected before and after all interventions on the animals.

At the end of each experiment, the animals were sacrificed through an intravenous dose of propofol (20 mg/kg) and fentanyl (10 mg/kg), followed by 40 mL of 19.1% potassium chloride solution. After the sacrifice, the animals were placed in plastic bags, with labels that clearly identified the origin, content, and the responsible researcher. They were then transported to be incinerated according to our institution routine protocol.

Statistical analysis

Statistical analysis was presented through means and standard deviations, as well as graphs of individual and medium profiles. For each of the measurements, including ICP, adjusted linear mixed regression analysis were applied, considering random effect in the intercept and normal distribution for the random effects[18]. Spearman correlation was calculated for PI and ICP values. The graphical analysis indicated that the random effect of the intercept appeared to differ between groups as well (experiment effect variability in group B was higher than in group A). Therefore, besides considering a random effect of the individual, the effect was considered distinct between groups. The analyses were performed using the R 3.4.0 software (R Core Team, 2017, Vienna, Austria). The results were interpreted using a significance level of 5%.

RESULTS

Twenty two-month-old hybrid pigs with an average weight of 18.46 kg (±1.12) were studied. They were divided in two groups of ten animals: group A (4 males, 6 females) and group B (4 males, 6 females). One pig in group B died before the end of the experiment and was excluded from the analysis. All animals were hemodynamically stable during the experimental procedure, except two animals of group B that presented refractory low blood pressure.

Table 2 shows the means and standard deviations observed for ICP measurements collected from the intraparenchymal monitoring and the TCD-based variables FVs, FVd, FVm, and PI. A moderate elevation of ICP was observed in group A and a significant increase was observed in group B after inflation of the balloon (Figure 1). No major ICP variation between the pre-HS and pre-deflation moments were observed in both groups.

From the adjusted model, Table 3 was constructed, comparing the groups for each moment and the differences between groups for each evaluated moment (basal, post-inflation, pre-HS, post-HS, pre-deflation and post-deflation). There was no statistical difference in ICP between groups before and after the end of the experiment. ICP was higher in group B than group A in the moments just after the insufflation, pre-HS, post-HS and pre-deflation. There was no statistical difference between groups in FVs, FVd, FVm, and PI at any point of the experiment. For transcranial Doppler analysis, data of two animals of group B were excluded due to severe hemodynamic instability (Figure 2). Hence, subjects without significant changes in systemic hemodynamics during the procedure were accounted for statistical analysis.

There was a moderate correlation between PI and ICP at three moments of the experiment (Spearman correlation coefficients): at baseline (r:0.661), post-inflation (r:0.543), and post-deflation (r:0.578), all with $p<0.05$. No significant correlation was found between ICP and FVs, FVd, and FVm. The dispersion of the correlations between ICP and PI are presented in Figure 2. It shows that the correlation of ICP with PI

Table 1. Experiment time points.

Group	0h to 1 h	1h from start	2.5h from start	3h from start	4h from start
A	Settings	4 mL balloon inflation	3% HS infusion	Balloon deflation	End
B	Settings	7 mL balloon inflation	3% HS infusion	Balloon deflation	End

HS: hypertonic saline solution; h: hour.

Table 2. Means and standard deviations of measurements by group and time point.

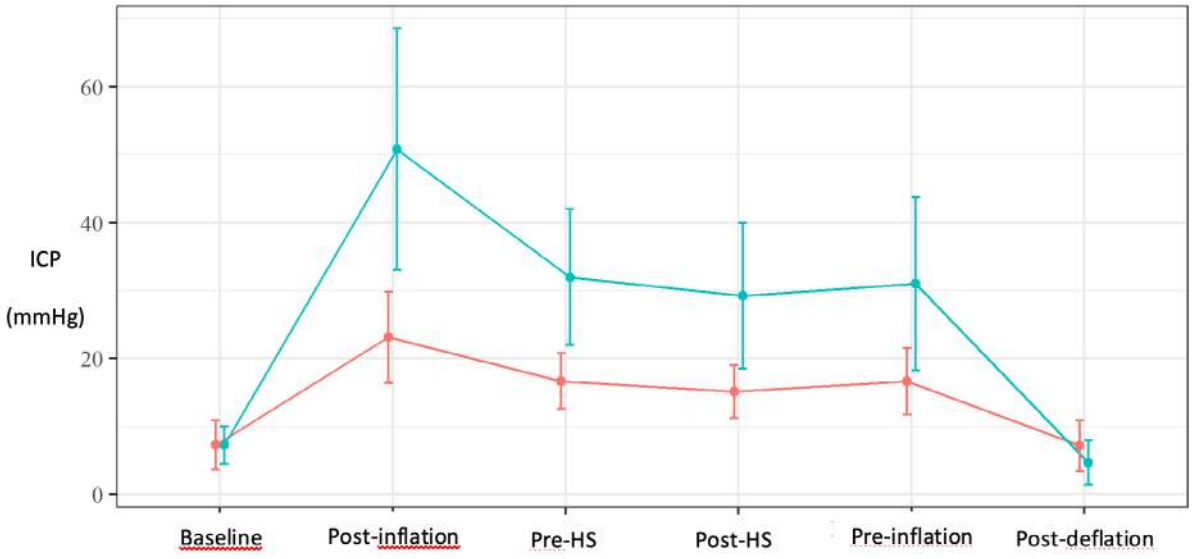
Parameter	Moment	Group A (n=10)	Group B (n=9)	Total (n=19)
ICP (mmHG)	Baseline	7.26±5.87	7.28±4.2	7.27±5.01
	Post-inflation	23.12±10.86	50.81±27.21	36.24±24.28
	Pre-HS	16.69±6.6	31.96±15.31	23.92±13.69
	Post-HS	15.17±6.26	29.21±16.42	21.82±13.83
	Pre-deflation	16.65±7.96	31.01±19.47	23.45±15.95
	Post-deflation	7.16±6.1	4.69±4.96	5.99±5.58
FVs (cm/s)	Baseline	75.32±48.05	67.93±29.45	71.82±39.43
	Post-inflation	80.32±53.33	59.42±27.84	70.42±43.37
	Pre-HS	89.88±46.06	57.81±26.04	74.69±40.41
	Post-HS	89.17±55.09	79.91±39.05	84.78±47.09
	Pre-deflation	89.76±41.75	71.31±27.27	81.02±35.94
	Post-deflation	94.99±49.08	93.76±35.36	94.41±41.96
FVd (cm/s)	Baseline	39.62±24.53	33.64±12.27	36.79±19.42
	Post-inflation	30.72±16.79	17.69±9.17	24.55±14.93
	Pre-HS	42.23±22.31	21.75±23.08	32.53±24.42
	Post-HS	45.39±24.76	27.55±36.62	36.94±31.41
	Pre-deflation	46.01±20.61	29.58±24.17	38.23±23.3
	Post-deflation	53.14±27.27	48.02±28.17	50.71±27.04
FVm (cm/s)	Baseline	51.52±32.21	45.07±17.72	48.47±25.87
	Post-inflation	47.25±27.97	31.6±14.07	39.84±23.32
	Pre-HS	58.11±28.13	33.77±22.69	46.58±27.94
	Post-HS	59.98±33.89	45±32.02	52.89±33
	Pre-deflation	60.59±26.82	40.45±23.01	51.05±26.49
	Post-deflation	67.09±33.65	63.26±29.07	65.27±30.75
PI	Baseline	0.69±0.15	0.74±0.19	0.71±0.17
	Post-inflation	1.02±0.31	1.3±0.39	1.15±0.37
	Pre-HS	0.82±0.3	2.54±3.68	1.63±2.62
	Post-HS	0.71±0.22	6.59±15.83	3.5±10.98
	Pre-deflation	0.73±0.2	11.73±31.31	5.94±21.62
	Post-deflation	0.63±0.19	0.87±0.65	0.75±0.47

FVs: systolic cerebral blood flow velocity; FVd: diastolic cerebral blood flow velocity; FVm: mean cerebral blood flow velocity; PI: pulsatility index; post-inflation: after balloon inflation; pre- and post-HS: pre- and post-hypertonic solution infusion; pre- and post-deflation: pre- and post-balloon deflation.

at baseline and shortly after balloon inflation is greater than the correlation between ICP and other PI values over time. As the elevation in ICP was varied widely among subjects, a precise cut-off was could not be calculated, although Table 2 indicates that for a sudden severe ICH (group B), PI elevation is progressive and less specific for intervention, except for a rapid relief (balloon deflation could simulate decompressive cranioctomy). Figure 3 shows a positive correlation between PI and ICP, especially with substantial elevation in ICP (>30 mmHg). A moderate elevation in ICP tends to respond better to interventions such as hypertonic saline, and PI will have more negative predictive value in these cases.

DISCUSSION

The present study makes important contributions in the development of an animal model with induced and reversible ICH. Correlations between ICP- and TCD-derived parameters were calculated. There was a moderate correlation between PI and ICP at three moments of the experiment. From the pre-HS moment to pre-deflation, there was no significant correlation. The variables FVs, FVd, and FVm were not correlated with ICP at any moment. The data obtained are in agreement with those of some studies and in contrast with others, as discussed below.



Group A: red line; Group B: green line; ICP: intracranial pressure; post-inflation: after balloon inflation; pre- and post-HS: pre- and post-hypertonic solution infusion; pre- and post-deflation: pre- and post-balloon deflation.

Figure 1. Average profile of intracranial pressure per group.

Table 3. Multiple comparisons of the intracranial pressure difference between groups B and A at different time points of the experiment.

Multiple comparisons	95%CI	p-value
7–4 mL (Baseline)	0.02 (-11.33–11.37)	0.998
7–4 mL (post-inflation)	27.69 (16.34–39,04)	<0.001
7–4 mL (pre-HS)	15.27 (3.91–26.62)	0.008
7–4 mL (post-HS)	14.04 (2.69–25.39)	0.015
7–4 mL (pre-deflation)	14.36 (3.01–25.71)	0.013
7–4 mL (post-deflation)	-2.47 (-13.82–8.88)	0.670

95%CI: 95% confidence interval; post-inflation: after balloon inflation; pre- and post-HS: pre- and post-hypertonic solution infusion; pre- and post-deflation: pre- and post-balloon deflation.

Correlation between intracranial pressure invasive monitoring and transcranial Doppler parameters

Invasive ICP monitoring devices have been developed throughout the 20th century and since then have become the gold standard method for this purpose, despite controversial results in some studies[5,6,19-21]. However, due to its potential complications, such as infection, hemorrhage, and misplacement, numerous studies have been conducted in recent years aimed at developing several non-invasive techniques for estimation of ICP[9,22-24].

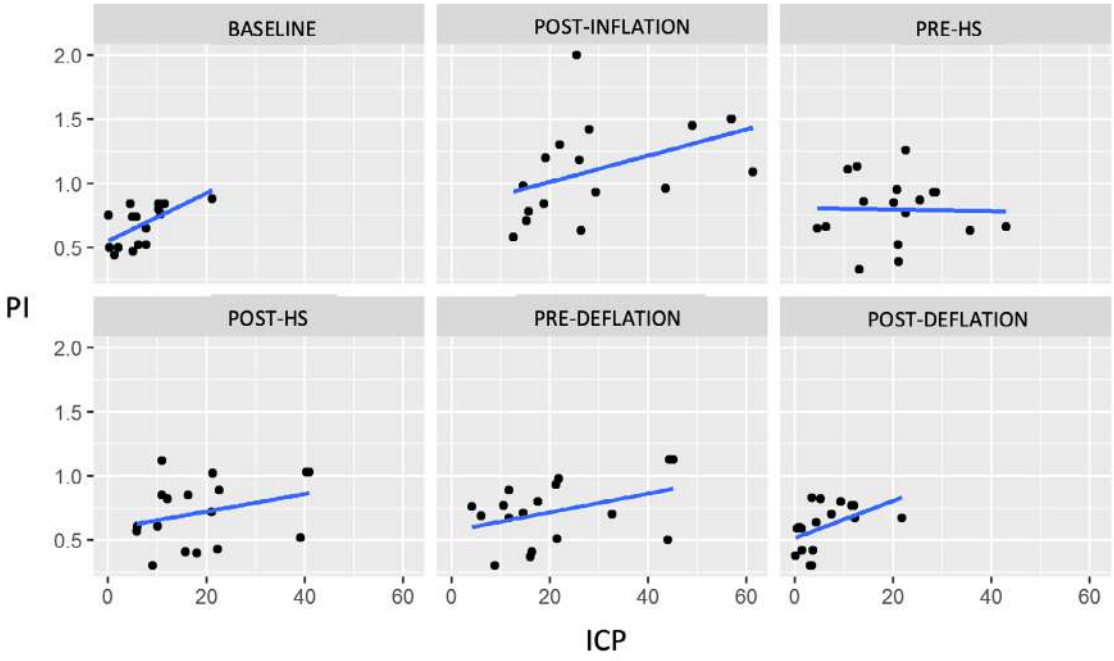
TCD is a promising technique with emphasis on PI as a parameter of non-invasive estimation of ICP[9,10,25,26]. TCD is an interesting method because of its availability, portability, and possibility of performing repeated non-invasive tests at bedside.

Bellner et al. investigated the relationship between ICP and TCD PI[9]. They studied 81 patients with various brain lesions (subarachnoid hemorrhage, TBI, and others). It was found a direct relationship between ICP and PI, with a high correlation coefficient (0.938). Similar results were reported in a study of 58 patients with severe TBI treated in the ICU according to the BTF guidelines[27]. Daily TCD was performed for PI comparison with invasive ICP monitoring. There was a strong correlation between PI and ICP, with a 0.779 correlation coefficient in the fifth day.

A retrospective study from Cambridge[10] included 53 patients who underwent an infusion test (consisting of infusing saline solution in the lumbar space, by lumbar puncture, for the study of circulatory disorders). The values of ICP (measured through the lumbar needle) and TCD blood flow velocities were also measured. One of the parameters studied for noninvasive ICP measurement was the PI obtained with TCD. There was statistical significance in the direct correlation between these two parameters (r: 0.45), showing good potential of PI for noninvasive estimation of ICP.

Other studies have also shown positive results regarding the correlation of ICP with PI in patients with brain lesions[28-31]. These studies are consistent with the results of our experiment in which a strong correlation was found between PI and ICP at three important moments. The correlation coefficient was 0.543 right after balloon inflation, when ICP elevation occurs. At the other moments, when ICP remains high but stable, PI lost its correlation with ICP. We can infer from this that PI may be important in monitoring the worsening of ICP and may be indicated in patients with this suspicion of deterioration.

Bouzart et al. conducted a prospective multicenter study in France in 2016[25]. A total of 356 patients with mild and moderate TBI (Glasgow between 9 and 15) were studied.



PI: pulsatility index; ICP: intracranial pressure; post-inflation: after balloon inflation; pre- and post-HS: pre- and post-hypertonic solution infusion; pre- and post-deflation: pre- and post-balloon deflation.

Figure 2. Dispersion between intracranial pressure and pulsatility index, without the animals 15 and 16.

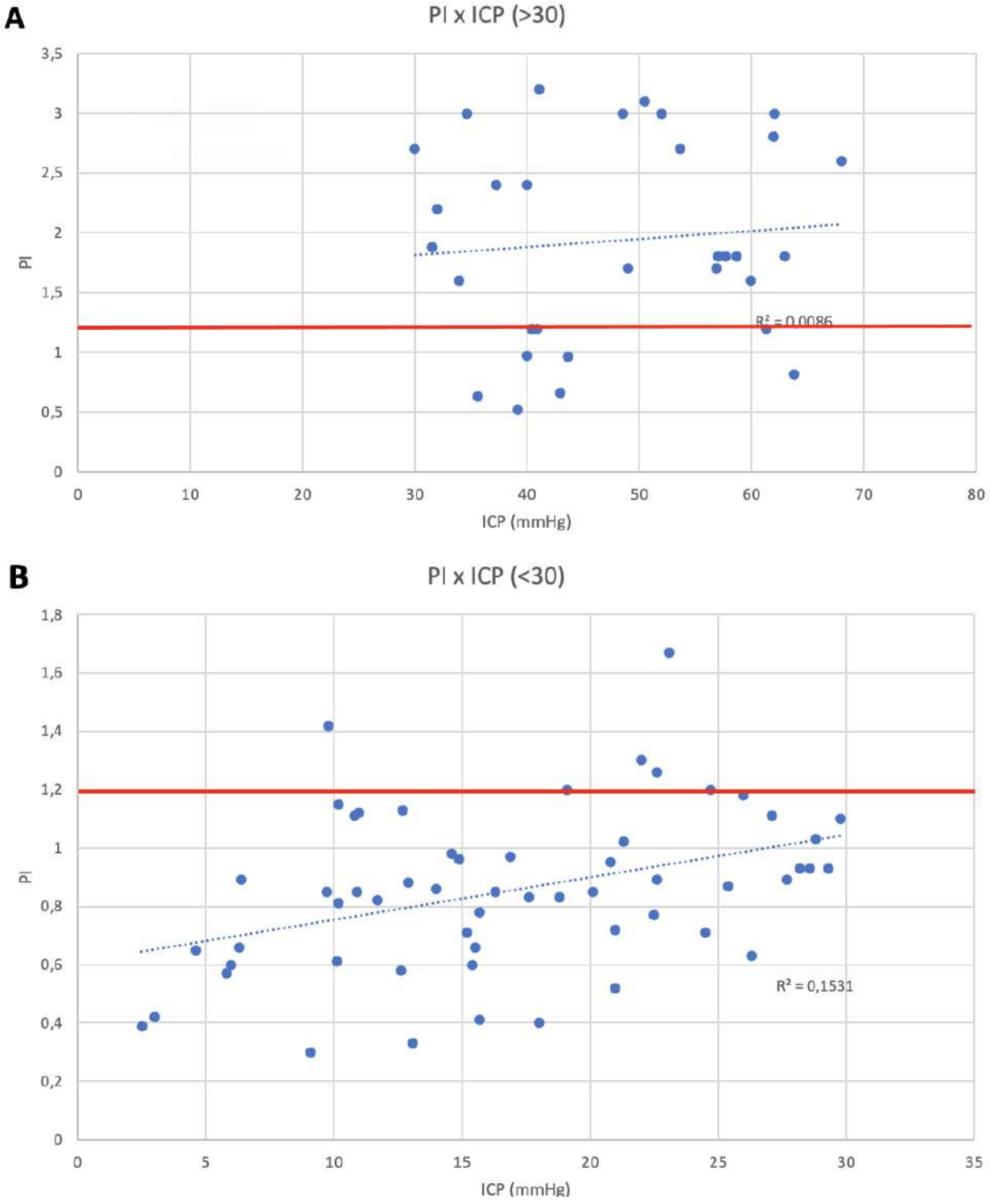
Bilateral TCD was performed up to 8 hours post-trauma. The objective was to evaluate TCD as a predictor of secondary neurological deterioration in these patients (which occurred in 6% of study patients) on the seventh day post-trauma. The normal TCD parameter considered was PI less than 1.25 and FVd greater than 25 cm/s. This parameter had sensitivity of 80% and specificity of 79% to predict neurological worsening. The negative predictive value was 98% and the positive predictive value was 18%, suggesting that the normal TCD result is more important in predicting prognosis than the abnormal TCD. Also, this study showed that PI and FVd are related to the prognosis of patients with mild to moderate TBI. This study, despite not evaluating the correlation of the TCD parameters with ICP, reinforces the possible utility of PI in patients with potential risk of neurological worsening.

However, there are many studies in the literature that contradict these positive correlations between ICP and PI. In 2016, another prospective study included 40 TBI patients who were treated in an ICU of a single hospital and who received a parenchymal catheter to monitor ICP[22]. Data were collected from ICP monitoring and TCD. One of the parameters analyzed for non-invasive evaluation of ICP was PI. There was no statistically significant correlation between PI and ICP. The results were consistent with those of Figaji et al., another prospective study that evaluated 34 children with severe TBI, who had ICP monitored[32]. TCD was performed in the middle cerebral artery ipsilateral to the ICP catheter. The aim of this study was to determine the correlation between PI greater than 1 and ICP greater than 20 mmHg, as well as PI less than 1 with ICP less than 20 mmHg. The conclusion of that study was that PI is not a good parameter for noninvasive assessment of ICP in children with TBI. These results are consistent with other published studies[7,22,23,33,34].

Effect of hypertonic saline solution infusion in the present model

As described in the literature review, hyperosmolar therapy is used to treat cerebral edema and ICH of various etiologies, and mannitol at 20% is the gold standard solution. However, HS, in different concentrations, has been studied for this purpose[35,36]. Hypertonic solutions act through the dehydration of brain tissue and decrease the inflammatory response of the brain to injury, as well as causing positive effects on homeostasis and cardiovascular hemodynamics[37,38]. Although there was no consensus on the best HS concentration for ICH control, in this study the 3% concentration was used because it was equiosmolar to 20% mannitol. In addition, it has shown good efficacy in intraoperative brain relaxation and in controlling ICH of various causes, with good safety and few side effects[39-41].

In the current study, groups A and B maintained stable ICP after HS infusion, without the ICP reduction effect demonstrated in other studies. Perhaps the present animal model of ICH is not adequate to evaluate HS effects. Balloon inflation



PI: pulsatility index; ICP: intracranial pressure.

Figure 3. Spearman's correlation. A positive trend was observed for intracranial pressure and pulsatility index correlation, although a pulsatility indexcut-off value of ≥1.2 (red line) was observed for an intracranial pressure cut-off value of 30 mmHg (A). In our study, animals disclosing intracranial pressure between 20–29 mmHg often presented pulsatility index values under 1.2 (B).

simulates an acute mass effect with a material that does not respond to changes in blood osmolarity. The benefits of HS are postulated as a result of an osmolar effect, which would not affect the balloon. Other effects of HS as increased cardiac output and inhibition of inflammatory changes are also not applicable in this model. This justifies the results obtained in this experiment, in which there was no change in ICP after infusion of HS. Therefore, the ICH model by balloon inflation simulates a disease process that can only be treated by surgical intervention.

Although the present study makes important contributions in the development of an animal model of induced ICH, it has some limitations. First, Doppler evaluations are highly operator-dependent with a significant learning curve. However, only one accurately trained sonographer performed the Doppler exams to minimize this limitation. Second, FVs, FVd, FVm, and PI parameters are also influenced by blood pressure and blood viscosity. Third, the intracranial solution infusions applied in the study were comparable to extremely elevated intracranial mass volume, which is not the most common situation in clinical practice, although suitable for study purposes.

Additionally, the lesions induced in the study were exclusively performed on the frontal lobe of swines. Theoretically, lesions with the same volume in the posterior fossa may disclose a different behavior on blood flow velocities of middle cerebral arteries. Finally, two animals presented hemodynamic instability, refractory to the stabilization attempts made by the researchers, and were excluded from the PI data analysis. Another limitation of this animal model is the absence of blood contact with brain tissue, with absence of inflammatory reactions caused by a true hematoma.

PI is mostly an indicator of cerebral perfusion pressure, as its formula is based on differences between systolic and diastolic velocities. Previous research used 1.4[42] as the threshold for this index to indicate ICH more accurately. However, in clinical practice, logic leads to individualization, since both intracranial compliance and pressure buffering mechanisms vary from person to person. Rheology, intravascular volume, and the cardiovascular system also play a determining role on cerebral hemodynamics[43]. Thus, the most valuable feature of a non-invasive technique such as TCD may be the opportunity of repeated evaluations and observing particular PI tendency during patient follow-up, associating this with further dynamic variables.

In conclusion, in this experimental study, transcranial Doppler pulsatility index was correlated with ICP monitored by intraparenchymal catheter, especially at the moment of abrupt elevation of ICP. This observation is relevant because similar studies cannot be performed in humans for ethical reasons.

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ARTICLE

Diffusion-weighted imaging as predictor of acute ischemic stroke etiology

Imágenes por difusión cerebral como predictor de la etiología del accidente cerebrovascular isquémico agudo

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ABSTRACT

Background: Topographic patterns may correlate with causes of ischemic stroke. **Objective:** To investigate the association between diffusion-weighted imaging (DWI) and Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. **Methods:** We included 1019 ischemic stroke patients. DWI were classified as: i) negative; ii) DWI single lesion (cortico-subcortical, cortical, subcortical ≥20 mm, or subcortical <20 mm); iii) scattered lesions in one territory (small scattered lesions or confluent with additional lesions); and iv) multiple lesions (multiple unilateral anterior circulation [MAC], multiple posterior circulation [MPC], multiple bilateral anterior circulation [MBAC], and multiple anterior and posterior circulations [MAP]). **Results:** There was a relationship between DWI patterns and TOAST classification (p<0.001). Large artery atherosclerosis was associated with small, scattered lesions in one vascular territory (*Odds Ratio* [OR] 4.22, 95% confidence interval [95%CI] 2.61–6.8), MPC (OR 3.52; 95%CI 1.54–8.03), and subcortical lesions <20 mm (OR 3.47; 95%CI 1.76–6.85). Cardioembolic strokes correlated with MAP (OR 4.3; 95%CI 1.64–11.2), cortico-subcortical lesions (OR 3.24; 95%CI 1.9–5.5) and negative DWI (OR 2.46; 95%CI 1.1–5.49). Cryptogenic strokes correlated with negative DWI (OR 4.1; 95%CI 1,84–8.69), cortical strokes (OR 3.3; 95%CI 1.25–8.8), MAP (OR 3.33; 95%CI 1.25–8.81) and subcortical lesion ≥20 mm (OR 2.44; 95%CI 1,04–5.73). Lacunar strokes correlated with subcortical lesions diameter <20 mm (OR 42.9; 95%CI 22.7–81.1) and negative DWI (OR 8.87; 95%CI 4.03–19.5). Finally, MBAC (OR 9.25; 95%CI 1.12–76.2), MAP (OR 5.54; 95%CI 1.94–15.1), and MPC (OR 3.61; 95%CI 1.5–8.7) correlated with stroke of other etiologies. **Conclusions:** A relationship exists between DWI and stroke subtype.

Keywords: Stroke; Ischemic Stroke; Diffusion Magnetic Resonance Imaging; Diagnosis.

RESUMEN

Antecedentes: Los patrones topográficos pueden correlacionarse con las causas del accidente cerebrovascular isquémico. **Objetivo:** Investigar la asociación entre imágenes ponderadas por difusión por resonancia nuclear magnética (dRNM) y el ensayo de Org 10172 en la clasificación de tratamiento agudo de accidentes cerebrovasculares (TOAST). **Métodos:** Fueron incluidos 1.019 pacientes con accidente cerebrovascular isquémico. Las dRNM fueron clasificadas como: i) negativa; ii) dRNM lesión única (cortico-subcortical, cortical, subcortical ≥20 mm, o subcortical <20 mm); iii) lesiones disgregadas un territorio vascular (pequeñas lesiones dispersas o confluentes con lesiones adicionales); y iv) lesiones múltiples (unilaterales de circulación anterior [MAC], de circulación posterior [MPC], bilaterales de circulación anterior [MBAC] y de circulación anterior y posterior [MAP]). **Resultados:** Existió relación entre los patrones de dRNM y la

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clasificación TOAST (p<0,001). La aterosclerosis de las arterias grandes se asoció con lesiones pequeñas y disgregadas en un territorio vascular (*Odds Ratio* [OR] 4,22, intervalo de confianza del 95% [IC95%] 2,61–6,8), MPC (OR 3,52; IC95% 1,54–8,03), y lesiones subcorticales <20 mm (OR 3,47; IC95% 1,76–6,85). Cardioembolias se relacionaron con MAP (OR 4,3; IC95% 1,64–11,2), lesiones cortico-subcorticales (OR 3,24; IC95% 1,9–5,5) y dRNM negativas (OR 2,46; IC95% 1,1–5,49). Los accidentes cerebrovasculares criptogénicos se relacionaron con dRNM negativas (OR 4,1; IC95% 1,84–8,69), accidentes cerebrovasculares corticales (OR 3,3; IC95% 1,25–8,8), MAP (OR 3,33; IC95% 1,25–8,81) y lesiones subcorticales ≥20 mm (OR 2,44; IC95% 1,04–5,73). Los accidentes cerebrovasculares lacunares se correlacionaron con lesiones subcorticales de diámetro <20 mm (OR 42,9; IC95% 22,7–81,1) y dRNM negativas (OR 8,87; IC95% 4,03–19,5). Finalmente, MBAC (OR 9,25; IC95% 1,12–76,2), MAP (OR 5,54; IC95% 1,94–15,1) y MPC (OR 3,61; IC95% 1,5–8,7) se relacionaron con accidentes cerebrovasculares de otras etiologías. **Conclusiones:** Existe relación entre dRNM y subtipo de accidente cerebrovascular.

Palabras clave: Accidente Cerebrovascular; Accidente Cerebrovascular Isquémico; Imagen de Difusión por Resonancia Magnética; Diagnóstico.

INTRODUCTION

A precise and early diagnosis of acute ischemic stroke (AIS) etiologic subtype is important for therapeutic decisions that may influence stroke recurrence, management, and prognosis[1,2]. The most frequently used method for causative subtype classification is the Trial of Org 10172 in Acute Stroke Treatment (TOAST), which divides AIS into subtypes, based primarily on infarction mechanism[1,2].

Diffusion-weighted imaging (DWI) is sensitive and specific for the early detection of hyper-acute ischemic lesions, even those of very small size[3-5]. Ischemic lesion topography on DWI may correlate with stroke subtypes. However, previous studies demonstrating this association were limited to specific stroke etiologies or DWI patterns, included transient ischemic attacks, were retrospective, included AIS of the anterior circulation only, or did not consider negative DWI results[5-13], which could represent a proportion as high as 13% of the AIS admitted to the emergency room (ER)[4].

In this study we aimed to determine the association between DWI ischemic topography and AIS stroke subtype using the causative TOAST classification. A large prospective cohort of consecutive, unselected patients with AIS admitted to out center was evaluated.

METHODS

In this prospective study, patients with AIS admitted to the ER between December 2012 and June 2019 were evaluated by the neurologist on call. Age, stroke risk factors, and time from stroke onset to arrival to the ER, defined as the last time at which the patient was known to be free of any neurological deficits, were recorded. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS). Patients were then studied with the local neuroimaging protocol, which has been described previously[4]. The protocol consists of a non-contrast brain computed tomography (NCCT) and, in patients without contraindication, an immediate spiral computed tomographic angiography to evaluate the cervical and intracranial arteries (CTA) and DWI-MRI. If a CTA could not be obtained, an acute magnetic resonance angiography (AngioMR) was performed.

The time from symptom onset to the time when the DWI was performed was recorded, as well as the model of the MRI equipment in which this study was carried out. Evaluations were performed either in a GE HdxT 1.5-T MRI or in a Siemens Skyra 3-Tesla and varied according to their availability upon arrival. A standardized protocol was applied including axial acquisitions and, in patients with negative results, thin coronal sections were also performed[4].

After the initial evaluation, most patients were transferred to the Stroke Unit for at least a 48-hour follow up. Telemetry monitoring was performed in all cases, and as soon as possible cardiologists carried out a transthoracic echocardiogram. Additional evaluations were performed as required to determine infrequent causes of AIS.

Patients with negative baseline DWI results in the ER were re-evaluated after 24 hours with either brain NCCT or MRI according to the preference of the attending neurologist.

Patients with repeated negative imaging, but with an evident neurovascular syndrome, and no other alternative diagnosis explaining the patient's initial symptoms after extensive workup were finally diagnosed as stroke[3].

DWI topography of the ischemic lesions was determined by an experienced stroke neurologist (AB), based on a modification of a previous classification[10]. In this article, we included negative baseline DWI results as a variable and we changed the subgroup criteria for single subcortical lesions from 15 mm to 20 mm. Ischemic baseline patterns were classified as follows: i) absence of acute lesion or normal baseline DWI; ii) single lesions group (which includes as subgroups cortico-subcortical lesion, pure cortical lesion, subcortical lesion with a diameter ≥20 mm or subcortical lesions with a

diameter <20 mm) (Figure 1); iii) scattered lesions of less than 15 mm in one vascular territory (SLVT) and scattered and confluent lesions of 15 mm or more (Figure 2); and iv) multiple lesions in multiple vascular territories (unilateral anterior circulation [MAC], posterior circulation [MPC], bilateral anterior circulation [MBAC], or both anterior and posterior circulation [MAP]) (Figure 3).

The reviewer was blinded to the clinical data of patients; the etiological stroke classification was made at the time of discharge by the treating neurologist, and according to the TOAST classification[2].

The Ethics Committee of Universidad del Desarrollo, Clínica Alemana de Santiago approved the protocol, and the patients or their relatives provided written informed consent as part of the local prospective stroke registry.

Statistical analysis

DWI patterns and their association with stroke etiology were described in an analysis of simple correspondence to identify closeness between the pattern and the etiology. The significance of this proximity was evaluated with Fisher's exact test. The strength of the association was calculated as *Odds Ratio* (OR) with a level of significance of 5% and 95% confidence interval (95%CI).

The significant associations are shown in a bi-plot obtained through a simple correspondence analysis.

Data were processed with the Stata v 14.0 software.

RESULTS

During the study period, 1108 consecutive AIS patients were admitted to the ER; 1019 (91.9%) were included in this analysis. Eighty-nine patients were excluded because of a contraindication for MRI (peacemaker, agitation, critical medical condition, or low quality of the DWI image).

Mean patient age was 72.5±17.4 years and 562 (55.5%) patients were women. Mean NIHSS was 3±7.1. Mean time from stroke onset to ER arrival was 322±1786 minutes and mean time from AIS onset to DWI was 376±1803 minutes. In relation to time to imaging, 450 (44.2%) patients were assessed with DWI within 4.5 hours of symptom onset and in 824 (80.9%) DWI was performed within the first 24 hours; 97 cases (9.5%) were evaluated between 24 and 48 hours and only 98 (9.6%) patients were assessed with DWI more than 48 hours after symptom onset. A 3T MRI was used in 193 (18.9%) of the cases, and 308 (30.2%) patients were treated with intravenous thrombolysis.

Ischemic lesion patterns in baseline DWI by the TOAST classification are described in Table 1. No lesion was found in baseline DWI evaluation of 142 patients (14%); a single lesion was observed in 483 patients (47.3%), scattered lesions in one vascular territory were observed in 198 cases (19.4%). Finally, multiple lesions in multiple vascular territories were found in 196 patients (19.3%).

The assessment of the association between baseline DWI patterns and AIS TOAST subgroups is shown in Figure 4 and Table 2. Large artery atherosclerosis (LAA) was associated with small scattered lesions in one vascular territory

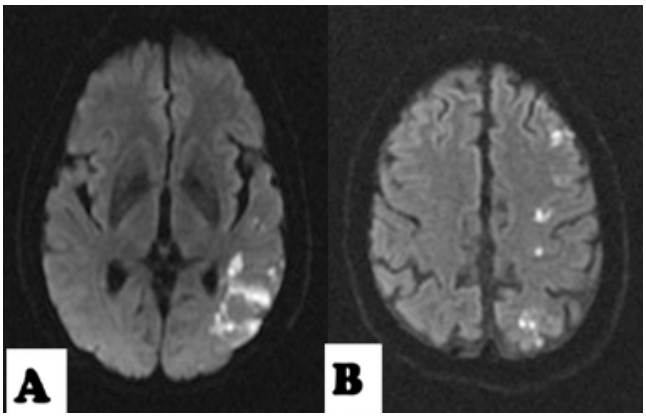


Figure 2. Scattered lesions in one vascular territory. A: scattered lesions or confluent lesions greater than 15 mm with an additional lesion. B: Scattered lesions in one vascular territory. A: small ones, less than 15 mm.

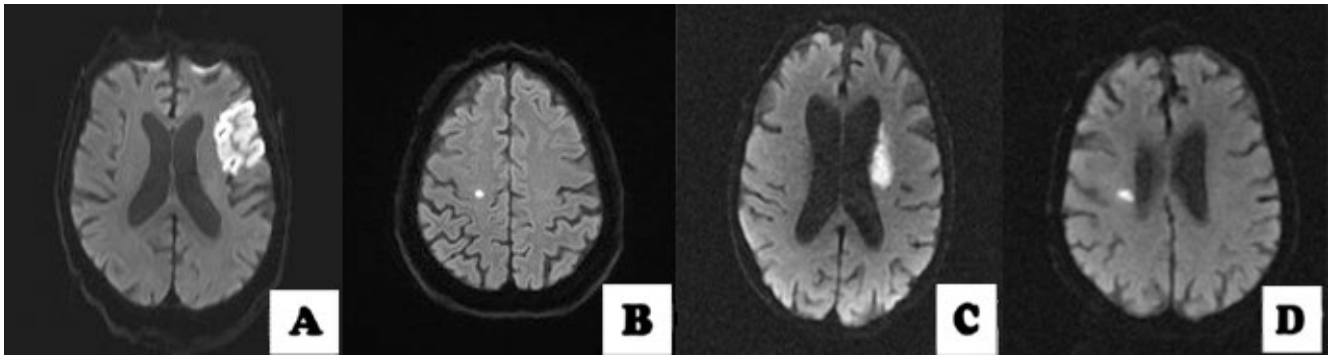


Figure 1. (A) cortico-subcortical lesion; (B): pure cortical lesion; (C) subcortical lesion with a diameter ≥20 mm; (D) subcortical lesion with a diameter <20 mm.

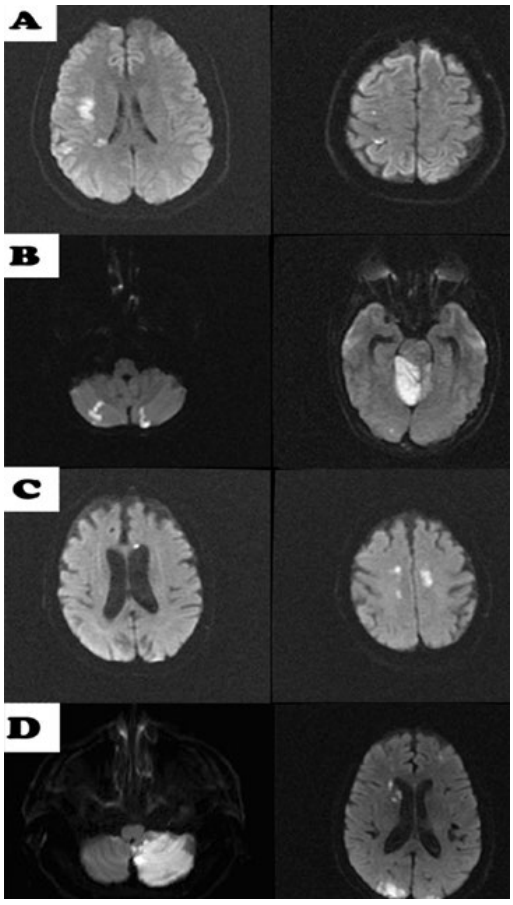
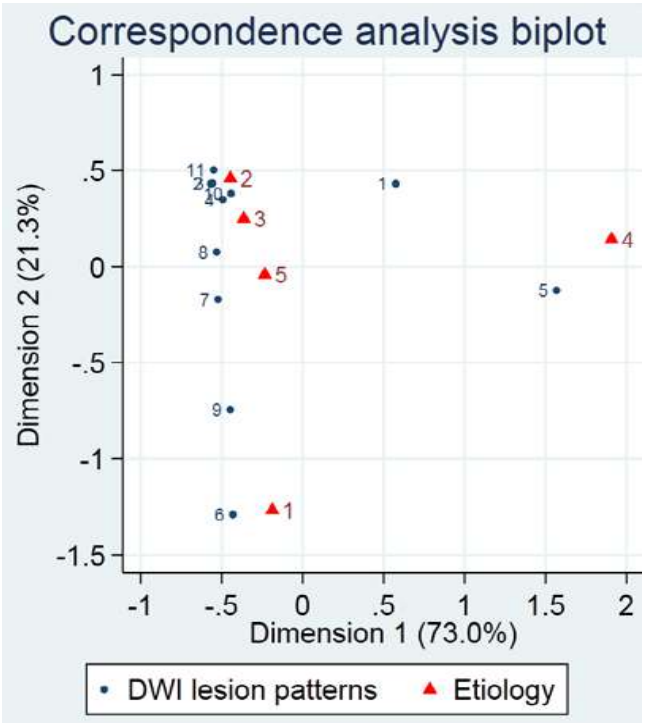


Figure 3. Multiple lesions in multiple vascular territories. (A) unilateral anterior circulation; (B) posterior circulation; (C) bilateral anterior circulations; (D) anterior and posterior circulations.



Red Triangle - 1: large-artery atherosclerosis, 2: cardioembolic, 3: cryptogenic, 4: lacunar disease, 5: other causes. Blue dots - 1: negative DWI, 2: cortico-subcortical lesion, 3: pure cortical stroke, 4: subcortical lesion with a diameter ≥20 mm, 5: subcortical lesion with a diameter <20 mm, 6: scattered lesions in 1 vascular territory (small ones, less than 15 mm), 7: scattered lesions in 1 vascular territory or confluent >15 mm lesions with an additional lesion, 8: multiple lesions (ML) in the unilateral anterior circulation, 9: ML in the posterior circulation, 10: ML in bilateral anterior circulation, 11: ML in anterior and posterior circulations.

Figure 4. Correspondence analysis biplot between diffusion-weighted imaging lesions patterns and etiology by Trial of Org 10172 in Acute Stroke Treatment posterior circulations.

Table 1. Ischemic lesion patterns at baseline diffusion-weighted imaging by Trial of Org 10172 in Acute Stroke Treatment classification.

DWI pattern/TOAST subtypes	LAA (n=173)	Cardioembolic (n=282)	Cryptogenic (n=289)	Lacunar (n=153)	Other causes (n=122)	Total (n=1,019)
Negative DWI	8	30	47	46	11	142
Single lesion						483
Corticosub-cortical	20	84	61	0	18	183
Cortical	5	18	26	0	5	54
Subcortical 20 mm and over	7	24	27	1	11	70
Subcortical less 20 mm	26	16	14	105	15	176
SLVT						198
SLVT Small (<15 mm)	61	22	33	0	15	131
SLVT Confluent lesion (≥15 mm)	16	25	20	0	6	67
Multiple lesions						196
MAC	4	10	5	0	4	23
MPC	18	9	17	0	13	57
MBAC	3	12	13	1	7	36
MAP	5	32	26	0	17	80

DWI: diffusion-weighted imaging; LAA: large-artery atherosclerosis; SLVT: scattered lesions in one vascular territory; MAC: multiple lesions in unilateral anterior circulation; MPC: multiple lesions in posterior circulation; MBAC: multiple lesions in the bilateral anterior circulation; MAP: multiple lesions anterior and posterior circulations.

Table 2. Associations between diffusion-weighted imaging patterns and Trial of Org 10172 in Acute Stroke Treatment subgroups.

DWI pattern	Etiology	OR	p-value	95%CI
Negative	LAA	1.00		
	LC	8.87	<0.001	4.03–19.52
	Undet	4.01	<0.001	1.84–8.7
	CE	2.46	0.029	1.1–5.49
	Other	2.04	0.13	0.80–5.24
Cortico-subcortical	LAA	1.00		
	CE	3.24	<0.001	1.9–5.52
	Undet	2.1	0.01	1.18–3.52
	Other	1.32	0.42	0.66–2.62
	LC	Empty		
Cortical	LAA	1.00		
	Undet	3.32	0.016	1.25–8.81
	CE	2.29	0.18	0.83–6.28
	Other	1.43	0.57	0.4–5.07
	LC	Empty		
Subcortical >20mm	LAA	1.00		
	Undet	2.44	0.04	1.04–7.73
	Other	2.35	0.08	0.88–6.24
	CE	2.2	0.07	0.92–5.23
	LC	0.15	0.08	0.01–1.28
Subcortical <20 mm	Undet	1.00	1.00	
	LC	42.9	<0.001	22.7–81.1
	LAA	3.47	<0.001	1.76–6.85
	Other	2.75	0.009	1.28–5.89
	CE	1.18	0.65	0.56–2.46
SSCL	Undet	1.00		
	LAA	4.22	<0.001	2.61–6.8
	Other	1.08	0.145	0.56–2.08
	CE	0.65	0.14	0.37–1.15
	LC	Empty		
SLVT	Other	1.00		
	LAA	1.97	0.18	0.74–5.18
	CE	1.88	0.17	0.75–4.7
	Undet	1.57	0.67	0.56–3.67
	LC	Empty		
MAC	Undet	1.00		
	CE	2.08	0.18	0.7–6.18
	Other	1.92	0.33	0.5–7.29
	LAA	1.34	0.66	0.35–5.07
	LC	Empty		
MPC	CE	1.00		
	Other	3.61	0.004	1.5–8.7
	Undet	3.61	0.004	1.5–8.7
	LAA	3.52	0.003	1.54–8.03
	LC	Empty		
MBAC	LC	1.00		
	Other	9.25	<0.001	1.12–76.2
	Undet	7.15	0.059	0.92–55.2
	CE	6.75	0.068	0.86–52.4
	LC	2.68	0.39	0.27–26
MAP	LAA	1.00		
	Other	5.54	0.001	1.94–15.1
	CE	4.30	0.003	1.64–11.2
	Undet	3.32	0.016	1.25–8.8
	LC	Empty		

DWI: diffusion-weighted imaging; OR: *Odds Ratio*; 95%CI: 95% confidence interval; LAA: large artery- atherosclerosis; LC: lacunar stroke; CE: cardioembolism; Other: stroke of other determined cause; Undet: Stroke of an undetermined cause, because the stroke was cryptogenic, 2 or more causes were identified, or there was an incomplete evaluation; SSCL: scattered lesions in one vascular territory of less than 15 mm; SLVT: scattered lesions in one vascular territory and confluent lesions of 15 mm or above; MAC: Multiple lesions in multiple vascular territories of unilateral anterior circulation; MPC: multiple lesions in the posterior circulation; MBAC: multiple bilateral lesions on anterior circulation; MAP: multiple lesions in both anterior and posterior circulation.

(OR 4.22; 95%CI 2.61–6.8), MPC (OR 3.52; 95%CI 1.54–8.03), and with subcortical lesions of less than 20 mm (OR 3.47; 95%CI 1.76–6.85).

Cardioembolic strokes (CE) were associated with cortico-subcortical lesions (OR 3.24; 95%CI 1.9–5.5), multiple lesions in the anterior and posterior vascular territories (OR 4.3; 95%CI 1.64–11.2) and with negative DWI results (OR 2.46; 95%CI 1.1–5.49).

Cryptogenic strokes (only 4.46% of total number of cryptogenic cases had incomplete etiological evaluation) were associated with normal negative DWI results (OR 4.1; 95%CI 1.84–8.69), cortical lesions (OR 3.3; 95%CI 1.25–8.8), subcortical strokes with a diameter ≥20 mm (OR 2.44; 95%CI 1.04–5.73), multiple lesions in the anterior and posterior vascular territories (OR 3.33; 95%CI 1.25–8.81) and finally with cortico-subcortical strokes (OR 2.01; 95%CI 1.1–3.52).

Lacunar strokes (LC) correlated with a subcortical lesion with diameter <20 mm (OR 42.9; 95%CI 22.7–81.1) and only negative DWI patterns (OR 8.87; 95%CI 4.03–19.52).

Finally, other etiologies correlated with multiple lesions in the anterior and posterior vascular territories (OR 5.54; 95%CI 1.94–15.1), MBAC (OR 9.25; 95%CI 1.12–76.2) and MPC (OR 3.61; 95%CI 1.5–8.7).

DISCUSSION

In this study we found an association between DWI lesion patterns and the TOAST causative classification; these have been previously described by some authors, but their studies included a limited number of patients[12,13], they were mainly retrospective, and did not include negative or normal DWI results[10,11], which are very frequent in the ER[4,5] especially in patients with low NIHSS[14].

LAA strokes were associated with scattered lesions in one vascular territory, with small scatter distribution. This finding has been demonstrated in other studies[10-12] and considered highly suggestive for this etiology[12].

MPC pattern was also associated with LAA strokes, a pattern that could be explained by a single atherosclerotic lesion in one of the vertebral arteries which could originate emboli to multiple arteries, including the basilar, cerebellar bilateral branches, and posterior cerebral arteries, causing multiple stroke lesions in the posterior circulation[15].

LAA could also present as subcortical DWI lesions with diameter <20 mm, a finding not described previously. However, Lee et al.[16] found that in their experience more than 53% of atherosclerotic middle cerebral artery lesions were clinically manifested as lacunar strokes and 30% or more had a small, deep subcortical lesion on DWI; the reasons for these lesions is the probable occlusion of a deep perforator lenticular artery by an atherosclerotic plaque in a mayor intracranial artery.

CE strokes were associated with lesions in multiple anterior and posterior arterial territories and cortico-subcortical lesions as described before[6,10,11]. We also found CE to be associated with negative DWI results; this is probably related to the fact that in our cohort patients with CE arrived earlier to the ER ($p<0.001$), probably because of the more dramatic symptoms (NIHSS was higher than in other etiologies, $p<0.001$). Early arrival to the ER is one of the factors that are critical for the negative DWI studies[4].

Strokes of undetermined etiologies were associated with negative DWI, a finding described previously[4]. We could not rule out that some of our cryptogenic AIS were stroke mimic, but in this group of cryptogenic strokes, 19 patients (15.5%) had a intracranial arterial occlusion in the symptomatic territory, 52 (36.6%) patients had a stroke detected in the follow-up imaging, and 3 (2.1%) had perfusion abnormalities when the RAPID program was applied. Additionally, this subtype of stroke etiology was associated with cortico-subcortical lesions, which had been described as typical of CE strokes. This finding could be explained by the inclusion in this group of 21 cases who had two possible etiologies: all of them had atrial fibrillation as well as other possible causes for their AIS. As a consequence, they were classified as AIS of undetermined etiology. Some of these AIS were probably the result of their atrial fibrillation and of their episode of CE. This is a limitation of the TOAST causative classification. In our study, sub-cortical lesions with a diameter ≥20 mm were associated with AIS of undetermined etiology; a similar result was published by Kang et al. for lesions in these locations but whose size was greater than 15 mm[10]. Finally strokes of undetermined etiologies were also associated with involvement of multiples territories in the anterior and posterior circulation, a frequent finding in cardio-embolic strokes. This could be explained by the inclusion of patients with covert cardioembolic strokes mainly caused by paroxysmal atrial fibrillation not detected by telemetry and in whom prolonged monitoring has been shown to provide a significant increase in the probability of detecting AF[17].

Lacunar strokes correlated with subcortical lesions whose diameter was <20 mm and with negative DWI results, a finding previously demonstrated[10,11]. Lacunar strokes had 60% less chance of abnormal DWI evaluation, probably due to their small size[3,4].

Finally other etiologies were associated with multiple ischemic lesions in both anterior, MAP, and MBAC circulations. Of the patients with other etiologies, 22 (1.9%) had cancer-associated ischemic strokes and 22 (1.9%) had coagulopathies associated with the ischemic stroke; both groups of diseases had been shown to produce ischemia in multiple brain arterial territories[15,18].

We can summarize our findings as follows: when there is an AIS with negative DWI the most likely etiology is cryptogenic and lacunar, unless, the patient has a high NIHSS in which case CE embolism could be the cause. Scattered lesions in one vascular territory should rise suspicion for LAA disease. Cortico-subcortical lesions are associated to CE etiology, as it is also the presence of multiple lesions in the anterior and posterior vascular territories. In this last group, cancer and coagulopathies could also be the etiology of this stroke. Finally, cryptogenic strokes can present with multiple DWI patterns.

Our study has several strengths: it included a large number of consecutive patients evaluated early in their evolution with DWI, with frequent addition of thin coronal sections for those cases with negative DWI, and with a few patients (less than 5%) with incomplete etiological studies.

Our study also has several important limitations, the main one is that it is a single-center experience in which we cannot rule out that some cases with negative DWI evaluations could correspond to stroke mimics. Also, DWI evaluations were performed on MRI with different field strength, which can influence the accuracy of DWI imaging. We also could not rule out the influence of the attending neurologist on the TOAST classification based on the DWI imaging. Furthermore, we did not study inter-observer agreement on the interpretation of DWI, and finally some DWI patterns could be associated with multiple etiologies. In conclusion we found an association between stroke subtypes by TOAST and the DWI lesion patterns.

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ARTICLE

Family quality of life among families who have children with mild intellectual disability associated with mild autism spectrum disorder

Qualidade de vida familiar entre famílias que têm filhos com deficiência intelectual leve associada ao transtorno do espectro do autismo leve

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ABSTRACT

Background: Intellectual disability (ID) and autism spectrum disorder (ASD) are often concomitant childhood developmental disorders. These disorders can alter family quality of life (FQoL). **Objective:** To investigate FQoL among families who have children with mild ID, associated with mild ASD. **Methods:** Cross-sectional descriptive study with 69 families who have children with mild ID and ASD, ranging from six to 16 years old, and who were provided with disability-related services in Brazil. Data were collected using a family sociodemographic questionnaire, an ID and ASD personal profile form, the Barthel index for activities of daily living and the Beach Center FQoL scale. **Results:** People with ID and ASD had an average score of 88.2±11.5 in the Barthel index, thus indicating moderate dependency in basic activities of daily living. The average total FQoL score (3.56±0.34) was lower than the scores for the "family interaction" (3.91±0.42; p<0.001), "parenting" (3.79±0.35; p<0.001) and "disability-related support" (3.98±0.16; p<0.001) domains; and higher than the scores for the "physical/material well-being" (3.19±0.64; p<0.001) and "emotional wellbeing" (2.75±0.62; p<0.001) domains. Parents' marital condition, monthly family income, family religious practice and effective communication skills among the people with ID and ASD were predictors for FQoL (R^2=0.407; p<0.001). **Conclusions:** FQoL was sustained through factors such as family interaction and parents' care for their children. Improving families' emotional wellbeing and physical and material conditions is likely to positively affect the FQoL of these families.

Keywords: Intellectual Disability; Autism Spectrum Disorder; Quality of Life; Family; Family Relations; Brazil.

RESUMO

Antecedentes: Deficiência intelectual (DI) e transtorno do espectro do autismo (TEA) são distúrbios do desenvolvimento infantil frequentemente concomitantes que podem impactar na qualidade de vida familiar (QVF). **Objetivo:** Esta pesquisa avaliou a QVF entre famílias que têm filhos com DI leve associada a TEA leve. **Métodos:** Pesquisa transversal e descritiva, que investigou 69 famílias com filhos com DI e TEA leves, com idades entre seis e 16 anos, que recebiam serviços relacionados à deficiência no Brasil. Os dados foram coletados por meio de formulário sociodemográfico, formulário de perfil da pessoa com DI e TEA, o índice de funcionalidade de Barthel e a Escala de QVF do Beach Center. **Resultados:** Os indivíduos com DI e TEA obtiveram pontuação média de 88,2±11,5 no índice de Barthel, o que indicou dependência moderada nas atividades básicas de vida diária. O escore médio da QVF total (3,56±0,34) foi menor que os escores dos domínios "interação familiar" (3,91±0,42; p<0,001), "cuidados dos pais com os filhos" (3,79±0,35; p<0,001) e "apoio ao deficiente" (3,98±0,16; p<0,001), e maior que os escores dos domínios "bem-estar físico-material" (3,19±0,64; p<0,001) e "bem-estar emocional" (2,75±0,62; p<0,001). Condição marital dos pais, renda mensal, prática religiosa e comunicação adequada dos indivíduos com DI e TEA foram preditores da QVF (R^2=0,407; p<0,001). **Conclusões:** A QVF foi sustentada por aspectos como a interação familiar e o cuidado dos pais com os filhos. Melhorar o bem-estar emocional e as condições físicas e materiais familiares provavelmente afetará positivamente a qualidade de vida dessas famílias.

Palavras-chave: Deficiência Intelectual; Transtorno do Espectro Autista; Qualidade de Vida; Família; Relações Familiares; Brasil.

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INTRODUCTION

Intellectual disability (ID) is a developmental disorder characterized by impaired general mental abilities. It results in deficits of both intellectual and adaptive functioning, such that individuals cannot achieve the standards of personal independence and social responsibility in one or more aspects of their daily lives[1]. ID has a global frequency of about 1 to 3%, varying according to age, and it is more common among males[2]. It has been estimated that 1.4% of the Brazilian population has some degree of ID[3]. ID can be classified as mild, moderate, severe or profound. Approximately 85% of people who have ID have mild ID. These individuals are characterized as not benefitting from the instruction that they receive for higher performance in their academic and working lives, having flaws in their processes of abstract conceptualization and fluctuating attention, but having autonomy in basic activities of daily life[1].

Autism spectrum disorder (ASD) is a developmental disorder characterized by persistent impairment in social reciprocal communication and social interaction, and also restricted and repetitive patterns of behavior, interests or activities[1]. ASD has an estimated global frequency of around 1 to 2%, but it is three to four times more common among males[1,4]. It can be classified as mild, moderate or severe, and the criterion adopted for assessing severity relates to the amount of support needed to address a person's needs, considering their difficulties[1].

ASD and ID are common comorbidities[2,4]. While at least 10% of individuals with ID have ASD, about 50 to 80% of individuals with ASD have some degree of ID[5,6]. Caring for individuals with ID and ASD often results in an emotional and financial burden on their families[7-9]. Having a family member with a disability alters the family's dynamics and quality of life[10,11].

Families can be defined as groups of people who are closely involved in the day-to-day affairs of the household and support each other regularly; whether related by blood, marriage or close personal relationship[12]. In this context, family quality of life (FQoL) can be understood as family wellbeing in a dynamic sense, subjectively perceived and informed by its own members, contemplating interactions between individual and family needs[13,14]. Research on the FQoL of families who have members with ID and/or ASD has been explored with the aim of shaping public policies that encourage care in this area, and also to contribute to evaluations on services and clinical interventions[14-16].

The present study had the aim of investigating FQoL in a sample of Brazilian families who have children with mild ID in association with mild ASD.

METHODS

Study design and setting

This was a descriptive cross-sectional study that was developed with support from the Association of Parents and Friends of Exceptional People of São Carlos (Associação de Pais e Amigos de Excepcionais de São Carlos, APAE). São Carlos is a city located in the state of São Paulo, in southeastern Brazil, with approximately 250,000 inhabitants. In 2010, its human development index was 0.8059[3]. APAE São Carlos was founded in 1962 and currently serves about 800 individuals with ID and/or ASD, offering specialized education and support.

This study was approved by the Human Research Ethics Committee of the Universidade Federal de São Carlos and participation was authorized through signing an informed consent declaration.

Participants

This study was developed using a purposeful convenience sample[17], consisting of families who had children with mild ID in association with mild ASD, and who had links to APAE São Carlos. The inclusion criteria were: (1) age range of the child between 6 and 16 years; (2) clinical diagnosis of mild ID confirmed through the Wechsler Intelligence Scale for Children (WISC-IV)[18]; and (3) clinical diagnosis of mild ASD confirmed through the Childhood Autism Rating Scale (CARS)[19]. We identified 69 families that met these inclusion criteria. All of these families were invited and agreed to participate in the study.

Data collection

Data collection was carried out using printed forms and was done individually by a single researcher in face-to-face situations with one interviewee at a time, between July 2018 and May 2019. Regarding the informant, in 56 families (81%), this was the mother; in six families (9%), the father; in four families (6%), an uncle or aunt; and in three families (4%), the grandfather or grandmother.

The data collection instruments were the "family sociodemographic profile" and the "ID and ASD personal profile" forms, the Barthel index and the Beach Center FQoL scale. The "family sociodemographic profile" form was designed for this study and asked for information on the number of people in the household, monthly family income, receipt of social benefits, supplemental health insurance plan, religion, parents' marital status, maternal and paternal education, parents' jobs and the number of siblings. The "ID and ASD person profile" form was also designed for the present study and asked for information on these individuals' gender, age, educational level, communication skills and autonomy indoors.

The Barthel index belongs to the field of assessment of basic activities of daily living and assesses the level of independence in relation to ten activities. The total score of this instrument ranges from 0 to 100, such that a score of 0–20 indicates total dependence; 21–60, severe dependence; 61–90, moderate dependence; 91–99, mild dependence; and 100, independence[20].

To assess FQoL, the Beach Center Family Quality of Life Scale (BCFQoLS) was used[21], in its version translated into

Portuguese[22]. This instrument consists of a 25-item, five-domain questionnaire (parenting, family interaction, emotional wellbeing, physical/material wellbeing and disability-related support), with five possible answers on a Likert scale to measure satisfaction. The sum of points obtained in each domain represents the FQoL grand total[21]. The scores for each BCFQoLS domain, along with the FQoL grand total, are transformed into a quinary ratio, and scores ≥4.0 indicate satisfaction[21,23].

Data analysis

The findings were presented as the mean, median and standard deviation (SD), or absolute frequency and percentage, according to the type of variable. The internal consistency of the BCFQoLS and Barthel index was assessed by means of Cronbach's alpha coefficient, and values above 0.70 were considered ideal.

The FQoL grand total was verified using the Kolmogorov-Smirnov test and was found to present normal distribution (D=0.09195; p=0.57223); therefore, parametric statistical tests were used. Differences in means between the several BCFQoLS domains and the FQoL grand total were determined using the paired Student's *t*-test. The effect of sociodemographic factors on the total FQoL level was determined by means of the independent (unpaired) Student's *t*-test or using analysis of variance (ANOVA) with the Tukey post-test, according to the number of variables analyzed.

Binary correlations between the different BCFQoLS domains and the FQoL grand total were determined using the Pearson linear correlation. The Pearson or Spearman correlation was used to verify the binary correlation between the total FQoL and each of the other variables of the study. The intensity of the correlation coefficient (r) was taken to be a weak correlation when it was between 0 and 0.3, a moderate correlation when between 0.3 and 0.6 and a strong correlation when above 0.6.

Multiple linear regression models were used for multiple correlation analysis in two ways: (1) enter - variables that were significant in the binary correlation with p<0.05 were all included in the model at the same time, to assess their contribution to the FQoL grand total; (2) stepwise - non-contributing variables were excluded by means of the step-by-step statistical program, to identify the most significant correlations. To verify the quality of the adjusted model, the coefficient of multiple determination (R^2) was calculated and the significance of the model was determined using ANOVA.

The significance level adopted was 5%. All analyses were performed using the JASP 0.10.2 software (https://jasp-stats.org/).

RESULTS

Descriptive results

The sample was characterized by a predominance of families comprising three or more people (97%; n=67), with an average monthly family income of R$ 2,806.52±1,493.75 (currency conversion: $ 1.00=R$ 5.67 on March 10, 2021). Most families were only using the Brazilian National Health System (57%; n=39) and were not receiving any social benefits (81%; n=56).

The mothers were on average 39±5.3 years old, with a minimum age of 29 and a maximum of 56 years; there was incomplete information about one mother. The fathers were on average 42±6 years old, with a minimum age of 32 and a maximum of 64 years. The individuals with ID and ASD were on average 9.5±2.6 years old; 85% (n=60) were male; and 62% (n=43) were literate. No person with ID or ASD had chronic health problems requiring regular use of medication.

Table 1 shows the results regarding the BCFQoLS and Barthel index. The result for the Barthel index was 88.2±11.5, which was compatible with moderate dependence. The average score for the FQoL grand total was 3.56±0.34, i.e. lower than what is considered satisfactory.

The differences in means between the various BCFQoLS domains and the FQoL grand total level are shown in Table 2. The mean value for the FQoL grand total was significantly higher than the scores obtained in the "emotional well-being"

Table 1. Results from the Beach Center Family Quality of Life Scale and Barthel index among the families investigated that had children with mild intellectual disability and autism spectrum disorder (n=69).

	Domains					FQoL grand total	Barthel index
	Family interaction	Parenting	Emotional wellbeing	Physical/material wellbeing	Disability-related support		
Mean	3.91	3.79	2.75	3.19	3.98	3.56	88.2
SD	0.42	0.35	0.62	0.64	0.16	0.34	11.5
Median	4.00	3.83	2.75	3.20	4.00	3.60	90.0
Minimum	2.33	2.33	2.00	2.00	3.50	2.48	45.0
Maximum	4.83	4.83	4.00	4.80	4.50	4.48	100.0
Cronbach's alpha	0.8520	0.7483	0.7707	0.8190	0.3402	0.8927	0.8189

BCFQoLS: Beach Center Family Quality of Life Scale; ID: intellectual disability; ASD: autism spectrum disorder; SD: standard deviation; FQoL: Family Quality of Life.

(2.75±0.62; p<0.001) and "physical/material well-being" (3.19±0.64; p<0.001) domains; and significantly lower than the scores obtained in the "family interaction" (3.91±0.42; p<0.001), "parenting" (3.79±0.35; p<0.001) and "disability-related support" (3.98±0.16; p<0.001) domains.

The "family interaction" (r=0.816; p<0.001), "parenting" (r=0.824; p<0.001), "emotional well-being" (r=0.707; p<0.001) and "physical/material well-being" (r=0.809; p<0.001) domains were strongly correlated with the FQoL grand total (Table 2). In addition, the "family interaction" and "parenting" domains presented a strong correlation with each other (r=0.693; p<0.001).

Relationships between the characteristics of families and children and satisfaction with family quality of life

The relationships between sociodemographic and family characteristics and FQoL are presented in Table 3. Differences in the mean distribution of FQoL were identified in relation to family income (p=0.021), access to supplemental health insurance (p=0.002), receiving social benefits (p=0.018), religious practice (p=0.011) and parents' marital status (p<0.001). Tukey's post-test showed that, regarding family income, there was a difference between the "up to R$ 2,000.00" and "between R$ 5,000.00 and R$ 10,000.00" groups (p=0.013).

Table 2. Mean differences and binary correlations across the multiple Beach Center Family Quality of Life Scale domains and the Family Quality of Life grand total in the sample investigated (n=69).

Pairwise comparison: FQoL (grand total) and domains		t	*p-value	r	#p-value
FQoL (grand total)	Family interaction	-11.875	<0.001	0.816	<0.001
FQoL (grand total)	Parenting	-9.165	<0.001	0.824	<0.001
FQoL (grand total)	Emotional wellbeing	14.961	<0.001	0.707	<0.001
FQoL (grand total)	Physical/material wellbeing	7.261	<0.001	0.809	<0.001
FQoL (grand total)	Disability-related support	-11.252	<0.001	0.423	<0.001

BCFQoLS: Beach Center Family Quality of Life Scale; FQoL: Family Quality of Life; *Paired-sample Student's *t*-test; #Pearson's linear correlation.

Table 3. Family Quality of Life grand total distribution according to the sociodemographic and family characteristics of the families investigated that had children with mild intellectual disability and autism spectrum disorder (n=69).

Demographic and family variables		FQoL grand total±SD	p-value
Family income (R$)†	Up to 2,000 (n=25)	3.44±0.27	0.021*
	2,000 to 3,000 (n=16)	3.56±0.41	
	3,000 to 5,000 (n=21)	3.60±0.33	
	5,000 to 10,000 (n=7)	3.87±0.17	
Supplemental health insurance plan	No family member is covered by supplemental health insurance (n=39)	3.44±0.36	0.002*
	Only the individuals with ID/ASD are covered by supplemental health insurance (n=13)	3.65±0.21	
	The whole family is covered by supplemental health insurance (n=17)	3.77±0.24	
Social benefits	Does not gain social benefit (n=56)	3.61±0.31	0.018**
	Gains social benefit (n=13)	3.36±0.38	
Religion	Does not profess a religion (n=14)	3.36±0.35	0.011**
	Professes a religion (n=55)	3.61±0.32	
Parents' marital status	Divorced or separated (n=20)	3.33±0.40	<0.001**
	Married or living together (n=49)	3.65±0.26	
Mother's job	Works outside the home, full-time or part-time (n=29)	3.51±0.27	0.195**
	Does not work outside the home (n=39)	3.62±0.36	
Mother's educational level	Primary level incomplete (n=6)	3.57±0.32	0.186*
	Primary level complete or secondary level incomplete (n=18)	3.45±0.47	
	Secondary level complete or tertiary level incomplete/complete (n=44)	3.62±0.25	
Father's educational level	Primary level incomplete (n=5)	3.42±0.26	0.176*
	Primary level complete or secondary level incomplete (n=8)	3.35±0.56	
	Secondary level complete or tertiary level incomplete/complete (n=48)	3.60±0.30	
	Postgraduate studies (n=8)	3.64±0.28	
Number of siblings	None (n=33)	3.48±0.26	0.116*
	One sibling (n=26)	3.66±0.35	
	Two siblings (n=10)	3.58±0.47	

FQoL: Family Quality of Life; ID: intellectual disability; ASD: autism spectrum disorder; SD: standard deviation; †The Brazilian Real (R$) is the official currency of Brazil: U$ 1.00=R$ 5.67, on March 10, 2021; *ANOVA; **independent (unpaired) Student's *t*-test.

Regarding access to supplemental health insurance, the difference observed was between the groups "no family member has a supplemental health insurance plan" and "every family member has a supplemental health insurance plan" (p=0.002).

The relationship of the individual and clinical characteristics of people with ID and ASD with regard to the FQoL is presented in Table 4. Differences in the mean distribution of the FQoL were identified according to the presence of effective communication (p=0.024).

Eight of the variables investigated correlated with the FQoL grand total and were included in the multiple linear regression model: family income, access to supplemental health insurance, receiving social benefits, religious practice, parents' marital status, paternal educational level, effective communication and educational level of individuals with ID and ASD. The multiple correlation analysis showed that the parents' marital status, family income, effective communication and religious practice were predictors of the FQoL grand total (Table 5). The coefficient of determination for this final model was R^2=0.407, which indicated that the model explained 40.7% of the variability found in the FQoL grand total results (p<0.001).

Table 4. Family Quality of Life grand total distribution according to the characteristics of the individuals investigated with mild intellectual disability and autism spectrum disorder (n=69).

Personal and clinical variables of the individuals with mild ASD and ID		FQoL grand total±SD	p-value
Age group (3 categories)	6 to 8 years (n=27)	3.58±0.23	0.413*
	8 to 12 years (n=29)	3.60±0.41	
	12 to 16 years (n=13)	3.45±0.35	
Sex	Female (n=9)	3.54±0.32	0.862**
	Male (n=60)	3.56±0.34	
Educational level	Literate (n=43)	3.61±0.33	0.096**
	Illiterate (n=26)	3.47±0.34	
Effective communication	Yes (n=52)	3.61±0.33	0.024**
	No (n=17)	3.40±0.33	
Autonomy for ADL indoors	No autonomy (n=46)	3.54±0.33	0.372**
	Total autonomy (n=23)	3.61±0.36	

FQoL: Family Quality of Life; ID: intellectual disability; ASD: autism spectrum disorder; SD: standard deviation; *ANOVA; **independent (unpaired) Student's *t*-test.

Table 5. Multiple correlations of Family Quality of Life grand total with the other variables, calculated by means of the linear regression method (n=69).

		Unstandardized β coefficients	Standardized β coefficients	p-value	R^2	ANOVA p-value
Multiple correlation – 'enter' method						
FQoL	Constant	2.833		<0.001	0.420	<0.001
	Family income	$5.220e^{-5}$	0.232	0.076		
	Supplemental health insurance plan	0.032	0.081	0.534		
	Social benefit	0.026	0.031	0.797		
	Religion	0.180	0.216	0.040		
	Parents' marital status	0.203	0.275	0.031		
	Father's educational level	0.043	0.091	0.413		
	Number of siblings	0.033	0.070	0.537		
	Effective communication	0.197	0.254	0.014		
Multiple correlation – 'stepwise' method						
FQoL	Constant	2.882		<0.001	0.407	<0.001
	Parents' marital status	0.240	0.325	0.002		
	Family income	$7.117e^{-5}$	0.316	0.002		
	Effective communication	0.210	0.270	0.007		
	Religion	0.189	0.228	0.025		

FQoL: Family Quality of Life.

DISCUSSION

Our sample was characterized by better results in the "disability-related support" domain, which was expected because it was a convenience sample in which all families received support from APAE São Carlos. Schlebusch et al. also found that the "disability-related support" domain had the highest score. The explanation for their result also seems to apply to our study: their research was conducted among vulnerable families in South Africa who received disability-related support services, in a country where the scope of this kind of service is limited — a condition analogous to our sample. Thus, the high score of this domain would be explained by the fact that these families feel privileged and grateful[11]. This result is also compatible with studies conducted in Canada among both native and migrant families that demonstrated the importance for FQoL of access to external support[24,25].

We consider that the higher scores of the "family interaction" and "parenting" domains can be explained by familism. Familism is a multidimensional construct that includes three dimensions operating within a family system: the structural dimension, which marks the spatial and social limits within which behaviors occur and attitudes acquire meaning (these limits are outlined by the presence or absence of family members); the attitudinal dimension, which refers to the expressed identification of family members with the interests and welfare of the family; and the behavioral dimension, which involves different degrees of attachment and affinity during contact between family members[26]. Familism is an especially important concept in families of Latin culture[27,28], such as in Brazil, highly oriented by family values. In the context of social policies in Brazil, this configuration favors the family viewed as the main agent that offers goods and services for the welfare of individuals with disabilities, such that the family takes on most of the functions that should be the responsibility of the state[29,30].

Based on our descriptive results, we consider that the marital status of the two parents can be a potential proxy for measuring the variability of the concept of familism. Our view is that among families in which the parents live together, this tends to translate into higher levels of familism than among families in which the parents live apart. In our study, the marital status of the two parents showed a significant relationship with the FQoL. Families in which the parents lived together, in comparison with families in which the parents lived apart, had higher average scores in the "family interaction" domain (3.99±0.34 *versus* 3.72±0.54; p=0.015) and in the "parenting" domain (3.85±0.25 *versus* 3.62±0.49; p=0.009). In the literature, it is suggested that this is a two-way phenomenon: on the one hand, not living together negatively impacts family relations; on the other hand, having a child with a disability implies higher divorce rates[31].

The low score in the "emotional wellbeing" domain was consistent with findings in the literature[9,11,22,23,25,32-36] and points to the criticality of emotional factors in FQoL in different cultures and social contexts. We consider that expansion of services offered by specialized professionals, such as psychologists and occupational therapists as well as organization of support groups for parents and guardians, would form viable solutions for this issue. Thus, initiatives that allow families more time to focus on issues that concern individuality and enable them to deal better with the daily stress of caregiving for a child with a disability are helpful.

The second domain that contributed to decreasing the FQoL in our sample, i.e. "physical/material wellbeing", indicated that, in Brazil, policies for better income distribution, aimed at easing financial constraints among families with children with ASD and ID seem to be crucial. The other two studies conducted in Brazil using the BCFQoLS also showed that there were lower scores in the "physical/material wellbeing" domain than for the total FQoL[22,35]. In countries with advanced economies, however, the "physical/material wellbeing" domain has usually scored better[9,23,24,32].

The family's financial health proved to be an important indicator of FQoL in our study. It was expressed in terms of three types of data: (1) household income range; (2) access to supplemental health insurance; and (3) a need to gain social benefits, while noting that the criterion for receive these benefits is, precisely, to have low income. Our correlation results between family income and FQoL were similar to those found in other studies[7,9,11], in which family income was also a predictor of FQoL.

Two other factors were significantly related to the FQoL. Firstly, families that professed some religion had, on average, higher FQoL. We evaluated the influence of religion only by asking whether or not the family professed any religion, without considering other non-religious elements that comprise spirituality. Even considering the limits of our study, our results are consistent with those of another study that showed that religious practices contribute to increased resilience among people with disabilities[37]. Families that professed some religion reported having a sense of strength that was gained through spirituality and also built social ties with members of their religious community who, in turn, promoted acceptance of the child and their disability[38]. Given that spirituality plays an important role in an individual's quality of life, it is not surprising that religious practices could also influence the FQoL. Further exploratory analysis on this topic may result in important contributions to this field.

Secondly, our results also showed that the presence of effective communication among children with ID and ASD was significantly associated with higher FQoL scores. In a study conducted in Ireland, Fitzgerald et al. showed that the level of independence of children with ASD, including their communicative abilities, correlated with the family burden and influenced their mothers' wellbeing[39]. Foley et al. compared families with children with Down syndrome whose communication skills were better and poorer and found

results consistent with ours: the families in which the children had better communication skills had higher FQoL scores[40]. Our results also suggest that FQoL can be improved through actions that encourage proper communication by children with ID and ASD. However, testing this hypothesis would require an analytical study with a control group. We believe that our results reinforce the relevance of developing such an agenda.

This was the first Brazilian study to apply the BCFQoLS to a sample of families that have children with ID and ASD. We consider that the methodology used for data collection was a strength in our study: we conducted face-to-face interviews, which allowed us to clarify the participants' doubts, thus increasing the reliability of the results. Moreover, use of validated instruments for classifying the degree of ID and ASD, and for assessing individuals' functionality with regard to basic activities of daily living, made our results more objective and specific.

One limitation of our study concerned the data collection: data were only gathered from one family member, usually the mother, as done in most other research conducted in this area. Our results also presented bias because they reflected the specific reality of the sample and the scenario within which the study was developed. Furthermore, the set of correlational analyses, along with the associations between the variables presented in this study, should be considered with caution, given the nature of the research design. We believe that multicenter and analytical studies should be conducted to obtain a broad overview of the possible influences of socioenvironmental factors on the FQoL, which would enable formulation of public policies at the national level.

In conclusion, our results showed that the FQoL of the families investigated was sustained through factors such as family interaction and parents' care for their children, and was negatively impacted by emotional wellbeing and physical and material conditions. We suggest that psychosocial support measures should be adopted in order to improve the emotional wellbeing of each family member, along with investments in social policies, material resources and human resources, so as to upgrade these families' physical and material conditions and thus reduce their burden of caring for children with ID and ASD. Additionally, FQoL may also be improved through actions that encourage effective communication by children with ID and ASD.

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ARTICLE

Speech and swallowing characteristics in patients with facioscapulohumeral muscular dystrophy

Caracterização da fala e da deglutição em pacientes com distrofia muscular facioescapuloumeral

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ABSTRACT

Background: Although facial muscle weakness is common in patients with Facioscapulohumeral Muscular Dystrophy (FSHD), the literature is scarce on the speech and swallowing aspects. **Objective:** To investigate speech and swallowing patterns in FSHD and assess the correlation with clinical data. **Methods:** A cross-sectional study was conducted. Patients with clinical confirmation of FSHD and aged above 18 years were included and paired with healthy control individuals by age and gender. Individuals who had neurological conditions that could interfere with test results were excluded. The following assessments were applied: speech tests (acoustic and auditory-perceptual analysis); swallowing tests with the Northwestern Dysphagia Patient Check Sheet (NDPCS), the Eat Assessment Tool (EAT-10), the Speech Therapy Protocol for Dysphagia Risk (PARD), and the Functional Oral Intake Scale (FOIS); disease staging using the modified Gardner-Medwin-Walton scale (GMWS); and quality of life with the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). The correlation between test results and clinical data was verified by non-parametric statistics. **Results:** Thirteen individuals with FSHD and 10 healthy controls were evaluated. The groups presented significant differences in the motor bases of phonation and breathing. Regarding swallowing, two (15%) individuals presented mild dysphagia and seven (53.8%) showed reduced facial muscles strength. These results were not correlated with duration of the disease, age at symptoms onset, and quality of life. Dysphagia was related to worsening disease severity. **Conclusions:** FSHD patients presented mild dysarthria and dysphagia. Frequent monitoring of these symptoms could be an important way to provide early rehabilitation and better quality of life.

Keywords: Muscular Dystrophy, Facioscapulohumeral; Dysarthria; Speech; Deglutition Disorders; Neuromuscular Diseases.

RESUMO

Antecedentes: Embora haja predomínio de fraqueza muscular facial na distrofia facioescapuloumeral (FSHD), é escassa a literatura sobre aspectos de fala e deglutição. **Objetivo:** Investigar os padrões de fala e deglutição na FSHD e correlacioná-los com dados clínicos da doença. **Métodos:** Estudo transversal. Pacientes com confirmação clínica de FSHD e idade acima de 18 anos foram incluídos e pareados por idade e sexo com controles saudáveis. Foram excluídos indivíduos que apresentassem condições neurológicas que pudessem interferir nos resultados dos testes. Aplicaram-se as seguintes avaliações: fala (análise acústica e perceptivo-auditiva); deglutição, por meio do *Northwestern Dysphagia Patient Check Sheet* (NDPCS), *Eat Assessment Tool* (EAT-10), Protocolo de Avaliação para Risco de Disfagia (PARD) e *Functional Oral Intake Scale* (FOIS); estadiamento da doença, por meio da *Gardner-Medwin-Walton scale* (GMWS); e qualidade de vida, com o *Medical Outcomes Study 36-Item Short-Form Health Survey* (SF-36). Resultados de fala e deglutição foram correlacionados com dados clínicos da doença por teste não paramétrico. **Resultados:** Foram avaliados 13 indivíduos com FSHD e dez controles saudáveis. Houve diferença significativa entre os grupos nas bases motoras fonação e respiração. Na deglutição, dois (15%) indivíduos apresentaram disfagia leve e sete (53,8%), força reduzida da musculatura da face. Esses resultados não foram correlacionados com tempo de doença, idade de início dos sintomas e qualidade de vida. A disfagia esteve relacionada com a gravidade da doença. **Conclusões:** Pacientes com FSHD apresentaram disartria e disfagia leves. O monitoramento frequente desses sintomas pode ser uma forma importante de proporcionar reabilitação precoce e melhor qualidade de vida.

Palavras-chave: Distrofia Muscular Facioescapuloumeral; Disartria; Fala; Transtornos de Deglutição; Doenças Neuromusculares.

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INTRODUCTION

Facioscapulohumeral Muscular Dystrophy (FSHD) is a genetic neuromuscular disease characterized by muscle weakness and progressive atrophy[1,2]. FSHD is one of the most frequent forms of muscular dystrophy in adults, with an estimated prevalence between four and ten per 100,000 population[3]. This disease primarily affects the facial muscles, scapula muscles, and humerus muscles[4]. One of the classical symptoms is weakness of the facial muscles, which is present in 80% of patients with FSHD, with the orbicularis and the greater zygomatic muscles being the most affected[5,6]. Although face muscular weakness is common in these individuals, the literature is scarce with regard to the speech (dysarthria) and swallowing (dysphagia) aspects.

Dysarthria is a speech disorder resulting from disturbances in neuromuscular control of speech mechanisms, which may compromise the functions of breathing, phonation, resonance, articulation, and prosody[7]. In a recent study, decreasing strength of facial muscles was found to be related to communication difficulties in patients with FSHD[8]. Despite the speech difficulty noted by these patients, very little is known about the characteristics of their dysarthria in FSHD, and its correlation with the clinical profile of the disease.

Dysphagia is a swallowing disorder caused by neurological disease and/or an obstruction that causes difficulty in safe deglutition from the mouth to the esophagus[9]. The literature about dysphagia in FSHD is also scare and most relates to its incidence. The prevalence of dysphagia in FSHD ranges from 2 to 25%, and it is usually characterized by a mild dysphagia that occurs in advanced stages[10-13]. In a study conducted with eight FSHD patients, six of them had mild dysphagia with fragmented swallowing and weakness of the tongue and jaw muscles[11].

AS there are no publications in the literature on the standardized, objective and detailed characterization of speech and swallowing aspects in FSHD, further studies in this area are needed to better understand the disease, and support the early rehabilitation of these individuals. Thus, the aim of this study was to characterize speech and swallowing patterns in patients with FSHD, and assess their correlation with clinical data on the severity of the disease.

METHODS

Study design and population

This was a cross-sectional study conducted at a neuromuscular genetic disease care center within a hospital in Porto Alegre, in the southern region of Brazil, from April to November 2019. Unrelated and healthy controls, matched for age and sex, were recruited from the community.

The inclusion criteria were:

- Clinical diagnosis of FSHD.
- Aged 18 years or over.

The exclusion criteria were:

- Presence of other neurological or systemic conditions that can impact speech and swallowing patterns (for example, head and neck tumor).
- Unsuccessful attempt at telephone contact.
- Individuals who did not show up for the scheduled appointment.
- Patients who refused to participate in the study.

Initially, 26 patients with FSHD were recruited from the database of the care center at the hospital, 13 of which were excluded for the following reasons: five due to contact failure, four due to missing scheduled appointment, three refused to participate in the study, and one was under 18 years of age. The final sample of the study comprised 13 individuals (seven families) with FSHD.

The project was approved by the hospital's Research Ethics Committee. All participants gave their written consent before participating in the study.

Data collection

Individual with FSHD underwent assessments and answered the following questionnaires:

- *Sociodemographic questionnaire*: a structured questionnaire to collect general patient data, such as age, sex, education level, age of onset of symptoms, and duration of illness.
- *Gardner-Medwin-Walton* (GMWS): a clinical scale to quantify the neurological severity of FSHD. The instrument is divided into 10 (0–9) increasing severity levels[14].
- *Medical Outcomes Study 36-Item Short-Form Health Survey* (SF-36): a quality of life assessment instrument consisting of 8 dimensions: physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional and mental health. Each dimension can be scored between 0 to 100 with higher scores indicating better health[15].
- *Mini-Mental State Examination (MMSE):* screening test translated and validated for the Brazilian population. The cutoff used for formal education is 28 points for more than 8 years; 26 points for 5 and 8 years; 25 points for 1 and 4 years; and 20 points for illiterate[16].

Speech assessment

- *Speech assessment:* this evaluation involves tasks to test the five subsystems of speech: phonation (sustaining the vowel /a/ in a single breath), resonance (sustaining the vowel /a/ in a single breath), prosody (counting from 20 to 30); respiration (sustaining the vowel /a/ in a single breath), and articulation (alternating the sequence of syllables [pataka] as fast as personal capacity allowed, repeatedly in a single breath; alternating the sequence I-U [i:ju:], repeatedly in a single breath). The Audacity software version 2.3.2 was used to record

patients in a soundproof environment with a KARSECT HT-9 microphone and an Andrea Pureaudio USB adapter positioned approximately 5 cm from the subject's lips.

- *Perceptual-auditory speech analysis:* for the auditory-perceptual analysis, five speech therapists blinded to the patients' diagnosis analyzed the recordings and classified each of the five speech subsystems as normal or altered (mild, moderate or severe). The speech therapists were trained and had a Kappa concordance coefficient greater than 0.90.
- *Speech acoustic analysis:* the PRAAT 5.1 software (www.praat.org) was developed by linguists Paul Boersma and David Weenink and its focus is sound analysis through parameters such as frequency, wavelength, decibels, among others[17]. The representation of these aspects, normative values, and corresponding speech tasks are described in the Table 1.

Swallowing assessment

A drink of water (100 mL) was offered during the functional test and the following instruments were applied:

- *Northwestern Dysphagia Patient Check Sheet* (NDPCS): comprises a brief clinical and functional evaluation of swallowing consisting of 28 items divided into three parts: medical history and behavioral variables, gross motor function, and an oral motor test[20].
- *Eat Assessment Tool* (EAT-10): evaluates the emotional impact and physical symptoms that swallowing problems may have on the individual's life, with a score ranging from 0 to 40; scores greater than 3 indicate a risk for oropharyngeal dysphagia[21].
- *Speech-Language Pathology Assessment for Dysphagia Risk* (PARD): used to classify normality, mild dysphagia, mild to moderate dysphagia, moderate dysphagia, moderate to severe dysphagia, and severe dysphagia[22].
- *Intake Scale* (FOIS): ranges from zero to seven, with a score of zero indicating that no oral diet is recommended and a score of seven indicating that a normal oral diet is recommended without restrictions[23].

Statistical analysis

The independent variables, the perceptual speech analysis, and the swallowing evaluation were presented through descriptive analyzes (absolute and relative frequencies and mean and standard deviation or median and interquartile range). The statistical test was selected according to the data distribution provided by the Shapiro-Wilk test and histograms. For the acoustic analysis of speech between groups, the Mann-Whitney test was used and for the correlation of speech scores with independent variables, the Spearman correlation test was used. Statistical significance was defined as $p<0.05$. The statistical software used was SPSS version 22.0.

RESULTS

Thirteen individuals (seven families) with FSHD and 10 healthy controls were enrolled. The mean duration of disease in the FSHD group was 6.7 (SD=5.9) years and six (46.1%) individuals in this group showed a neurological severity of 4 in the GMWS scale. The FSHD group presented lower scores of quality of life in the dimensions of physical function, role-physical, and bodily pain than the control group. Table 2 shows the clinical and demographic characteristics of individuals with FSHD and controls.

Speech results

Auditory-perceptual analysis of the subsystems of speech of the FSHD and control groups are shown in Table 3. A statistical difference was found between the FSHD and control

Table 1. Acoustic evaluation: motor bases, tasks performed, and outcomes.

Motor base	Assignment	Resulting variable
Phonation	Sustaining the A vowel in a single breath.	**Fundamental frequency (Fo):** For Brazilian Portuguese speakers, the frequency range of normality for females is 150–250 Hz and 80–150 Hz for males[18]. ***Jitter rap*:** The normative values of PRAAT is 0.680% as a threshold for pathology for *jitter rap*[17]. ***Shimmer local*:** The normative values of PRAAT is 3.810% as a threshold for pathology for *shimmer local*[17].
Resonance	Sustaining the A vowel in a single breath.	Extraction of the third and fourth formants of sustained vowel A.
Prosody	Counting from 20 to 30	**Fundamental frequency of count:** maximum fundamental frequency (Fo max), minimum fundamental frequency (Fo min), and standard deviation of fundamental frequency.
Breathing	Sustaining the A vowel in a single breath.	**Maximum phonation time (MPT):** For Brazilian Portuguese speakers, the standard of normality for females is 14 seconds and for males, 20 seconds[18].
Articulation	Alternating repetition of [pataka] the fastest in a single breath. Repetition diphthong I-U [i:ju:] alternately in a single breath.	**Diadochokinesis (DDK):** Young adults 6.58 syllables per second and elderly people, 6.13 syllables per second[19]. Extraction of the first and the second formants of repetition of two combined vowels.

Table 2. Demographic data of the FSHD and control groups.

		FSHD (n=13)	Controls 1 (n=10)	p-value
Female		9 (69.2%)	6 (60%)	0.663
Age		49.5 (13.2)	45.6 (12.2)	0.474
Educational level (years)		8.6 (4.1)	-	
Age of disease onset		42.7 (15.9)	-	
Disease duration		6.7 (5.9)	-	
GMWS — severity level	Normal — 0	1 (7.7%)	-	
	1	2 (15.4%)		
	2	0 (0%)		
	3	0 (0%)		
	4	6 (46.1%)		
	5	2 (15.4%)		
	6	1 (7.7%)		
	7	0 (0%)		
	8	1 (7.7%)		
	Severe - 9	0 (0%)		
MMSE	Normal	6 (46.1%)		
	Altered	7 (53.9%)		
SF-36	Physical Function	30 (7.5–45.0)		
	Role-Physical	0 (0–62.5)		
	Bodily Pain	21 (15–46)		
	General Health	27 (26–48.5)		
	Vitality	60 (25–65)		
	Social Function	50 (31.2–75)		
	Role-Emotional	33.50 (0–83.2)		
	Mental Health	76 (42–89)		

Data are reported means (standard deviation), except for sex, MMSE, and GMWS scores which are reported as frequency. SF-36 data are reported as medians (interquartile range). FSHD: Facioscapulohumeral muscular dystrophy; GMWS: Gardner-Medwin and Walton Scale; MMSE: Mini Mental State Examination; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey.

Table 3. Auditory-perceptual analysis.

	FSHD		Controls	
	(n=13)	Classification	(n=10)	Classification
Phonation	6 (46.2%)	Mild impairment	1 (7.7%)	Mild impairment
Respiration	1 (7.7%)	Mild impairment	0 (0%)	-
Resonance	1 (7.7%)	Mild impairment	0 (0%)	-
Articulation	3 (23.1%)	Mild impairment	0 (0%)	-
Prosody	0 (0%)	-	0 (0%)	-

Data are expressed as frequency. FSHD: Facioscapulohumeral muscular dystrophy.

groups regarding the phonation and respiration subsystems (Table 4). The speech data from the acoustic analysis did not show a significant correlation with GMWS scores, duration of the disease, age at onset of symptoms, or the quality of life of these individuals.

Due to sex difference in fundamental frequency of speech, the acoustic analysis was performed between groups of females only. Only the respiration subsystem showed a significant difference between female FSHD and control participants [5.95 (3.72–7.50) and 9.37 (8.46–11.45), p=0.009]. The speech acoustic in males was not performed because of the small sample size (there were only four male participants with FSHD). This result did not have a significant correlation with the clinical data (Table 5).

Swallowing results

NDPCS results were verified to identify items that showed the greatest changes. Seven (53.8%) patients presented altered oral muscle tone while nine (69.2%) demonstrated no pharyngeal contraction of the gag reflex. Also, six

Table 4. Comparison of acoustic parameters between groups.

	FSHD (n=13)	Controls 1 (n=10)	p-value
Jitter (local)	0.70% (0.44–1.23)	0.33% (0.23–0.75)	0.044*
Jitter (rap)	0.36% (0.21–0.65)	0.18% (0.11–0.39)	0.032*
Shimmer (local)	10.79dB (8.72–14.39)	7.90dB (4.72–10.43)	0.030*
FF average vowel	161.02Hz (127.23–191.91)	162.03Hz (111.55–207.98)	0.951
FF minimum vowel	125.12Hz (93.35–168.20)	94.64Hz (76.92–155.36)	0.264
FF maximum vowel	251.18Hz (171.20–403.76)	215.16Hz (129.90–411.85)	0.804
FF SD vowel	18.86Hz (3.50–59.85)	20.38Hz (1.11–47.56)	0.951
MPT vowel[a]	6.09 (3.61–9.33)	9.37 (8.28–12.25)	0.047*
FF average counting	187.96Hz (144.01–216.71)	168.28Hz (99.62–186.10)	0.094
FF minimum counting	77.13Hz (73.69–92.82)	80.24Hz (77.24–85.89)	0.620
FF maximum counting	442.60Hz (348.69–487.03)	445.17Hz (253.37–491.90)	0.710
FF SD counting	70.45Hz (39.96–84.77)	39.17Hz (20.93–58.32)	0.063
PATAKA[a]	5.59 (4.73–6.07)	5.62 (4.61–6.45)	0.852
IU[a]	0.88 (0.81–0.98)	0.95 (0.83–1.24)	0.336
IU F1	523.04Hz (457.17–570.53)	510.80Hz (470.88–622.22)	0.598
IU F2	1752.25Hz (1671.29–1823.87)	1836.56Hz (1614.20–1904.91)	0.251
IU F3	2964.16Hz (2807.62–3095.68)	2983.76Hz (2856.18–3038.25)	0.687
IU F4	4032.51Hz (3939.74–4112.93)	3926.34Hz (3833.21–4030.95)	0.114

Data are reported as medians (interquartile range); *p<0.05; FSHD: Facioscapulohumeral muscular dystrophy; FF: Fundamental Frequency; MPT: maximum phonation time; [a]syllables per second.

Table 5. Correlations between speech disorders, clinical variables, and quality of life.

	Jitter (local)		Jitter (rap)		Shimmer (local)		MPT	
	p-value	r	p-value	r	p-value	r	p-value	r
Initial symptoms	0.127	-	0.066	-	0.072	-	0.129	-
Length of illness	0.128	-	0.249	-	0.053	-	0.868	-
GMWS	0.406	-	0.738	-	0.603	-	0.334	-
SF-36 Physical Function	0.665	-	0.411	-	0.485	-	0.559	-
SF-36 Role-Physical	0.983	-	0.657	-	0.622	-	0.991	-
SF-36 Bodily Pain	0.114	-	0.073	-	0.110	-	0.355	-
SF-36 General Health	0.053	-	0.053	-	0.151	-	0.437	-
SF-36 Vitality	0.872	-	0.843	-	0.760	-	0.914	-
SF-36 Social Function	0.408	-	0.188	-	0.636	-	0.328	-
SF-36 Role-Emotional	0.199	-	0.107	-	0.092	-	0.668	-
SF-36 Mental Health	0.964	-	0.552	-	0.324	-	0.205	-

MPT: maximum phonation time; GMWS: Gardner-Medwin and Walton Scale; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey.

(46.1%) presented deviated lip protrusion and nine (69.2%) reported not being able to move their lips, such as in pouting and whistling. Of the 13 patients with FSHD, two (15%) were diagnosed with mild dysphagia. The average EAT-10 score was 1.15 (±1.86). Regarding the functionality, 85% of the patients presented a FOIS 7 and 15% were a FOIS 6 (15%).

Regarding the NDPCS instrument, there was a positive correlation with the GMWS (r=0.604, p=0.029), showing that the greater the neurological severity the higher the score on this instrument. When the two patients who had a diagnosis of mild dysphagia were individually analyzed, we found that both scored the highest values in the GMWS (eight and six). There was no correlation between the swallowing data from the NDPCS instrument with other clinical data and with quality of life: initial symptoms (p=0.805); duration of illness (p=0.609); physical function (p=0.148); role-physical (p=0.186); bodily pain (p=0.869); general health (p=0.053); vitality (p=0.446); social function (p=0.753); role-emotional (p= 547); and mental health (p=0.250).

DISCUSSION

In this study, we carried out a detailed characterization of speech and swallowing in FSHD patients undergoing treatment at a neuromuscular genetic disease care center in southern Brazil. Almost half of the patients were diagnosed with mild dysarthria after auditory-perceptual and acoustic analysis of their speech, with changes in the phonation and respiration subsystems. We found mild dysphagia in 15% of the patients, and the risk for dysphagia observed with the EAT-10 is compatible with swallowing findings.

Almost half of the patients with FSHD had alterations in the motor base of phonation in the auditory-perceptual analysis when compared to the control group. In the acoustic analysis including both sexes, alterations in the motor bases of phonation and breathing were observed, corroborating the findings in the auditory-perceptual analysis. This indicates the importance of carrying out both analyzes, as the acoustic analysis proved to be complementary to the auditory analysis[7]. Auditory-perceptual analysis assesses the global impression of vocal quality and is considered the gold standard of analysis[24].

Regarding the motor base of breathing, measured in the acoustic analysis by the maximum phonation time (MPT), patients with FSHD presented values well below normal and lower than the control group[18]. One hypothesis is that this reduction in maximum phonation time may be related to muscle fatigue and weakness[8,25,26]. FSHD patients have respiratory muscle weakness as an intrinsic characteristic of the disease, which can involve the diaphragm and expiratory abdominal muscles[27]. Clinically, these individuals can have communication difficulties and fatigue with long speeches. Additionally, breathing is closely related to phonation as it affects the synchrony between aerodynamic and myoelastic mechanisms, leading to coordination disorders in affected individuals[28].

In the phonation subsystem, six (46.2%) patients presented mild changes in the auditory-perceptual analysis. As in the acoustic analysis, patients with FSHD had significantly higher values for shimmer and jitter when compared to the control group. Changes in this motor base possibly also occur due to fatigue, muscle weakness, or breathing changes. These changes in vocal quality interfere with speech intelligibility and can have a critical impact on communication skills, which in turn limits the individual's occupational, educational and social abilities. Correct characterization of these changes can allow a more specific and early rehabilitation[29].

Even though FSHD patients had reduced strength in facial muscles, impaired articulation was observed in three (21.3%) patients. In the acoustic analysis, this motor subsystem was similar in patients and control groups. Diadochokinesis is widely used to measure the articulatory quality of neurological patients[30]. The initial hypothesis is that since this was a sample with a predominance of individuals with mild disease, joint damage may not yet have been apparent in this population.

In the swallowing evaluation, only 15% of the patients had mild oropharyngeal dysphagia, characterized by changes in the pharyngeal phase (delay in pharyngeal swallowing, reduction in pharyngeal elevation, and multiple swallowing). In a videofluoroscopy study, it was observed that the decrease in tongue strength in patients with FSHD is consistent with the delay in pharyngeal swallowing[11]. Changes in swallowing were related to worsening disease severity. These data are in line with the literature, where the reported prevalence of dysphagia in patients with FSHD ranges from 2 to 25%, being generally characterized by mild dysphagia and occurring in more advanced cases of the disease[8,10-13].

The majority of patients had reduced strength of facial muscles and absence of the GAG reflex. These findings agree with those of other studies that mainly reported weakness of the tongue and jaw and decreased resistance to cheek compression[8,11]. Patients presented deviated lip protrusion and reported not being able to make certain lip movements (such as puckering and whistling) and this may be related to the orbicularis oris and zygomaticus major muscles, which are the most affected muscles in these patients[5].

Regarding the eating function, 85% of the patients maintained a normal oral diet (FOIS 7) and 15% had some food restriction (FOIS 6). The self-assessment of the risk for dysphagia of patients with FSDH measured by the EAT-10 was compatible with swallowing findings, demonstrating reliability in patients' self-perception, which may be useful in the early identification of symptoms.

It is important to note that there was no correlation between speech and swallowing changes with quality of life. This might indicate that the current mild changes might not impact quality of life. In addition, as changes were also unrelated to the duration of the disease and the age of onset of symptoms, they may not follow the course of the disease but occur at different times and require constant clinical attention to detect symptoms.

The main limitation of this work was the sample size and the lack of a molecular diagnosis of FSHD. Considering that previous reports suggest that FSHD-related D4Z4 contractions are responsible for 95% of FSHD cases, our results must be interpreted as mainly related to this subtype of the disease[3]. Another limitation of this work relates to the lack of objective assessment of swallowing in these patients. The above findings show that the topic is relevant and would be best investigated longitudinally, to identify at what point in the course of the disease these changes occur and how they vary in the course of the disease.

In conclusion, FSHD patients had mild dysarthria (with changes in the phonation and respiration subsystems) and mild dysphagia, which is associated with disease severity. Thus, the frequent monitoring of these symptoms by physicians may be important to ensure early rehabilitation and a better quality of life for these patients.

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ARTICLE

Evaluation of neurological disorders that develop concurrently with COVID-19 pneumonia: a retrospective analysis

Avaliação de transtornos neurológicos concomitantes à pneumonia por COVID-19: análise retrospectiva

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ABSTRACT

Background: During the pandemic, many neurological symptoms have been evaluated as complications of COVID-19 pneumonia. **Objective:** To investigate the frequency and characteristics of neurological findings, and their effects on the prognosis of patients with COVID-19 pneumonia who consulted with the Neurology department. **Methods:** Data on 2329 patients who were hospitalized with the diagnosis of COVID-19 pneumonia in our hospital were scanned. The clinical, laboratory and radiological findings relating to treatment of 154 patients who required neurological consultation were retrospectively evaluated by reviewing the clinical notes. **Results:** The number of COVID-19 pneumonia patients who required neurological consultations while hospitalized in the ICU was 94 (61.0%). The most common symptom among these patients was hyperactive delirium. Mean age, ferritin levels and CRP values of those with delirium were higher, while the mean lymphocyte percentage were lower, than those of the patients without delirium. Epileptic seizures were observed in eight patients without an epilepsy diagnosis. Two patients were diagnosed with GBS and one patient with ICU neuropathy. The D-dimer levels of patients with acute hemorrhagic CVD and the thrombocyte levels of patients with acute ischemic CVD were found to be higher than in patients without acute ischemic CVD. **Conclusion:** The proportion of patients who required neurological consultations was higher in the ICUs. We observed neurological symptoms more frequently in the advanced age group. There were no significant increases in the incidence of other neurological conditions except delirium, in COVID-19 patients. We think that further studies are needed to support our data.

Keywords: COVID-19; Neurology; Referral and Consultation; Central Nervous System Diseases; Peripheral Nervous System Diseases.

RESUMO

Antecedentes: Durante a pandemia, muitos sintomas neurológicos foram avaliados como complicações da pneumonia por COVID-19. **Objetivo:** Investigar a frequência e as características dos achados neurológicos e seus efeitos no prognóstico de pacientes com pneumonia por COVID-19 que consultaram o departamento de Neurologia. **Métodos:** Foram analisados os dados de 2.329 pacientes internados com diagnóstico de pneumonia por COVID-19 em nosso hospital. Os achados clínicos, laboratoriais e radiológicos relativos ao tratamento de 154 pacientes que necessitaram de consulta neurológica foram avaliados retrospectivamente por meio da revisão das anotações clínicas. **Resultados:** O número de pacientes com pneumonia por COVID-19 que necessitaram de consultas neurológicas enquanto internados na UTI foi de 94 (61,0%). O sintoma mais comum entre esses pacientes foi o delírio hiperativo. A média de idade, os níveis de ferritina e os valores de PCR daqueles apresentando delírios foram maiores, enquanto a porcentagem média de linfócitos foi menor do que em pacientes sem delírios. Crises epilépticas foram observadas em oito pacientes sem diagnóstico de epilepsia. Dois pacientes foram diagnosticados com SGB e um paciente com neuropatia na UTI. Os níveis de dímero D de pacientes com DCV hemorrágica aguda e os níveis de trombócitos de pacientes com DCV isquêmica aguda foram maiores do que em pacientes sem DCV isquêmica aguda. **Conclusão:** A proporção de pacientes que necessitaram consultas neurológicas foi maior nas UTIs. Observamos sintomas neurológicos com mais frequência em pacientes de faixa etária avançada. Não houve aumentos significativos na incidência de outras condições neurológicas, exceto delírio, em pacientes com COVID-19. Acreditamos que mais estudos são necessários para apoiar nossos dados.

Palavras-chave: COVID-19; Neurologia; Encaminhamento e Consulta; Doenças do Sistema Nervoso Central; Doenças do Sistema Nervoso Periférico.

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INTRODUCTION

The World Health Organization (WHO) declared that COVID-19 constituted a pandemic on March 11, 2020[1]. According to WHO data, the virus had infected 172,956,039 people worldwide as of June 7, 2021, and had caused 3,726,466 deaths[2].

Two coronaviruses previously identified as SARS-CoV-1 and MERS-CoV have caused large-scale epidemics[3,4]. SARS-CoV-2 may have higher neuroinvasive potential than previous coronaviruses[5].

Viruses enter the central nervous system (CNS) essentially through hematogenous and neuronal retrograde propagation pathways. SARS-CoV-2 can also bind to angiotensin receptor 2 (ACE2), which is expressed in the capillary endothelium of the blood brain barrier (BBB), to access the CNS[6,7]. The ACE2 receptor is expressed intensely in the cerebellum, thalamic nuclei, inferior olivary nucleus, ventrolateral medulla and tractus solitarius nucleus, in the CNS[1,8]. SARS-CoV-2 has higher affinity for the ACE2 receptors found in neurons and endothelial cells than does SARS-CoV-1[7].

The mechanisms that have been suggested for the development of various neurological syndromes include direct viral neuronal damage, a hyperinflammatory syndrome secondary to viremia, para-infectious and post-infectious inflammatory or immune-mediated disorders, sepsis, hyperpyrexia, hypoxia, hypercoagulopathy and critical illness. Several neurological conditions, including encephalopathy, meningoencephalitis, ischemic stroke, acute necrotizing encephalopathy and Guillain-Barré syndrome (GBS), have been found to coexist with COVID-19[9].

Considering the high rates of COVID-19 infection in the general population, it is important to distinguish whether COVID-19 is associated with neurological involvement or whether coexistence of neurological diseases is coincidental, with support from scientific data[10].

In our study, we retrospectively reviewed the files of 2,329 patients who had been diagnosed with COVID-19 pneumonia and hospitalized in the wards or intensive care units (ICUs) of our institution. We conducted statistical analyses on the data regarding neurological findings, demographic data, relationships with other chronic diseases, radiology and laboratory findings and drug use, with regard to 154 patients who required neurological consultations (NC).

METHODS

The files of 2,329 patients with a diagnosis of COVID-19 pneumonia who were hospitalized in the wards and ICUs of our institution, between March 23, 2020, and October 1, 2020, were examined. The clinical findings, radiological findings and treatment records of 154 patients who required NC due to neurological symptoms were screened retrospectively by evaluating the consultation notes and patient files. The reason for requesting NC, neurological diagnoses, neurological examination findings and radiological data of all patients were examined. Patients under 18 years of age, those with a negative PCR test and/or without findings compatible with COVID-19 pneumonia on chest computed tomography imaging were not included in the evaluation.

The study protocol was approved by the Republic of Turkey Ministry of Health Scientific Research Platform and by Firat University Medical School Clinical Research Ethics Board.

The age, sex, ICU admission and length of hospitalization of the patients who required NC were evaluated. The PCO_2, pH, PaO_2/FiO_2 ratio, positive end expiratory pressure (PEEP), oxygen saturation, lymphocyte, white blood cell (WBC), thrombocyte, ferritin, D-dimer, pro-brain natriuretic peptide (pro-BNP), fibrinogen and C-reactive protein (CRP) values of the patients were recorded. The treatments that they received were recorded. The frequencies of neurological or non-neurological chronic comorbid diseases among the patients in this group were examined. The neurological findings magnetic resonance imaging (MRI), CT, electroencephalography (EEG) and electromyography (EMG) findings of the patients were evaluated. The demographic data, risk factors, treatments and radiological and laboratory findings of patients who were diagnosed with delirium, acute ischemic or hemorrhagic stroke were evaluated. Delirium patients were identified by using the Richmond Agitation Sedation Scale (RASS). RASS is a 10-point scale, where (0) indicates a calm and alert state, while the levels from +1 to +4 indicate increasing levels of agitation and the levels from -1 to -5 indicate increasing levels of sedation[11]. It has been stated that patients with RASS scores between -4 and +4 can be evaluated as having delirium[12].

Statistical analysis

The data were analyzed by using the Statistical Package for the Social Sciences (SPSS) v.22 software (SPSS Inc., Chicago, IL, USA) Descriptive statistics were expressed as the number and percentage for categorical data and as the mean±standard deviation for continuous data. Pearson chi-square analysis was used to compare categorical variables between groups. The Kolmogorov-Smirnov test was used to evaluate the normality of distribution of continuous variables. The one-way ANOVA test was used to compare the normally distributed numerical measurements in more than two groups. Student's *t*-test was used for comparison of paired groups. $P<0.05$ were accepted as statistically significant.

RESULTS

The files of a total of 2,329 COVID-19 pneumonia patients were screened in this study. The number of patients who required NC was 154. NC were requested for

94 patients (61.0% of the patients with COVID-19 pneumonia seeking NC) and were not requested for 486 patients (22.3% of all COVID-19 pneumonia patients) who were hospitalized in the ICU (p<0.001). The proportion of males among the patients who required NC was 64.3% and it was 56.5% among who did not require NC (p=0.058). The mean age of the patients who required NC (72.3±15.0 years) was found to be significantly higher than the mean age of the patients who did not require consultations (64.4±17.1 years) (p<0.001). The mean age was 72.3±15.0 years (range: 21–96) and 99 patients (64.3%) were male. The most commonly used antiviral medication among the patients who required NC was favipiravir (67.5%). At least one antibiotherapy agent was given to 97.6% of the patients, anticoagulants to 90.3% and steroid medication to 63.6%. While 36.4% of the patients who required NC were intubated, 33.8% died. The demographic characteristics and disease related features of the patients are given in Table 1.

Table 1. Demographic characteristics and disease-related features of the patients.

		Number	%		Mean±SD
Sex	Male	99	64.3	Age	72.3±15.0
	Female	55	35.7	Hospital stay (days)	12.8±11.3
				Ph	7.4±0.1
Hospitalization	Ward	60	39.0	PCO_2	39.3±10.9
	ICU	94	61.0	Lymphocyte (%)	16.7±25.7
Intubated		56	36.4	WBC	11.6±7.8
Exitus		52	33.8	Thrombocyte	217.1±103.9
HT		79	51.6	Ferritin	552.7±564.1
LF		2	1.3	D-dimer	2.8±3.6
CRF		8	5.2	Pro-BNP	5358.9±9102.3
DM		39	25.3	Fibrinogen	510.2±212.2
DVT		1	2.6	CRP	9.3±7.7
Delirium		95	61.7		
COPD		24	15.6		
Cancer		4	2.6		
CF		28	18.2		
AF		8	17.4		
CAD		57	37.0		
Acute hemorrhagic CVD		6	3.9		
Chronic hemorrhagic CVD		10	6.5		
Acute ischemic CVD		26	16.25		
Acute SVT		1	2.6		
Chronic ischemic CVD		57	37.0		
Parkinson's disease		10	6.5		
Epilepsy		5	3.2		
Dementia		43	27.9		
Guillain-Barre syndrome		2	1.9		
Critical disease neuropathy		1	2.6		
Moxifloxacin		46	74.2		
Azithromycin		36	23.4		
Tocilizumab		2	1.3		
Ritonavir+Lopinavir		6	3.9		
Oseltamivir		20	13.0		
Favipiravir		104	67.5		
Enoxaparin		139	90.3		
Deltacortril		98	63.6		
Chloroquine		89	57.8		

ICU: intensive care unit; HT: hypertension; LF: liver failure; CRF: chronic renal failure; DM: diabetes mellitus; DVT: deep vein thrombosis; COPD: chronic obstructive pulmonary disease; CF: cardiac failure; AF: atrial fibrillation; CAD: coronary artery disease; CVD: cerebrovascular disease; SVT: sinus vein thrombosis.

In comparing respiratory parameters of the COVID-19 patients between those hospitalized in the wards and those in the ICUs, it was found that the PaO_2/FiO_2 ratios and oxygen saturation levels of the patients hospitalized in the wards were significantly higher ($p<0.001$). However, no statistically significant difference was found between pH and PCO_2 parameters. It was found that the mean PEEP value of the patients hospitalized in the ICU was 8.4±2.0 (Figure 1).

It was observed that the most common neurological symptom among the patients was hyperactive delirium. The most common findings on both MRI and CT were cerebrocerebellar atrophy and presence of common ischemic gliotic areas. The other most common findings, following atrophy and chronic ischemic gliotic areas in CT, were chronic infarction (17.6%) and acute infarction (8.4%). In addition, intracerebral hemorrhage was observed in six patients (4.6%). EMG was performed on eight patients with complaints of paraparesis, tetraparesis and hypoesthesia. The EMG findings included diffuse sensorimotor polyneuropathy compatible with ICU neuropathy in one patient, polyneuropathy with acute axonal damage in one patient and EMG findings compatible with acute demyelinating-type sensorimotor polyneuropathy in one patient. EEG examinations were performed on four patients presenting confusion who were hospitalized in wards. In two patients, a slowdown in the background rhythm was observed in delta activity, whereas the EEG was normal in two patients (Table 2).

Delirium was detected in 61.7% of the patients who required NC. When the patients who required NC were evaluated according to the subtypes of delirium, it was found that hyperactive delirium was present in 75.8%, hypoactive delirium in 13.7% and mixed- type delirium in 10.5% of all the delirium patients. The RASS scores of the patients were found to be 1.94±0.73 in hyperactive delirium, -1.89±0.77 in hypoactive delirium and 1.53±0.45 and -1.53±0.45 in mixed-type delirium, respectively. There were no significant differences between the delirium subtypes in terms of RASS scores. In addition, there were no significant differences between the delirium subtypes in terms of pH, PCO_2, PaO_2/FiO_2 ratio, PEEP, oxygen saturation, WBC, lymphocyte, thrombocyte, CRP, fibrinogen, ferritin, D-dimer and pro-BNP levels (Figure 2).

The delirium rate was found to be significantly higher among patients who died and those with CRF and dementia. This rate was found to be significantly lower among those with acute CVD and those with a previous diagnosis of CVD (Figure 3).

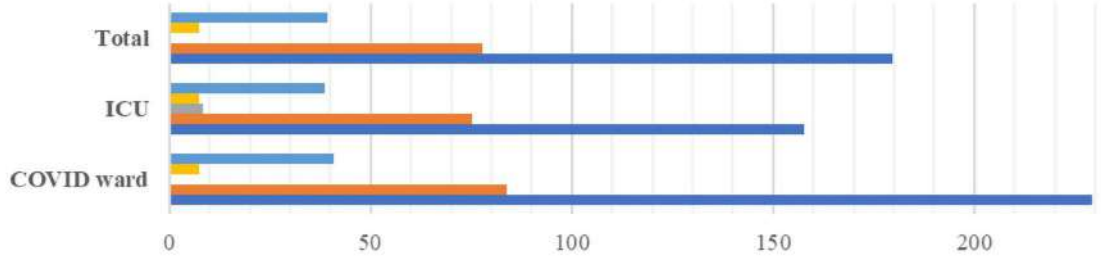
The average age and the ferritin and CRP levels were significantly higher among patients with delirium than among those without delirium, whereas the lymphocyte percentage was found to be significantly lower in those with delirium (Figure 4).

The D-dimer levels of patients with acute hemorrhagic CVD were found to be significantly higher than those of patients without this ($p=0.03$) (Figure 4).

The thrombocyte levels of patients with acute ischemic CVD were found to be significantly higher than those of patients without this ($p<0.001$) (Figure 4).

DISCUSSION

In the literature there are large numbers of meta-analyses, reviews and case reports on neurological involvement in



	COVID ward	ICU	Total
PCO_2	40.9	38.7	39.3
pH	7.4	7.4	7.4
PEEP		8.4	
Oxygen saturation	83.8	75.1	77.8
PaO_2/FiO_2	229.4	157.6	179.6

ICU: intensive care unit; PEEP: positive end expiratory pressure.

Figure 1. Comparison of respiratory parameters of patients in COVID wards and intensive care units. The PaO_2/FiO_2 ratio and O_2 saturation values of the patients hospitalized in the COVID ward were found to be significantly higher than the values of the patients hospitalized in the intensive care unit ($p<0.001$). However, no significant difference was observed between the COVID ward and ICU, regarding PCO_2 ($p=0.317$) and pH ($p=0.691$) values. The mean PEEP value of intensive care patients was 8.4±2.0.

Table 2. Neurological symptoms and magnetic resonance imaging, computed tomography and electromyography findings of the patients.

	Number	%
Neurological symptoms		
Paraparesis and tetraparesis	3	1.9
Hyperactive delirium*	82	52.9
Epileptic seizure	13	8.4
Hypoactive delirium* (encephalopathy such as lethargy, stupor or confusion)	23	14.9
Coma	6	3.88
Acute focal neurological deficit (hemiparesis, aphasia, etc.)	24	15.6
Headache	9	5.8
Dizziness	9	5.8
Syncope	4	2.6
Anisocoria	2	1.3
MRI findings		
Acute infarction bilaterally in hemispheres	3	4.2
Acute infarction in the left hemisphere	12	16.7
Acute infarction in the right hemisphere	7	9.7
Chronic infarction	10	13.9
Thrombus in the right transverse sinus	1	1.4
Hemorrhagic infarction in the right hemisphere	1	1.4
Cerebrocerebellar atrophy or common ischemic gliotic areas	29	40.3
Other (craniectomy defect or intracranial mass)	4	5.5
CT findings		
Hematoma in the brain stem and cerebellum	2	1.5
Hematoma in the right hemisphere and subarachnoid hemorrhage	4	3.1
Acute infarction	11	8.4
Chronic infarction	23	17.6
Cerebrocerebellar atrophy or common ischemic gliotic areas	66	50.4
Other (hydrocephalus, craniectomy defect, intracranial mass, calcification or vascular occlusion)	10	7.6
EMG findings		
Diffuse sensorimotor polyneuropathy	1	12.5
Polyneuropathy with acute axonal damage	1	12.5
Acute demyelinating-type polyneuropathy	1	12.5
Normal	5	62.5
EEG findings		
Diffuse deceleration in delta frequency	2	50
Normal	2	50

MRI: magnetic resonance imaging; CT: computed tomography; EEG: electroencephalography; EMG: electromyography. *The data on mixed-type delirium patients are included in this group.

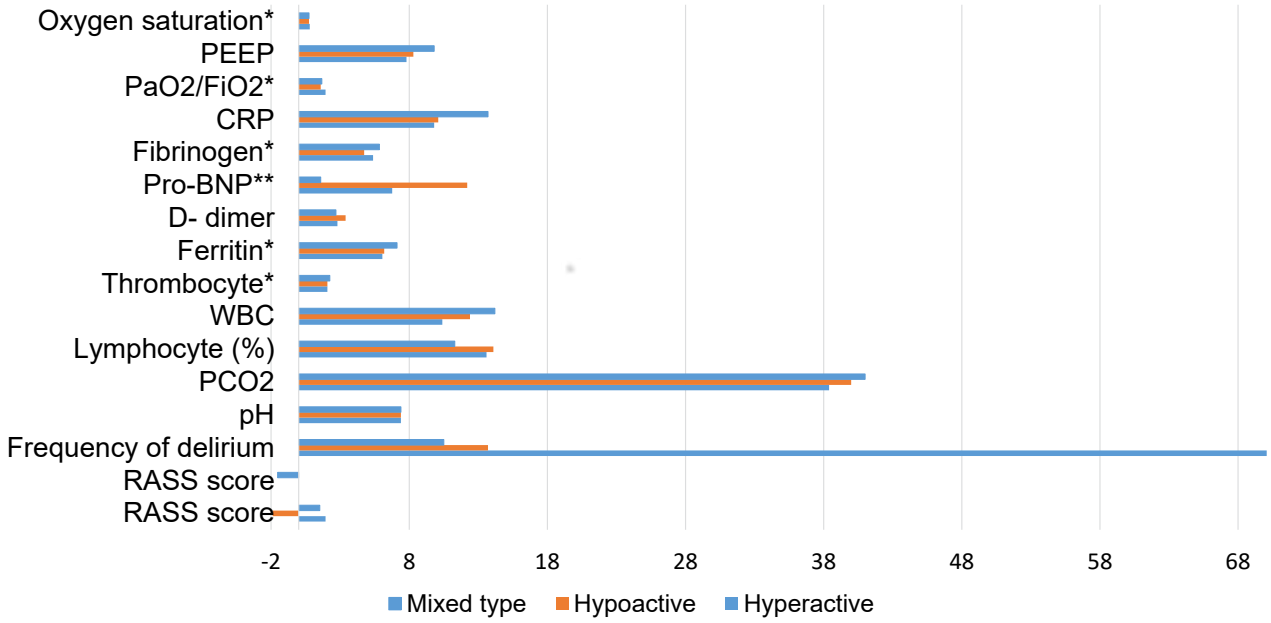
patients with COVID-19. In this study we aimed to identify accompanying neurological diseases depending on clinical findings, radiological images and laboratory data.

Helms et al. found that the mean age of COVID-19 patients with neurological symptoms who were hospitalized in the ICU was 62 years, and that 75% of them were male. They reported that 82% of the patients hospitalized in the ICU had neurological symptoms and that the most common symptom was delirium[13]. In our study, the mean age of the patients who required NC was 72 years, and 64% of the patients were male. In this study, we evaluated the COVID-19 patients hospitalized in both the wards and the ICU. The proportion of the patients who required NC was 61% in the ICU and 39% in the wards.

In a study evaluating COVID-19 patients hospitalized in the ICU, it was observed that the most common comorbidities were cardiovascular diseases, respiratory diseases and DM among patients with neurological symptoms[13]. In our study, the most common chronic diseases among patients who required NC were HT (51.6%), previous ischemic stroke (37%), coronary artery disease (37%), dementia (27.9%) and DM (25.3%), respectively. While 36.4% of the patients who required NC were intubated, 33.8% died. In the study by Mao et al. [14], it was reported that the rate of developing neurological symptoms was higher among patients with severe disease, as in our study data.

It has become known that headache and dizziness are common among COVID-19 patients. The frequency of headache in COVID-19 was found between 3 and 12.1% in one study, while it was 27% in another study[15,16]. In a study, it was reported that dizziness was observed in 8% of COVID-19 patients[16]. In our study, nine patients (5.8%) with resistant headache and nine patients (5.8%) with persistent dizziness had consultations with the Neurology department.

Epileptic seizures developed in 13 patients (0.5% of all patients and 8.4% of the patients who required NC). Three of these patients had common myoclonic seizures that developed after cardiopulmonary resuscitation and the other patients had generalized tonic-clonic seizures (GTCS). Five of these 13 patients had been diagnosed with epilepsy, and all the epileptic patients had GTCS, while eight patients had epileptic seizures for the first time. Three of patients who had GTCS without a diagnosis of epilepsy had acidosis in blood gas analysis, fever, electrolyte disturbance and severe hypoxia that triggered seizures. No emergency pathological condition was detected through brain CT and diffusion MRI. These seizures were considered to be provoked seizures. No antiepileptic treatment was started. Antiepileptic treatment was started in all patients except the patients who had got provoked seizures. EEG was recommended after COVID-19 treatment. A very small number of retrospective studies have reported seizures in COVID-19, with incidence ranging from 0.5 to 1.4%. All types of seizures have been reported in COVID-19 patients[17].



	RASS score	RASS score	Frequency of delirium	pH	PCO_2	Lymphocyte (%)	WBC	Thrombocyte*	Ferritin*	D- dimer	Pro-BNP**	Fibrinogen*	CRP	PaO_2/FiO_2*	PEEP	Oxygen saturation*
Hyperactive	1.94		75.8	7.4	38.4	13.6	10.4	2.078	6.057	2.8	6.7744	5.38	9.8	1.939	7.8	0.802
Hypoactive	-1.89		13.7	7.4	40	14.1	12.4	2.075	6.196	3.4	12.1945	4.744	10.1	1.588	8.3	0.753
Mixed type	1.53	-1.53	10.5	7.4	41	11.3	14.2	2.255	7.123	2.7	1.594	5.843	13.7	1.675	9.8	0.743
p*				0.523	0.765	0.787	0.33	0.866	0.872	0.706	0.772	0.359	0.3	0.241	0.153	0.195
*1/100 of the true value is used to normalize the graphic **1/1000 of the true value is used to normalize the graphic																

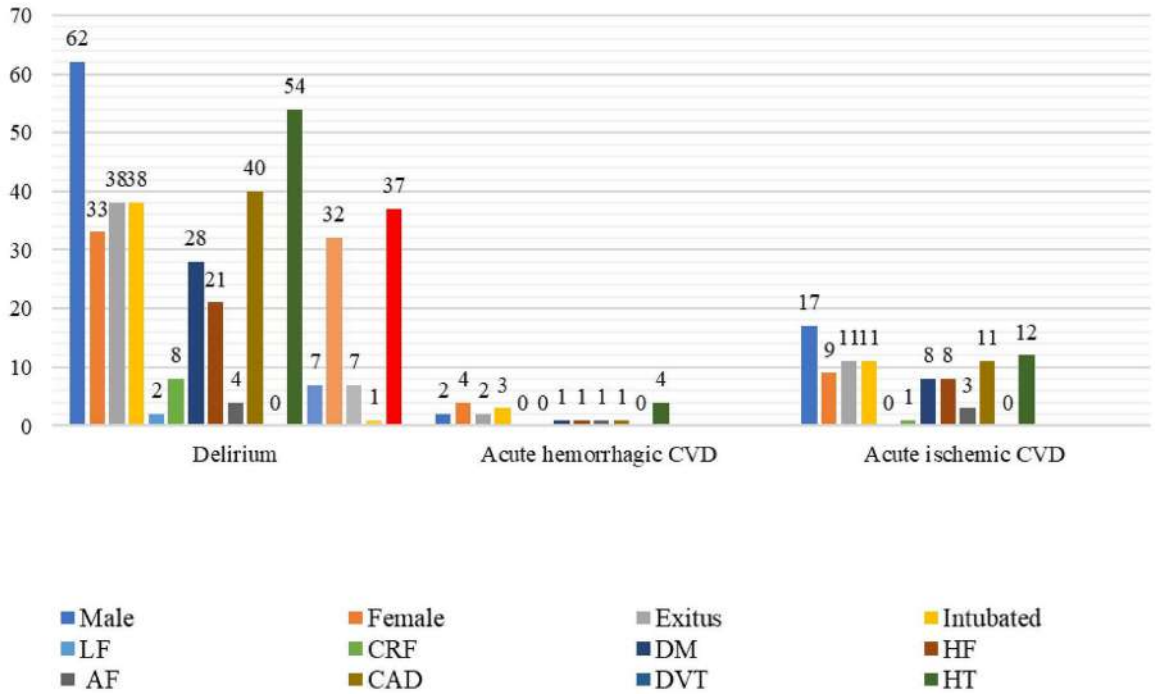
RASS: Richmond Agitation Sedation Scale.

Figure 2. Richmond Agitation Sedation Scale scores and respiratory, infectious and coagulation parameters in delirium subtypes. When the patients who required neurology consultations were evaluated according to the subtypes of delirium, it was found that hyperactive delirium was present in 75.8%, hypoactive delirium in 13.7% and mixed-type delirium in 10.5% of the patients. There were no statistically significant differences between the subtypes of delirium in terms of RASS scores. There were no significant differences between delirium subgroups in terms of respiratory, infectious or coagulation data, as indicated in the table above (p>0.05).

Brain and/or diffusion MRI was performed on 66 patients, and brain CT was performed on 116 patients who required NC. The most common radiological findings were cerebrocerebellar atrophy and diffuse ischemic gliotic areas, which were detected in 40.3% of MRI and 50.4% of CT examinations. Consistently, Helmes et al. and Kandemir et al. reported that the most common CNS imaging finding in COVID-19 patients was bilateral signal changes in FLAIR in MRI[13,18].

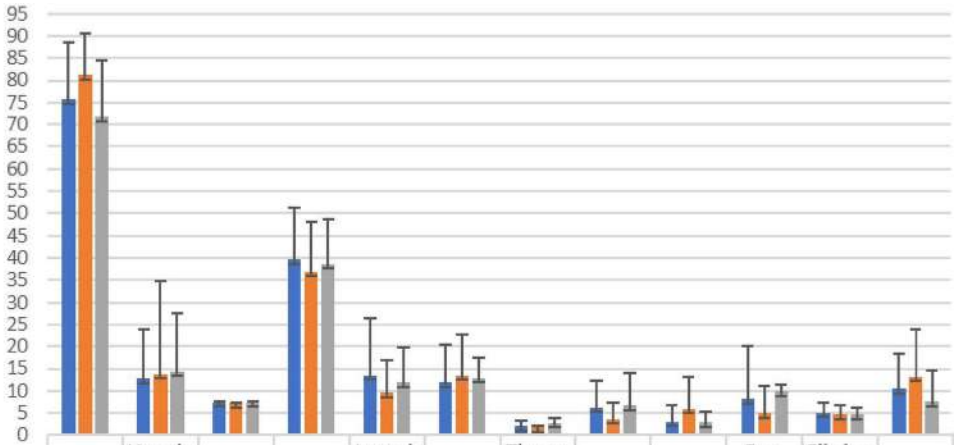
EMG was performed on eight patients. Acute-onset ascending paraparesis was observed in one patient, tetraparesis in two patients, and hypoesthesia in five patients. The complaints of the patient with acute ascending paraparesis developed 15 days after the diagnosis of COVID-19. In the EMG, acute demyelinating-type sensorimotor polyneuropathy without f response was detected. The first patient with tetraparesis developed tetraparesis on the ninth day of hospitalization, due to COVID-19. In the EMG, motor neuropathy with acute axonal damage without f response was observed. The second patient was intubated for 34 days due to COVID-19 and was evaluated because of tetraparesis after being extubated. In the EMG, subacute-period diffuse sensorimotor polyneuropathy was detected. In accordance with these findings, two patients were diagnosed with GBS and one patient was diagnosed with ICU neuropathy. EMG's on five patients was found to be normal. In the review conducted by Koralnik et al., similar relationships between COVID-19 were reported[4]. In Koralnik et al.'s study, the EMG results were consistent with demyelination in two patients and axonal neuropathy in three patients. SARS-CoV-2 was not detected in CSF by means of RT-PCR in any of the patients[4].

Despite the increasing number of case series, it is not clear whether SARS-CoV-2 causes GBS or whether this association is coincidental. Keddie et al.[19] examined the relationship between COVID-19 disease and GBS, in their epidemiological cohort study they reported that there was no increase in the incidence of GBS during the COVID-19 pandemic; rather, there was a decrease in comparison with previous years. In addition, they reported that they did not detect any



LF: liver failure; AF: atrial fibrillation; CRF: chronic renal failure; CAD: coronary artery disease; CVD: cerebrovascular disease; DM: diabetes mellitus; DVT: deep vein thrombosis; HT: hypertension; HF: heart failure.

Figure 3. Incidence of chronic diseases among patients with delirium, acute ischemic cerebrovascular disease and acute hemorrhagic cerebrovascular disease. The rate of delirium was found to be significantly higher among patients who died and those with chronic renal failure ($p=0.024$) and dementia ($p<0.001$). The rate of delirium was found to be significantly lower among patients with acute cerebrovascular disease ($p<0.001$) and those with a previous diagnosis of cerebrovascular disease ($p=0.012$). No statistically significant association was observed between acute ischemic and hemorrhagic cerebrovascular disease patients and other chronic diseases ($p>0.05$).



	Age	Hospital stay (days)	pH	PCO_2	Lymphocyte (%)	WBC	Thrombocyte *100	Ferritin *100	D-dimer	Pro-BNP *1000	Fibrinogen *100	CRP
Delirium	75.7	12.8	7.4	39.6	13.5	11.9	2.101	6.28	3.1	8.1594	5.136	10.5
Acute hemorrhagic CVD	81.2	13.8	7.3	36.9	9.6	13.5	1.775	3.684	6	4.961	4.724	13.2
Acute ischemic CVD	71.7	14.4	7.4	38.6	11.9	12.9	2.838	6.639	3	9.8135	4.717	7.6

CRP: C-reactive protein.

Figure 4. Age, length of hospital stay and laboratory parameters among patients with delirium, acute ischemic cerebrovascular disease and acute hemorrhagic cerebrovascular disease. The average age ($p<0.001$), ferritin ($p=0.04$) and C-reactive protein ($p=0.015$) were significantly higher among patients with delirium than among those without delirium, whereas lymphocyte values ($p=0.048$) were found to be significantly lower among those with delirium. The D-dimer levels ($p=0.03$) in patients with acute hemorrhagic cerebrovascular disease were found to be significantly higher than the levels in patients without acute hemorrhagic cerebrovascular disease. The thrombocyte levels ($p<0.001$) in patients with acute ischemic cerebrovascular disease were found to be significantly higher than the levels in patients without acute ischemic cerebrovascular disease.

molecular similarity in SARS-CoV-2 that could cause, such as molecular mimicry, as in *C. jejuni* and CMV[19]. It has been theorized that GBS may occur due to different unidentified autoantibodies, viral neurotoxins or, with low probability, direct infection of the peripheral nerve by the viruses[20].

In our study, the most common reason for requesting consultations was delirium (61.7%). The mean age of the patients with delirium was significantly higher than the age of those without delirium (p<0.001). In addition, ferritin (p=0.04) and CRP levels (p=0.015) were found to be significantly higher and lymphocyte levels (p=0.048) were significantly lower in patients with delirium than in those without delirium. These findings support the notion that cytokine storms cause delirium, in these patients.

The death rate was statistically higher among patients with delirium. In fact, considering that the risk of developing delirium was proportional to the severity of the disease and advancing age, this finding was an expected result. On the other hand, there was no statistically significant difference between the patients with and without delirium, in terms of the duration of intubation and hospital stay. In the study conducted by Helms et al., increased levels of protein, Ig-G and IL-6 were detected in the CSF of patients hospitalized in the ICU due to COVID-19 who developed delirium, and SARS-CoV-2 RNA was not isolated. Therefore, like in our study, it was suggested that delirium was related to a systemic inflammatory response and cytokine storm[13].

In the study conducted by the Strasbourg group, agitation was observed in 69% and confusion in 65% of the patients hospitalized in the ICU due to COVID-19[9].

According to the results of this study, delirium (hyperactive or agitated, hypoactive and mixed-type) was the reason for requesting a consultation in more than half of the cases assessed. When the patients who required NC were evaluated according to the subtypes of delirium, it was found that hyperactive delirium was present in 75.8%, hypoactive delirium in 13.7% and mixed-type delirium in 10.5% of the delirium patients. There were no statistically significant differences between the subtypes of delirium in terms of RASS scores or respiratory, infectious or coagulation parameters. The presence of dementia and CRF caused a statistically significant increase in the rate of delirium development. Interestingly, the incidence of delirium was found to be statistically lower in patients with a history of CVD and acute CVD. We think that this was due to the fact that patients with CVD were not included in the delirium category, since the etiology of the changes of consciousness had been clarified.

The second most common reason for requesting a NC was acute focal neurological deficits (15.6%). In our study, the rate of patients with acute hemorrhagic CVD, among all the patients with COVID-19 pneumonia, was 0.25%. The D-dimer values of patients with acute hemorrhagic CVD were found to be statistically significantly higher than those of patients without this (p=0.03). In this group, four of the six patients had been diagnosed with HT. Three of these patients were using low-molecular-weight heparin treatment prophylactically because of the previous diagnosis of COVID-19. Three patients were diagnosed with COVID-19 at the time of hemorrhagic CVD diagnosis. In this group, uncontrolled HT or prophylactic anticoagulant agents used for high D-dimer levels are likely to cause intracerebral hemorrhage. In a case series presented by Fayed et al., one of the three COVID-19 patients with intracerebral hemorrhage had an increased D-dimer level and one patient was using anticoagulant[21].

In the present study, acute ischemic CVD patients constituted 1.1% of all hospitalized patients diagnosed with COVID-19 pneumonia. MRI revealed areas of acute infarction in the left hemisphere, at a rate of 16.7%; in the right hemisphere at a rate of 9.7%; and bilaterally at a rate of 4.2%. In a cohort study, ischemic stroke was reported in 2-6% of the patients hospitalized with COVID-19[3]. Although the rates of ischemic CVD in COVID-19 patients are variable, in our study we detected lower rates, compared with the literature. This situation may have been due to the fact that the anticoagulant and/or antiaggregant treatment was started as soon as the disease was detected, if there was no reason why this treatment would increase the risk of bleeding in the patients with COVID-19 pneumonia. According to our data, the mean thrombocyte level was found to be significantly higher in acute ischemic CVD patients than in those without this condition (p<0.001). The finding that thrombocytosis increased the risk of ischemia was expected. However, our findings contradict other studies in the literature, in which it was reported that high D-dimer, fibrinogen and CRP levels increased the risk of stroke, in patients with concurrent COVID-19 and acute ischemic CVD. In a cohort study, 96 stroke patients who experienced vascular events associated with proinflammatory coagulopathy were found to have high CRP, D-dimer and ferritin levels[3]. In addition, in a recently published study, Sonkaya et al. compared mid-cerebral artery blood flow velocities in 20 people diagnosed with COVID-19 and 20 healthy volunteers, by means of transcranial Doppler USG. They showed that cerebral autoregulation is impaired in COVID-19 patients. It was found that the mean blood flow velocities in patients diagnosed with COVID-19 were higher (p=0.00), and that vasomotor reactivity was decreased, compared with healthy volunteers (p=0.00). This situation was thought to have been due to endothelial dysfunction[22].

The limitations of this study were that CSF examinations were not performed on any patient, CK values were not included in the study and EEGs were not performed on the ICU patients presenting confusion.

In conclusion, we determined that NC were requested more frequently for intensive care patients. As expected, it was observed that the mean PaO_2/FiO_2 ratio and oxygen saturation levels of the patients hospitalized in the ICU were significantly lower than those of the patients in the ward. The most common neurological condition was

delirium, and it was observed more frequently among critically ill patients. Contrary to data in the literature, the rate of acute ischemic CVD was low and there was a statistically significant positive correlation between thrombocytosis and acute ischemic disease. Also, contrary to expectations, there was a statistically significant relationship between elevated D-dimer levels and acute hemorrhagic CVD. We anticipate that the complications of SARS-CoV-2 seen in acute and long-term follow-ups will become more clearly defined for neurologists in the future. We think that further studies with larger patient groups are needed to support our data.

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ARTICLE

Evaluation of upper extremity ataxia through image processing in individuals with multiple sclerosis

Avaliação da ataxia da extremidade superior por processamento de imagem em indivíduos com esclerose múltipla

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ABSTRACT

Background: Impaired dexterity is a frequently reported disability among people with ataxic multiple sclerosis (MS). **Objective:** To quantify and standardize the evaluation of upper extremity coordination disorder among patients with multiple sclerosis (MS), using the Tablet Ataxia Assessment Program (TAAP). **Methods:** The X and Y axis movements of 50 MS patients and 30 healthy individuals who were evaluated using the International Cooperative Ataxia Rating Scale (ICARS) were also assessed using TAAP. The functional times of the participants' right and left hands were recorded using the nine-hole peg test (NHPT). The upper extremity coordination of individuals with MS was evaluated using the upper extremity kinetic functions section of ICARS. **Results:** The deviations for the X and Y axis movements of the MS group were greater than those of the control group ($p<0.05$). Significant correlations were shown between TAAP scores and NHPT and ICARS scores. The strongest correlation was found between NHPT and ICARS in the dominant hand ($r_{nhpt}=0.356$, $p_{nhpt}=0.001$; $r_{icars}=0.439$, $p_{icars}=0.000$). In correlating the Y axis with ICARS, the deviations in the Y axis were found to be greater in the non-dominant hand than those in the X axis ($r_{yright}=0.402$, $p_{yright}=0.004$; $r_{yleft}=0.691$, $p_{yleft}=0.000$). **Conclusion:** Measurement using TAAP is more sensitive than other classical and current methods for evaluating ataxia. We think that TAAP is an objective tool that will allow neurorehabilitation professionals and clinicians to evaluate upper extremity coordination.

Keywords: Multiple Sclerosis; Ataxia; Upper Extremity; Diagnosis.

RESUMO

Antecedentes: Destreza prejudicada é uma deficiência frequentemente relatada em pessoas com esclerose múltipla (EM) atáxica. **Objetivo:** Nosso objetivo é quantificar e padronizar a avaliação do distúrbio de coordenação da extremidade superior em pacientes com EM usando o *Tablet Ataxia Assessment Program* (TAAP). **Métodos:** Os movimentos dos eixos X e Y de 50 EM e 30 indivíduos saudáveis que foram avaliados com a *International Cooperative Ataxia Rating Scale* (ICARS) também foram avaliados com TAAP. Os tempos funcionais das mãos direita e esquerda dos participantes foram registrados usando o teste de nove pinos (NHPT). A coordenação da extremidade superior de indivíduos com EM foi avaliada com a seção de funções cinéticas da extremidade superior do ICARS. **Resultados:** Os desvios para os movimentos dos eixos X e Y do grupo MS foram maiores do que os do grupo controle ($p<0,05$). Correlações significativas foram mostradas entre os escores do TAAP e os escores do NHPT e do ICARS. A correlação mais forte foi encontrada entre NHPT e ICARS na mão dominante ($r_{nhpt}=0,356$, $p_{nhpt}=0,001$, $r_{icars}=0,439$ e $p_{icars}=0,000$). Na correlação do eixo Y com ICARS, observou-se que os desvios no eixo Y foram maiores na mão não dominante do que no eixo X ($r_{yright}=0,402$, $p_{yright}=0,004$, $r_{yleft=}0,691$ e $p_{yleft}=0,000$). **Conclusão:** A medição com TAAP é mais sensível do que outros métodos clássicos e atuais de avaliação de ataxia. Acreditamos que o TAAP seja uma ferramenta objetiva que permitirá aos profissionais de neurorreabilitação e médicos avaliar a coordenação dos membros superiores.

Palavras-chave: Esclerose Múltipla; Ataxia; Extremidade Superior; Diagnóstico.

INTRODUCTION

Ataxia is defined as a disorder in the coordination of voluntary muscle movement. It is not a disease but, rather, a physical finding[1] and is seen in approximately 75% of patients with multiple sclerosis (MS)[2]. Ataxia can present as trunk or limb ataxia or as a combination of the two. While trunk ataxia results from midline damage in the cerebellar

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Authors' contributions: FE: study design, data analysis; IY: interpretation of sensor data, patient recruitment and evaluation; AUU: drafting the work or revising it critically for important intellectual content; MA: interpretation of data for study, drafting the work or revising it critically for important intellectual content.

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vermis and associated pathways, extremity ataxia can be lateralized by ipsilateral cerebellar lesions[1]. Lower extremity ataxia is defined as gait disturbances. Upper extremity ataxia is characterized by tremor and dysynergy[3]. In upper extremity ataxia, disturbances are observed in daily life activities such as inability to write, inability to fasten buttons and difficulty in picking up small objects. Extremity ataxia is clinically evaluated by means of the toe-nose and knee-heel test[3].

In addition to surgical and pharmacological treatments, physiotherapy modalities such as exercise, thermal applications and electrotherapy are widely used to cope with ataxic symptoms. Various scales such as the International Cooperative Ataxia Rating Scale (ICARS)[4] and the Ataxia Assessment and Rating Scale (SARA)[5] are used to detect ataxia in MS patients and to verify the effectiveness of treatments. These assessment methods consist of sub-parameters evaluating posture, gait, speech and upper extremity performance. On these scales, which are based on subjective evaluations by observers, terms such as "no sensitivity," "mild," "moderate" and "severe" are used in assessing disability.

However, new assessment methods that are one level higher than classical evaluations are also used in assessing ataxia. Two of these are the nine-hole peg test (NHPT) and the box block test (BBT). NHPT is part of the Multiple Sclerosis Functional Composite (MSFC). For MS clinical studies, the MSFC measures an outcome. MSFC correlates better with magnetic resonance imaging (MRI) variables than does EDSS[6,7]. It also correlates significantly with the disease-related quality of life reported by the patient[8].

NHPT has advantages, as well as mild drawbacks. It has been reported in studies that this test is not sensitive enough to detect mild impairment in manual dexterity (EDSS<3) in individuals, and that NHPT scores vary greatly in severely disabled individuals (EDSS>6.0)[9]. In addition, material is required for NHPT and BBT tests, and the inability to provide a comfortable evaluation create disadvantages for clinicians. It is obvious that there is a need for more sensitive, easier-to-apply and more reproducible tests for evaluating upper extremity function.

While data can often be obtained easily and quickly through the development of technology, the inadequacy of ataxia clinical rating systems such as ICARS and SARA, which are still in use, is alarming. Use of valid and reliable assessment tools is extremely important for testing new therapeutic approaches and for setting goals. Therefore, the aim of our observational, cross-sectional study was to evaluate upper extremity ataxia in MS patients using TAAP, which is an objective assessment method. TAAP is the abbreviation for tablet ataxia assessment program. Upper extremity ataxia was investigated using a sensor mounted on the patient's index finger, and kinematic information was evaluated through a program loaded on the tablet.

METHODS

Ethics committee

Written informed consent was obtained from all patients. The study was conducted in accordance with the Declaration of Helsinki and later amendments. Approval was obtained from Necmettin Erbakan University Non-Invasive Clinical Research Ethics Committee.

Participants

This study was conducted between December 1, 2019 and October 15, 2020, at the Neurology Clinic of Meram Faculty of Medicine, Necmettin Erbakan University. Sixty-three MS patients whose diagnoses had been made in accordance with the McDonald criteria and 30 healthy individuals were evaluated[10]. Thirteen patients were excluded from the study in accordance with the following exclusion criteria (Figure 1): having an acute attack with impairments in activities such as walking, speaking and vision, in the last three months; presence of orthopedic, neurological (sensory impairment and apraxia) or systemic problems that prevented participation in the evaluations; peripheral vestibular problems; advanced cognitive dysfunction; and increased tonus that affected upper extremity function. Extremity tremor was evaluated by means of spiral drawing from the upper extremity kinetic functions section of ICARS. Patients who scored ≤ 1 in this section were included in the study.

Ataxic multiple sclerosis group

In accordance with a cerebellar evaluation using the Expanded Disability Status Scale (EDSS), patients with extremity ataxia symptoms alone were included in this group. To eliminate trunk ataxia as much as possible, the following EDSS measurements were applied:

- Trunk ataxia≤1
- Romberg test≤1
- Upper limb ataxia≥1
- Functional reach test≤25 cm

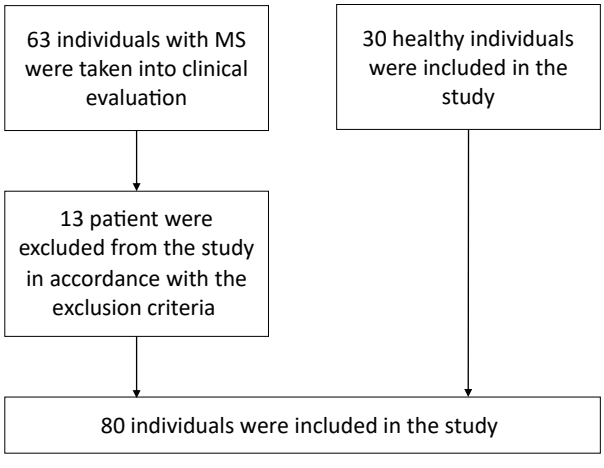

Figure 1. Tablet Ataxia Assessment Protocol.

Control group

Inclusion criteria for healthy individuals

No neurological disease was diagnosed, no dizziness or loss of sensation in the foot and no scars or foot or ankle problems that would affect plantar sensation. The individuals were informed about the purpose and methods of the study.

Evaluation protocol

Clinical evaluation

Physical characteristics and history

The patients' age, height, weight, family history of MS, medications used, last date of corticosteroid use, previous attacks and presence of systemic or orthopedic diseases were recorded in detail.

Nine-Hole Peg Test

In Kellor et al., the NHPT as defined by Godkin was applied to MS patients[11]. It has been shown that NHPT for upper extremity rehabilitation assessment and treatment of MS is by far the most commonly used measurement and has been used in 63% of published studies[12]. For this reason, NHPT is widely considered to be a gold standard measurement for dexterity. In this test, firstly, the dominant hand is used to insert nine rods of 3.2 cm in length into the holes in the apparatus, one by one, as quickly as possible. In the second stage, the rods are removed sequentially; the length of time that the patient takes to insert and remove the rods is recorded. The same process is repeated for the other hand[13].

International Ataxia Rating Scale

ICARS is a test developed to evaluate the severity of ataxia[4,14]. The validity and reliability of the Turkish version were established by Salcı et al[15]. In this test, scores for kinetic functions were determined separately for each hand using the finger-nose test (which tests the intentional tremor of the fingers) and the finger-finger test (which tests pronation-supination alternating movements). "Drawing the curved spiral" was omitted from the scoring because it evaluated the dominant hand. Other evaluations of upper extremity kinetic functions were included in the scoring.

Expanded Disability Status Scale

EDSS was developed to follow the disease progression of MS through evaluating the brainstem, pyramidal system, cerebellar and cerebral system, vision, sensory problems, bladder-bowel problems and ambulation. The scores obtained from all these functional system (FS) evaluations are converted into a single score, and the severity of the disease is graded between 0 and 10[16].

Data analysis

The data were analyzed using software in the Android operating system, through the Opencv library. The software works with the logic of following a 6 mm radius colored point (marker) in images obtained in real time. We determined the color of this point as pink. Through knowing the point diameter, the image can be scaled and sized; therefore, it can be calculated how many mm of displacement the point makes on the vertical and horizontal axes during its movement on the screen.

After the software has been started and the images start to flow to the screen, the user selects the "marker" with his finger on the touch screen and, thus, introduces the "marker" color to the software. After this step, the software calculates the displacements of the "marker" in the horizontal and vertical axes (Figure 2). The position of the "marker" at the time at which the "marker" color is defined is accepted as the zero position by the software. This makes error analysis difficult, as the sign of tremors or displacements may also be negative. While calculating the average error amount, the same magnitude of negative error zeroes the positive error. This situation causes the error average of vibration movements of equal amplitude to be obtained as zero.

To avoid this situation, instead of calculating the average error value on the horizontal and vertical axes, the root mean square error (RMSe), which is frequently used in statistics, was used[17]. In the following equation, the RMSe expresses the squared error; the equation shows how the squared error is calculated for a test series consisting of "n" samples.

$$RMSe = \sqrt{\frac{e_1^2 + e_2^2 + \cdots + e_n^2}{n}} = \sqrt{\frac{\sum_{i=1}^{n} e_i^2}{n}}$$

Statistics

IBM's Statistical Package for the Social Sciences, version 20, analysis program (SPSS Inc., an IBM Company, Chicago, IL, USA) was used for the statistical analysis. Descriptive statistics were used for demographic data. Means±standard deviations and frequency values were used for the measured variables and percentages.

The G*Power software package (G*Power Ver. 3.0.10, Franz Faul, Kiel University, Germany) was used to determine the sample size required for the study[18]. To determine the number of patients in the group, Germatoni et al. was used as a reference[19]. Fifty-one individuals were included in each group, with 80% sample size power (d=0.50 effect width, α=0.05 type I error, β=0.20 type II error).

Normal data distribution was evaluated using the Shapiro-Wilk test. The significance level of our data, which did not have a normal distribution, was analyzed using the Mann-Whitney U test. The relationship between independent variables was examined by means of Spearman correlation analysis. The significance level was taken to be $p<0.05$ for nonparametric evaluations[20,21].

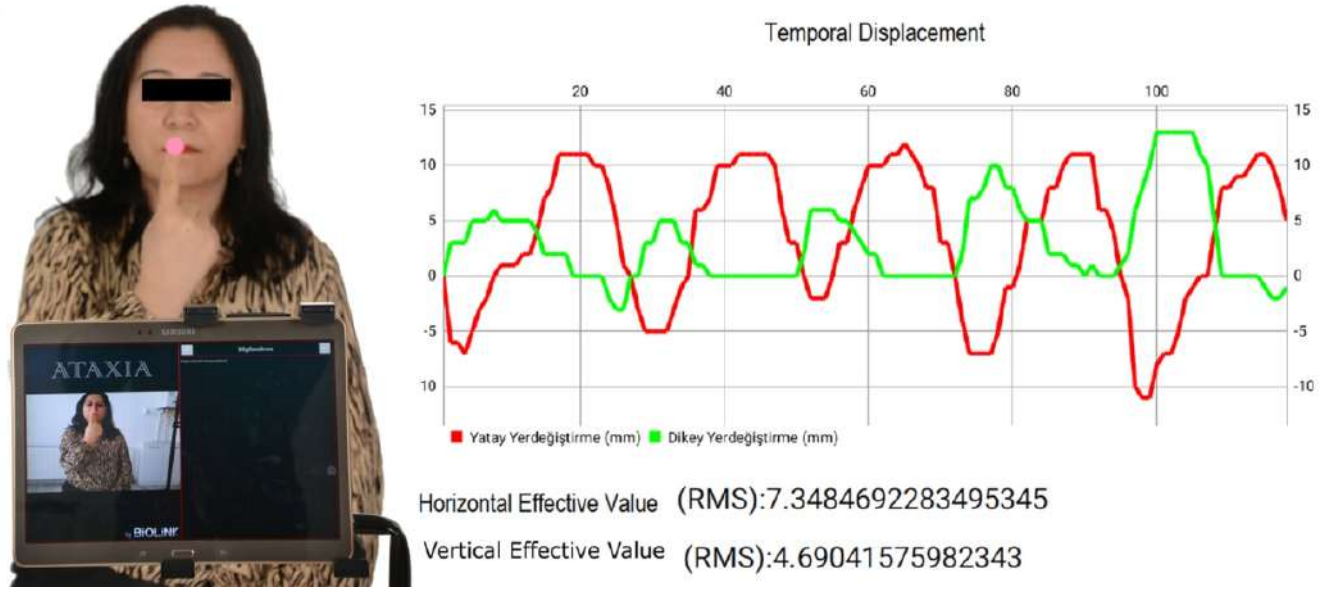

Figure 2. Tablet Ataxia Assessment Program.

RESULTS

The descriptive characteristics of the participants in the study are provided in Table 1. Fifty MS patients (aged 34.58±8.50 years) and 30 control group individuals (aged 34.66±11.93 years) were included in the study. The EDSS average score was X: 3.18, SD±1.7 (Table 1). The differences in average age and gender of the healthy and MS individuals were evaluated in independent groups by comparing them using a Mann-Whitney U analysis. It was determined that there was no significant difference in average age distributions between the groups (p>0.05; Table 1), and that the groups were homogeneous/similar.

The right hand was dominant in all patients and in the control group. Comparison of the mean NHPT, TAAP and ICARS scores of the right and left hands of the healthy individuals and MS patients with extremity ataxia showed that the differences between the groups were significant (p<0.05; Table 2).

Tablet Ataxia Assessment Program

The ataxia parameters of TAAP on the X and Y axes were significantly different between the groups (p<0.05). In comparisons between groups, the dominant and non-dominant upper extremity ataxia data of the individuals with MS were found to be higher on the X and Y axes than those of the control group. Among individuals with MS, the data on the Y axis of the non-dominant hand were higher than those of the dominant hand (p<0.05) (Table 2).

Nine-Hole Peg Test

The NHPT has long been regarded as an indicator of hand awkwardness. Comparison between the two groups showed that the NHPT scores for the dominant and non-dominant hand of individuals with MS were higher than those of the control group. Among the individuals with MS, the scores for the non-dominant hand were higher than those for the dominant hand (p<0.05) (Table 2).

The X and Y values of the dominant hand showed a moderate positive correlation with ICARS (r=0.439, p<0.001;

Table 1. Distribution of descriptive characteristics of multiple sclerosis patients and healthy individuals.

Features		Multiple sclerosis (n=24)		Control group (n=36)		p-value
Age (years)		34.58±8.52		35.23±12.40		0.944
EDSS		3.18±1.70		-		-
Sex	Male	n=10	20%	n=12	40%	0.054
	Female	n=40	80%	n=18	60%	

N: number; EDSS: Expanded Disability Status Scale; Mann-Whitney U test; p<0.05.

Table 2. Comparison of evaluation parameters of multiple sclerosis patients and healthy individuals.

Tests	Multiple sclerosis (n=50)	Control group (n=30)	p-value*
NHPT (right)	24.54±4.34	20.03±1.73	0.000
NHPT (left)	25.96±4.26	21.93±2.25	0.000
X (right)	6.74±3.52	3.93±1.11	0.000
Y (right)	7. 24±2.27	3.07±1.38	0.000
X (left)	8.10±3.81	5.33±1.53	0.000
Y (left)	8.39±2.78	3.43±1.38	0.000
ICARS (right)	5.86±2.33	-	-
ICARS (left)	6.20±2.23	-	-

NHPT: Nine-Hole Peg Test; X: X axis; Y: Y axis; ICARS: International Cooperative Ataxia Scale; data are expressed as mean±SD; *Spearman and Pearson correlation analyses; p<0.05.

r=0.402, p=0.004, respectively). While the TAAP data of the dominant hand shows weak-moderate positive correlation with the data on the X axis, a strong positive correlation with the data on the Y axis was determined (r=0.356 p=0.001; r=0.639, p<0.001, respectively). The X and Y TAAP data of the dominant hand showed weak-moderate positive correlations with EDSS (r=0.353 p=0.012; r=0.334, p=0.018, respectively). In the ICARS kinetic functions section, a strong positive correlation was found between the right and left hand and EDSS (r=0.600, p<0.001; r=0.638, p<0.001, respectively) (Table 3).

DISCUSSION

In this study, the usability of the TAAP was examined through correlating the X horizontal and Y vertical data obtained from patients with ataxic MS, in order to quantify and standardize functional changes in upper extremity movements, using TAAP (Table 3). Our study differed from studies in which extremity ataxia was evaluated using current methods[22,23], given that we excluded trunk ataxia as much as possible. It is difficult to evaluate pure limb ataxia. For this reason, some positioning is used to evaluate the extremity ataxia. For example, the knee-heel test is performed in a lying-down position, with the aim of excluding trunk ataxia in the lower extremity.

However, we did not have an alternative for excluding trunk ataxia from assessment of upper extremity ataxia, given that this is performed in a sitting position. Therefore, in the evaluation of upper extremity ataxia, we set some parameters for elimination of trunk ataxia, and we made the evaluation accordingly. The most important result obtained in our study was the fact that the measurement parameters for MS patients with coordination problems in the X and Y axes were higher than those of the control group, and the correlation of TAAP with NHPT was significant. In other words, MS patients with coordination problems showed more deviation from the axis of movement during movement than did the control group.

The methods used to assess cerebellar ataxia in most previous studies were semi-quantitative scales based on subjective predictions by observers (e.g. ICARS[4], SARA[5] and Short Ataxia Rating Scale[24]). Alongside the development of technology, there has been a search for quick and objective measurement methods[25-27]. However, most of these measurement methods have been used to evaluate ataxia in diseases other than MS[27-29]. The numbers of studies evaluating upper extremity ataxia in patients with MS are limited. Ueda et al. instructed 49 people with spinocerebellar degeneration to follow a spiral pattern. They analyzed the area between the spiral lines by means of the Image J software. These areas were correlated using SARA and cerebellar volume[25].

Erdeo et al. evaluated upper extremity ataxia using areas of deviation from the spiral line on the tablet and could not find any significant difference in the patients' dominant hand data using ICARS and EDSS[26]. Our study was an advanced version of the study by Erdeo et al. and had the aim of creating a gold standard test. Nguyen et al. investigated upper extremity ataxia using a sensor mounted on a spoon and then evaluated

Table 3. Correlation of evaluation parameters among multiple sclerosis patients and healthy individuals.

		NHPT (right)	NHPT (left)	X (right)	Y (right)	X (left)	Y (left)	ICARS (right)	ICARS (left)	EDSS	Age
NHPT (right)	r p	1.000	0.630** 0.000	0.356** 0.001	0.639** 0.000	0.228* 0.042	0.520** 0.000	0.511** 0.000	0.446** 0.001	0.532* 0.000	0.223* 0.047
NHPT (left)	r p		1.000	0.322* 0.004	0.491** 0.000	0.523** 0.000	0.666** 0.000	0.356* 0.011	0.535** 0.000	0.343** 0.015	0.147 0.308
X (right)	r p			1.000	0.401** 0.000	0.351** 0.001	0.399** 0.000	0.439** 0.000	0.254 0.075	0.353* 0.012	0.177 0.116
Y (right)	r p				1.000	0.236 0.098	0.069 0.634	0.402** 0.004	0.196 0.173	0.334** 0.018	0.080 0.478
X (left)	r p					1.000	0.503** 0.000	0.239 0.095	0.292* 0.040	0.517** 0.000	0.022 0.847
Y (left)	r p						1.000	0.238 0.095	0.691** 0.000	0.292* 0.040	0.182 0.105
ICARS (right)	r p							1.000	0.769** 0.000	0.600** 0.000	0.418** 0.003
ICARS (left)	r p								1.000	0.638** 0.000	0.350* 0.013
EDSS	r p									1.000	0.471** 0.001
Age	r p										1.000

NHPT: Nine-Hole Peg Test; X: X axis; Y: Y axis; ICARS: International Cooperative Ataxia Scale; EDSS: Expanded Disability Status Scale; *difference between groups (p<0.05); **: high level of significance.

the patients' kinematics information using an internet-enabled phone. The data obtained were correlated with the results from the NHPT and the box-block test[27]. In our study, the data obtained through the TAAP on the X and Y axes were found to correlate with data obtained via the NHPT.

In a study conducted by Maurel et al. on 19 patients with Friedreich's ataxia and 15 healthy people, these individuals were instructed to perform three tasks (circling, marking and forearm supination). The joint angle and extremity speeds while performing these tasks were evaluated[23]. Especially in ataxia patients, both the duration of duty and the number of drawing and marking errors were greater. The clinical application was more difficult than in our study, in which only a tablet was required to evaluate ataxia[30-32].

There are studies evaluating all parameters with ataxia, as well as studies involving the lower or upper extremities[30-32]. In a study by Krishna et al., finger-nose and knee-heel ataxia tests were performed by connecting a sensor to the hand and ankle of the patient. The results were correlated with the sub-parameter of SARA[33]. In particular, the angular velocity increased and rotational movement in the Y axis was found to be higher than in the X and Z axes.

It has also been reported that ataxic movements are more common in the non-dominant extremities. In our study, the Y-axis parameter was more correlated with the ICARS scale in the dominant and non-dominant hand than was the X axis. The reason for this was that upper extremity ataxia caused more deviations in the Y axis than in the X axis. In our study, the data from the non-dominant hand were found to be higher than those from the dominant hand. In this regard, our study is similar to that of Krishna. We think that this difference was not due to excessive ataxic movements in the non-dominant hand but, rather, to weak motor skills of the hand. In this aspect, our study differs from the literature[23,25].

Different studies have used video analysis methods, sensors and optoelectronic systems in ataxia evaluations[34-36]. In all those studies, the numbers of individuals included in the study were less than in our study. Additionally, those studies required special instruments and sophisticated analysis methods. This makes it difficult to apply ataxia assessments in a clinical setting. Our method is advantageous in that it is easier to apply. If TAAP is installed on phones as an application, all experts working in the clinic can easily apply it. TAAP can be used in patient evaluations and also, with an additional dashboard, it can be used for rehabilitation purposes among patients, through biofeedback.

This study had some limitations. We evaluated the X and Y axis parameters, but we did not include the Z axis in the evaluation because it is difficult to ensure the reliability of the Z axis in terms of depth perception with a single camera. In addition, just as it is not possible to separate balance and coordination with precise boundaries, pyramidal problems cannot be completely ruled out.

In conclusion, we designed a low-cost system that enabled evaluation of upper extremity ataxia quickly, easily and objectively among patients with ataxic MS. The correlations of the data that we obtained, both with other objective tests and with commonly used clinical scales were promising. We anticipate that TAAP will become the first-choice tool for clinicians and physiotherapists in evaluating and following up diseases that involve ataxia, including both MS and other diseases, as well as in clinical rehabilitation studies.

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ARTICLE

Quality of life of patients with Parkinson's disease: a comparison between preoperative and postoperative states among those who were treated with deep brain stimulation

Qualidade de vida de pacientes com doença de Parkinson: uma comparação dos estados pré-operatório e pós-operatório daqueles tratados com estimulação cerebral profunda

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ABSTRACT

Background: Deep brain stimulation (DBS) is a well-established procedure for treating Parkinson's disease (PD). Although its mechanisms of action are still unclear, improvements in motor symptoms and reductions in medication side effects can be achieved for a significant proportion of patients, with consequent enhancement of quality of life. **Objective:** To investigate the impact of DBS on the quality of life of PD patients. **Methods:** This was a retrospective longitudinal study with collection of historical data in a neurosurgery center, from June 2019 to December 2020. The sample was obtained according to convenience, and the Parkinson's Disease Questionnaire (PDQ-39), Unified Parkinson's Disease Rating Scale (UPDRS) III and IV, Trail-Making Test and Verbal Fluency Test were used. **Results:** Data were collected from 17 patients (13 with subthalamic nucleus DBS and 4 with globus pallidus pars interna DBS). Significant improvement (p=0.008) on the UPDRS III was observed in comparing the preoperative without DBS with the postoperative with DBS. About 47.0% of the patients showed post-surgical improvement in QoL (p=0.29). Thirteen patients were able to complete part A of the Trail-Making Test and four of these also completed part B. Almost 60% of the patients scored sufficiently on the semantic test, whereas only 11.8% scored sufficiently on the orthographic evaluation. No association between implant site and test performance could be traced. **Conclusions:** Improvements in quality of life and motor function were observed in the majority of the patients enrolled. Despite the limitations of this study, DBS strongly benefits a significant proportion of PD patients when well indicated.

Keywords: Parkinson Disease; Deep Brain Stimulation; Quality of Life.

RESUMO

Antecedentes: A estimulação cerebral profunda (ECP) é um procedimento bem estabelecido para o tratamento da doença de Parkinson (DP). Embora seus mecanismos de ação não sejam claros, a melhora dos sintomas motores e a redução dos efeitos colaterais dos medicamentos são contempladas em uma proporção significativa de pacientes, com melhora da qualidade de vida. **Objetivo:** Investigar o impacto da ECP na qualidade de vida de pacientes em DP. **Métodos:** Trata-se de um estudo longitudinal retrospectivo, com coleta de dados históricos em um centro de neurocirurgia, de junho de 2019 a dezembro de 2020. A amostra foi feita por conveniência, e os questionários *Parkinson's Disease Questionnare* (PDQ-39), *Unified Parkinson's Disease Rating Scale* (UPDRS) III e IV, *Trail Making Test* e Teste de Fluência Verbal foram utilizados. **Resultados:** Dos dados coletados de 17 pacientes (13 ECP em núcleo subtalâmico e ECP em globo pálido interno) notou-se melhora significativa (p=0,008) no UPDRS III ao se comparar o pré-operatório sem ECP com pós-operatório com ECP, e cerca de 47,0% deles apresentaram melhora pós-cirúrgica na qualidade de vida (p=0,29). Treze pacientes conseguiram completar a parte A do *Trail Making Test* e quatro também completaram a parte B. Quase 60,0% dos pacientes obtiveram pontuação suficiente no teste semântico, enquanto apenas 11,8% obtiveram pontuação suficiente na avaliação ortográfica. Não foi possível rastrear a associação entre local do implante e desempenho. **Conclusões:** Melhora na qualidade de vida e na função motora foi observada na maioria dos pacientes. Apesar das limitações do estudo, a ECP beneficia fortemente uma proporção significativa de pacientes em DP quando bem indicada.

Palavras-chave: Doença de Parkinson; Estimulação Encefálica Profunda; Qualidade de Vida.

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INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by motor and nonmotor symptoms that is caused by progressive degeneration of dopaminergic neurons of the substantia nigra[1,2]. Lewy bodies, in which the main component is alpha-synuclein protein, form in the substantia nigra in PD.

Deep brain stimulation (DBS) is a well-established treatment for the motor fluctuations and symptoms of PD. Although its mechanism of action is still unclear, satisfactory results are achieved when patients are properly selected. The targets most used are the subthalamic nucleus (STN), the globus pallidus pars interna (GPi) and the intermediate ventral nucleus of the thalamus (Vim)[3-5].

Several issues need to be carefully evaluated when considering a surgical procedure. Currently, studies recommend implementation in patients over 5 years of age and under 70 years of age who have reached the maximum tolerable dose of the main drug (800 mg per day for 3 months), with motor symptoms that at some point were responsive to it. The objectives of stimulation are to alleviate the motor symptoms of the disease and reduce the adverse effects of drugs. The procedure is well indicated if an improvement of at least 30% is observed, in comparing scores from UPDRS III ON and OFF medication[6-15].

The symptoms most responsive to stimulation are tremor, bradykinesia, stiffness and dyskinesia, but the degree of individual response is variable[6,7]. The adverse effects of DBS include axial symptoms, speech dysfunctions, cognitive or behavioral changes, dyskinesia, spontaneous muscle contractions and paresthesia, each at different degrees of intensity and incidence[7-9].

Use of DBS is associated with an improvement in quality of life (QoL), compared with pharmacological treatment alone. However, the degree of improvement varies according to prior drug responsiveness, the predominant symptom and presence of comorbidities[10].

Therefore, the objective of this study was to investigate the quality of life of PD patients who underwent DBS, comparing preoperative and postoperative conditions, and to assess postoperative motor and nonmotor symptoms in those patients.

METHODS

This was a retrospective uncontrolled analytical observational longitudinal cohort study that was approved by our institution's research ethics committee. All participants signed an informed consent statement. It was conducted at the Hospital Universitário Cajuru (HUC), Curitiba, Paraná, Brazil, from June 2019 to December 2020.

Patients

The sample was obtained according to convenience and consisted of adult patients diagnosed with PD, without cognitive problems, who were able to answer the questionnaires. All the patients underwent DBS targeted at the STN or GPi and had at least three months of follow-up after the surgical procedure. PD had been diagnosed clinically, in accordance with the presence of at least three of the following: resting tremor, bradykinesia, rigidity and postural instability.

Patients with other movement disorders and/or severe cognitive and psychiatric problems that had previously been diagnosed, those who underwent DBS targeted at the Vim and those who underwent ablative surgeries were excluded.

Questionnaires

Preoperative questionnaires were applied during the preoperative examination, to confirm the indication for the surgery. The criterion for the postoperative evaluation was that it should be applied at least three months after the first regulation of the device, which led to variable periods after the surgery. This was due to the availability of the clinical care, as determined by the demand from patients within the public system in Brazil (Sistema Único de Saúde, SUS). In general, the examiners for the PDQ-39 and UPDRS questionnaires that were applied preoperatively were specialist doctors (neurologists and neurosurgeons). The questionnaires that were applied postoperatively were administered by the same examiners, watched by medical students who were undergoing training.

The questionnaires applied postoperatively were examined by medical students who were undergoing training and were under the supervision of specialists in the field.

An identification questionnaire was applied, which asked for the subjects' medical record number, age, date of birth, gender, date of data collection, age at the time of diagnosis, date of implementation of the DBS, date of completion of the electrode threshold, target site, disease pattern, smoking, harmful use of alcohol, comorbidities, medications with continuous use, education, income and marital status.

To evaluate quality of life, the PDQ-39 questionnaire was applied both before and after use of DBS. This had been adapted for use in Portuguese by Health Services Research Unit (Department of Public Health and Primary Care, University of Oxford) in 2005. It consists of eight dimensions: mobility, activities of daily living, emotional wellbeing, stigma, social support, cognition, communication and body discomfort. In total, there are 39 questions with scores ranging from 0 (never) to 4 (always) that are summed for each dimension before the final score is calculated. The final score ranges from 0 (indicating no problem) to 100 (maximum problem level)[11].

For this study, the UPDRS parts III and IV were also applied. The score for each item ranges from 0 (normality) to 4[12]. Data for the preoperative UPDRS III scale were collected from the medical records and the scale was divided into ON and OFF medication. This is also known as the

levodopa challenge test, in which 50 to 100% of the levodopa dose is provided in addition to the one usually taken by the patient, in order to identify the best response. An improvement of 30–50% is generally considered necessary for the surgical procedure to be indicated. The OFF preoperative score refers to the patient's baseline state. The postoperative score, applied by the same examiner, was obtained in a state of ON stimulation and ON medication.

The Trail-Making Test has two parts: part A evaluates motor function, while part B requires mental flexibility. Thus, this test accesses the combined performance of motor and cognitive function. The time taken for application of each part of the test needs to be counted. At the end, the times are added, resulting in a final score. Patients who were unable to perform the test within 300 seconds were given a score of 300[13,14]. This test was applied only after implementation of DBS.

Lastly, an adapted verbal fluency test was applied based on a previous study. This was done only after implementation of DBS. In the first evaluation, patients were asked to say as many words as possible starting with a certain letter (e.g. B) within 60 seconds. They were then asked to say as many words as possible within a single category (e.g. animals), within 60 seconds. The score was given by the sum of the number of words (repeated words were counted only once and words that did not fit were deleted). A result consisting of 13 words or more was considered sufficient (or 9 words, in the case of illiterate patients)[13,14].

Statistical analysis

Frequency tables and contingency tables were created. The data distribution was determined through the Shapiro-Wilk test. Chi-square and Fisher tests were used to compare nominal and categorical data. Mann-Whitney U and unpaired t tests were used to compare numerical data. A regression analysis was performed as well, to verify the significancy of the findings through a parametric test. Both tests resulted in the same conclusion. P values < 0.05 were considered significant. All tests were calculated using the GraphPad Prism 6.0 software.

RESULTS

Between January 2009 and January 2020, 98 patients underwent DBS at our neurosurgery center. The flow diagram for patient selection can be seen in Figure 1.

From the 17-patient sample, fourteen (82.3%) were male and three (17.6%), female. The median age was 57 years, with a range from 46 to 76 years. The patients' sociodemographic data and initial symptoms are described in Table 1. All the patients were using Levodopa and most were using one or more potentiating drugs.

The patients had, on average, been diagnosed approximately 12.1±4.2 years earlier when they underwent the first DBS procedure and 14.6 years had passed since receiving the diagnosis, at the time of data collection. The median age at

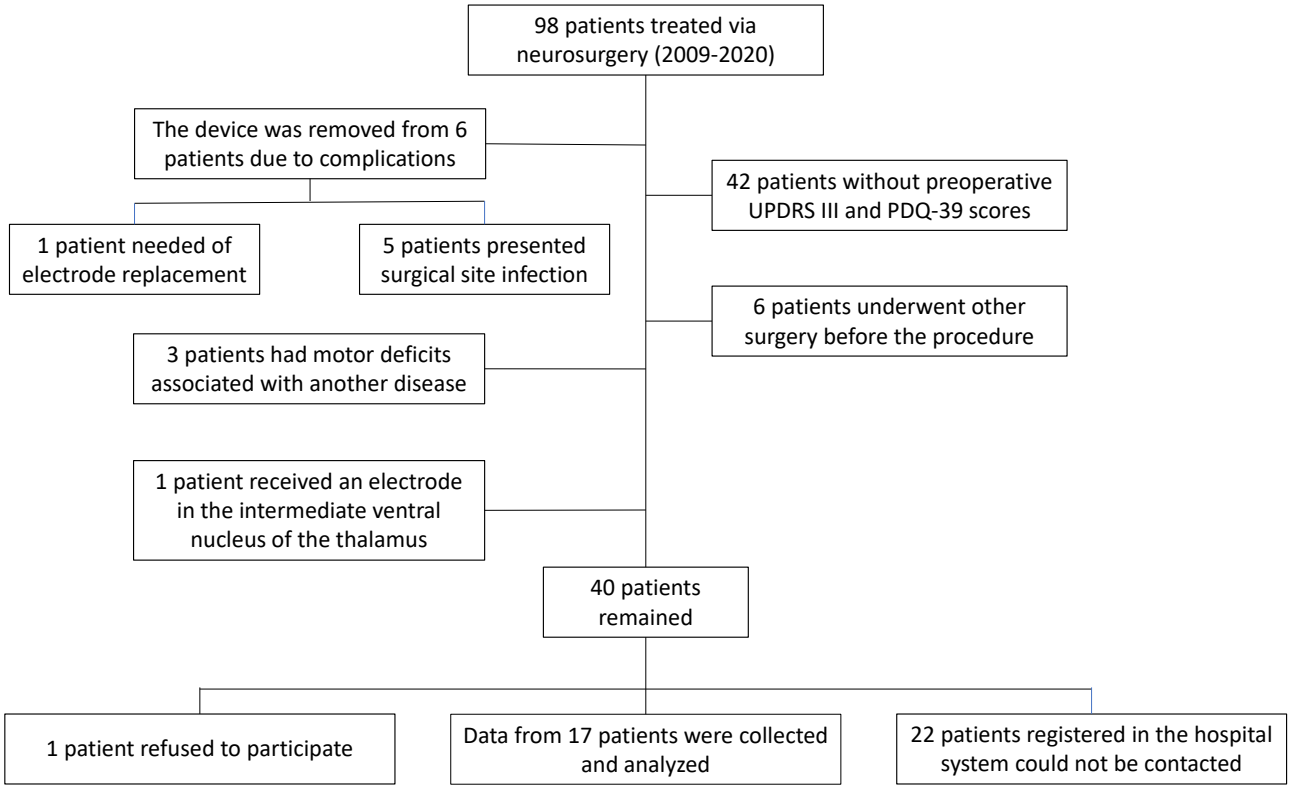

Figure 1. Distribution of patients during research data collection.

Table 1. Sociodemographic data of the patients in this study and frequencies of initial symptoms (n=17).

Sociodemographic data		Frequency
Lifestyle habits	Smoker/ex-smoker	3 (17.6%)
	Alcoholism	1 (5.9%)
Education	Elementary/middle school incomplete	3 (17.6%)
	Elementary/middle school complete	4 (23.5%)
	High school complete	7 (41.2%)
	Higher education incomplete	1 (5.9%)
	Higher education complete	2 (11.8%)
Initial symptoms	Tremor and stiffness	5 (29.4%)
	Tremor e bradykinesia	4 (23.5%)
	Bradykinesia	4 (23.5%)
	Stiffness and bradykinesia	3 (17.6%)
	Bradykinesia and postural instability	1 (5.9%)

Table 2. Relationship between the main preoperative symptoms and the stimulation site chosen.

Stimulation site and symptoms		Frequency
STN (n=13) (76.5%)	Tremor	3 (27.3%)
	Dyskinesia	3 (27.3%)
	Bradykinesia and tremor	2 (15.4%)
	Stiffness	2 (15.4%)
	Dyskinesia and tremor	1 (7.7%)
	Bradykinesia	1 (7.7%)
	Stiffness and bradykinesia	1 (7.7%)
GPI (n=4) (23.5%)	Dyskinesia	4 (100%)

STN: subthalamic nucleus; GPI: globus pallidus pars interna.

the first surgery was 55 years. The STN was the implementation site for 13 patients (76.5%), while GPi was chosen for four patients (23.5%). Twelve patients (70.6%) underwent operations bilaterally. Among the five patients with unilateral implementation, three (60.0%) received DBS in the STN and two (40.0%) in the GPi.

Nine patients (52.9%) had the tremor-dominant subtype. Among these, five (44.4%) showed improvements in motor function and quality of life, three (33.3%) had an improvement only in motor function and one (11.1%) improved only on the QoL scale. The most prominent symptoms before surgery are described in Table 2.

Comparing the results from the preoperative UPDRS III scale (OFF medication) and from the postoperative scale (ON medication and ON DBS), thirteen patients (76.5%) had improved scores. The mean improvement in this comparison was 49.6% (±20.4%). Among these 13 patients with improvements in relation to the preoperative OFF score, ten (76.9%) also improved in relation to the levodopa challenge test (ON medication), performed preoperatively. The mean improvement in this case was 29.3% (±15.6%). For nine (69.2%) of the 13 patients with motor improvement, the evaluation was made one year or more after the last surgical procedure. Two (50.0%) of the four patients without improvement on the UPDRS III scale had been diagnosed with PD more than 15 years earlier. Eight (61.5%) of the 13 patients with motor improvement were under 60 years of age. The distribution of scores can be observed in Figure 2a, 2b and 2c.

Regarding the assessment of quality of life through the PDQ-39, eight patients (47%) reported having improvements in quality of life after surgery, by an average of 48.3% (±30.3%), although this change was not statistically significant (p=0.29). Six (75%) of the eight patients with improved quality of life were less than 60 years of age. Three patients (37.5%) with unilateral electrode implantation had an average improvement in the PDQ-39 of 47.2% (±40.8%).

The individual evaluation of the domains in the PDQ-39 revealed that the domain that benefited the most was well-being, in which 68.75% of the patients showed improvements in relation to the presurgical scale. Furthermore, 31.25% showed improvement in mobility, and all of these patients also showed improvement in wellbeing and were under 60 years old. Out of the total number of patients under 60 years old, 55.56% showed improvements in both mobility and wellbeing. There were eight patients with worsening cognition, among whom 62.5% were over 60 years old, while 71.43% of the seven patients with improved cognition were under 60 years old. However, these results were not statistically significant. It is important to note that one of the patients included in the present study did not have presurgical data relating to each domain separately and was excluded from the individual analyses on the PDQ-39 domains. The distribution of scores on the PDQ-39 scale can be seen in Graph 1C. Most patients, when subjectively questioned, reported having substantial improvements in quality of life and motor function.

Among the 17 patients, five (29.4%) had had less than one year of follow-up after undergoing DBS, at the time of data collection. There was no relationship between a length of follow-up of less than one year and more promising results regarding motor function and quality of life.

Among the 13 patients with STN stimulation, twelve (92.3%) had improvements in UPDRS III score in relation to the preoperative OFF score, and six (46.1%) also showed improvements in the PDQ-39 score. Three (75.0%) of the four patients with GPi stimulation did not have any improvement in motor function and two (50.0%) reported having an improvement in quality of life. All the patients with postoperative improvement in relation to the preoperative UPDRS III ON had bilateral electrode implantation.

Part IV of the UPDRS was evaluated only in the postoperative period. The distribution of patients in different states of disease according to age and time since diagnosis can be seen in Table 3.

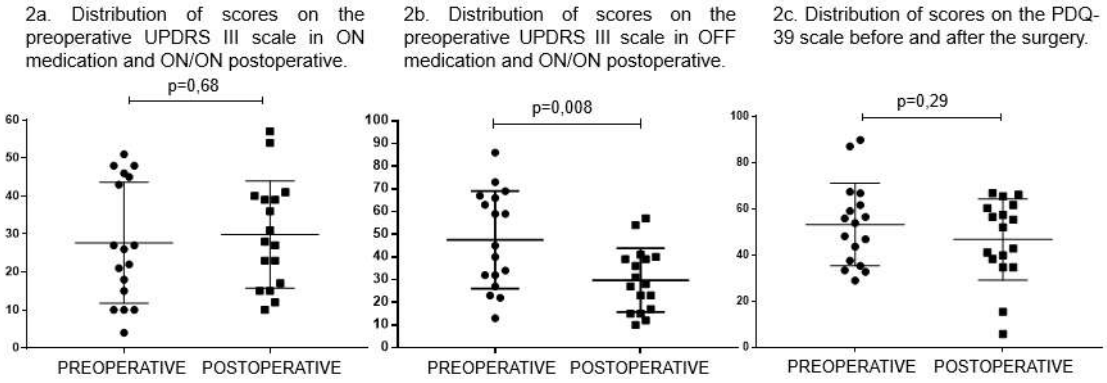

Figure 2. Distribution of Unified Parkinson's Disease Rating Scale III and Parkinson's Disease Questionnaire scores.

Table 3. Motor staging (Unified Parkinson's Disease Rating Scale IV) in relation to age and time since diagnosis (n=17).

Hoehn & Yahr stage			Age (years)*	Time since diagnosis (years)
0	No illness	-	-	-
1	Unilateral disease	1 (5.9%)	53	13
2	Bilateral disease without balance deficit	5 (29.4%)	54 (49–65)	14 (9–18)
3	Mild to moderate bilateral disease, some postural instability, but there is an ability to live independently	10 (58.8%)	59 (46–76)	14.8 (8–22)
4	Severe disability, but still able to walk or stand without help	1 (5.9%)	71	21
5	Confined to bed or wheelchair	-	-	-

* In the "age" column, the number outside the parentheses indicates the median age, and the numbers inside the parentheses indicate the minimum and maximum age.

Table 4. Semantic and phonemic verbal fluency test and DBS sites (n=17).

Verbal fluency test			
Semantic		Phonemic	
Sufficient	10 (58.8%)	Sufficient	2 (11.8%)
STN	7 (70%)	STN	1 (50%)
GPI	3 (30%)	GPI	1 (50%)
Insufficient	7 (41.2%)	Insufficient	15 (88.2%)
STN	6 (85.7%)	STN	12 (80%)
GPI	1 (14.3%)	GPI	3 (20%)

STN=13 patients; GPI=4 patients. STN: subthalamic nucleus; GPI: globus pallidus pars interna.

Regarding the Trail-Making Test, thirteen patients (76.5%) completed part A, and four of these (30.8%) completed part B. Four patients (23.5%) did not complete part A and did not proceed to the second part of the test. Two patients (50.0%) who completed both parts of the test had undergone GPi stimulation and two (50.0%) had undergone STN stimulation. The four patients (10.8%) who completed the test had a subtype of disease other than dominant tremor.

The distribution of the patients in the parts of the verbal fluency test according to the stimulation site is shown in Table 4.

DISCUSSION

Although DBS is a surgical procedure with a great impact on QoL, it is not clearly demonstrated in the literature how much it interferes in the most diverse areas of life of patients with PD. The sample obtained in our study was equivalent to more than a third of the population with potential for analysis. Our research reiterated some results already reported by others[3,16-20], but it also came up with other data, thus raising questions for possible future investigation.

In this study, a significant improvement in general motor function compared with the presurgical OFF period could be seen. Nevertheless, this cannot indicate any definitive conclusion regarding the efficacy of the method, considering that the comparison was with patients who were ON DBS and ON medication. Among the patients without any improvement in motor function, half presented disease at a more advanced stage.

The preoperative levodopa challenge test requires at least 30–50% improvement of motor symptoms in relation to the OFF phase, without medication. Furthermore, the indication should be individualized and should include assessment of nonmotor symptoms[6,21,22]. The presence of comorbidities such as frank dementia or severe cognitive dysfunction formally contraindicate stimulation, as there will be no benefit from treatment[7,9]. If the criteria are met, there is a higher likelihood of favorable results from stimulation[23].

The clinical worsening that was noticed in a few patients after DBS may be attributed to the disease progression itself. However, it is usually possible to adjust the stimulation patterns, with at least partial improvement of the condition[9,19,24,25].

In the present study, no statistically significant improvement in QoL was observed through the PDQ-39, and bilateral stimulation did not reveal any greater impact, as had been reported by two other studies[26,27]. Despite the objective results, there was a substantial improvement in QoL according to the subjective perception of most patients. These assessments were made based on the patient's report of perceived improvement or worsening of the clinical condition.

Objective scales for quality-of-life assessment are widely used, but some studies have also found no correlation between the scores obtained through the objective questionnaire and the overall satisfaction subjectively reported by patients[16,17]. Frizon et al. proposed three variables capable of predicting improvement in up to 81.4% of the cases: PDQ-39 preoperatively, percentage of improvement of UPDRS-III after levodopa use and years since the onset of symptoms. According to the literature, worse preoperative PDQ-39 scores and high percentage of medication response are predictors of greater chance of improvement in quality of life[18,23,24,28].

Moreover, in large meta-analyses, an average improvement of 34.5% in the quality of life of patients with bilateral stimulation assessed through the PDQ-39 was reported, with a range from 14 to 62%. The average improvement through bilateral stimulation in the present study was slightly higher (41%; SD 27.5%). Few studies have been conducted regarding unilateral stimulation. The study by Slowinski et al., 2007, showed a mean improvement of 15% among patients with a unilateral electrode, while the study by Frizon et al. showed a median improvement of 34.6% among patients with unilateral stimulation, compared with an improvement of 44.1% among those with bilateral stimulation[18,20].

It was not possible to observe any influence from more recent surgeries (less than one year) on motor function and quality of life in most of the patients. This was contrary to what most studies have shown, i.e. that the greatest benefit of therapy was within the first 6 to 12 months after surgery. Some other studies have indicated differences in motor outcomes, with worsening as the time elapsed after the procedure increased. However, those studies used longer intervals (five years) as the cutoff because it was believed that the main effects of STN-DBS could last for up to five years. The effects of GPi-DBS would last for a slightly shorter time, independently of the onset of PD. Motor fluctuations, dyskinesia and activities of daily living should also be improved through stimulation, although a decline in the benefit over the years has been identified[19,25].

One group reported rates of improvement in UPDRS III score of 45% over five years and 42% over ≥9 years, which were similar to the rates observed in the present study. In addition, there is evidence that some patients can expect improvement even after 10 years of stimulation, but with reductions in the UPDRS-III score of 25.3%[19].

Compared with STN, GPi stimulation does not allow significant reductions in medication intake. However, it has a direct effect on inhibition of drug-related dyskinesias, with a reduction in incidence of up to 80%. Thus, GPi-DBS enables increases in daily dosage with fewer concomitant side effects, and also improvement of nonmotor symptoms that are responsive to dopaminergic medication. According to Chao et al., the main advantage of DBS, regardless of the implementation site, is the potential for adjusting the stimulator at any time after surgery in order to maximize benefits and minimize adverse effects[3,4,22,29].

Studies have indicated there is no significant difference in UPDRS results between implementation sites, except for the slight improvement of stiffness and axial symptoms seen with GPi-DBS[15,23,24,26]. However, we observed that STN-DBS produced a more significant improvement of symptoms during the OFF medication period. A previous study showed that there was an improvement in UPDRS-III of around 41% under these circumstances[30]. Thus, STN-DBS would be better indicated for patients with low levodopa tolerance, in order to enable greater postoperative dose reduction[3,7,15,24].

Although most studies have suggested that GPi is the most appropriate site, considering cognitive and neuropsychiatric symptoms, discrepancies in the results still exist among different centers. Authors who obtained more favorable outcomes with GPi-DBS used higher doses of dopaminergic medication, and this factor may explain this finding[23,24,28].

The results found in the current study emphasized the deterioration of executive function. This was characterized by increased time taken to perform the Trail-Making Test, part B. Therefore, as noticed in previous studies, a possible relationship with older age and the natural progression of the disease was identified. Nonetheless, despite the hypotheses, the impact of DBS on executive function is not yet well established, and existing studies have demonstrated discordant results. Some cognitive changes observed after brain stimulation can be evaluated through the Trail-Making Test. In the study by Sáez-Zea et al. there was an increase in the time taken to perform part B of the test, both among patients with STN-DBS and among those treated only with pharmacotherapy. However, it is noteworthy that there was a statistically significant relationship between older age and longer time taken to perform this part of the test. Both the neuropsychological and the motor changes observed after surgery vary according to disease subtype, lead position, distribution of electric current and changes in drug therapy[28,30].

Semantic and phonemic verbal fluency were found to have become impaired after surgery in our patients. Phonemics were worsened regardless of implantation site, while semantics became more impaired in patients with

STN-DBS. This was possibly due to decreased activation of the lower prefrontal and temporal cortex of the left cerebral hemisphere. Longer follow-up (more than one year), education level and age did not interfere with the outcomes, which differed from the results obtained in the study by Olchik et al., where these factors were associated with worse cognitive performance[2].

Speech disorders occur in up to 89% of individuals with PD, regardless of age and length of time with the disease[25]. Although some studies have shown that DBS helps to improve speech mechanisms, most have demonstrated that patients with STN-DBS present deteriorated speech intelligibility, and this procedure has also been associated with negative impacts on intonation, rhythm and articulation, and hypophony has been found to be the most frequent effect[25,28,31,32]. In patients who underwent GPi-DBS, speech deterioration has not been so commonly reported. However, its effects on speech have been less studied than those of STN-DBS[31,32]. Although phonemic verbal fluency was more affected, semantics were also impaired[25,28,30].

The limitations of this study were its small sample size and cross-sectional design; strict inclusion criteria; and the impossibility of expanding the face-to-face evaluation due to paralyzation of outpatient activities caused by the Covid-19 pandemic. Further research to understand QoL after DBS to treat PD is still required.

In conclusion, both quality of life and motor function presented improvements through DBS, although quality-of-life improvements were not statistically significant. Nonmotor symptoms did not present a favorable outcome in most patients. Despite the favorable results achieved through DBS for treating PD, further research is still required.

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ARTICLE

Possible roles of sestrin2 in multiple sclerosis and its relationships with clinical outcomes

Possíveis papéis da sestrina2 na esclerose múltipla e suas relações com resultados clínicos

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ABSTRACT

Background: Characterized by demyelination, inflammation and axonal damage, multiple sclerosis (MS) is one of the most common disorders of central nervous system led by the immune system. There is an urgent and obvious need for biomarkers for the diagnosis and follow-up of MS. **Objective:** To investigate serum levels of sestrin2 (SESN2), a protein that responds to acute stress, in MS patients. **Methods:** A total of 85 participants, 40 patients diagnosed previously with relapsing-remitting MS and 45 healthy controls, were included. Serum SESN2 parameters were investigated in blood samples drawn from each participant in the patient and control groups. **Results:** SESN2 levels were significantly lower in MS patients than in controls (z: -3.06; p=0.002). In the ROC analysis of SESN2, the predictive level for MS was 2.36 ng/mL [sensitivity, 72.50%; specificity, 55.56%; p=0.002; area under the curve (AUC)=0.693]. For the cut-off value in both groups, SESN2 was an independent predictor for MS [Exp (B)=3.977, 95% confidence interval (95%CI) 1.507–10.494 and p=0.013]. **Conclusions:** The decreased expression of SESN2 may play a role in MS pathogenesis, and SESN2 could be used as a biomarker for MS and as immunotherapeutic agent to treat MS.

Keywords: Multiple Sclerosis; Sestrins; Apoptosis; Biomarkers; Inflammation; Oxidative Stress.

RESUMO

Antecedentes: Caracterizada por desmielinização, inflamação e dano axonal, a esclerose múltipla (EM) é uma das doenças mais comuns do sistema nervoso central liderada pelo sistema imunológico. Há uma necessidade urgente e óbvia de biomarcadores para o diagnóstico e acompanhamento da EM. **Objetivo:** Investigar os níveis séricos de sestrina2 (SESN2), uma proteína que responde ao estresse agudo, em pacientes com EM. **Métodos:** Foram incluídos 85 participantes, 40 pacientes com diagnóstico prévio de EM recorrente-remitente e 45 controles saudáveis. Os parâmetros do SESN2 sérico foram investigados em amostras de sangue coletadas de cada participante nos grupos de paciente e controle. **Resultados:** os níveis de SESN2 foram significativamente mais baixos em pacientes com EM do que em controles (z: -3,06; p=0,002). Na análise ROC do SESN2, o nível preditivo para MS foi 2,36 ng/mL [sensibilidade, 72,50%; especificidade, 55,56%; p=0,002; área sob a curva (AUC)=0,693]. Para o valor de corte em ambos os grupos, SESN2 foi um preditor independente para MS [Exp (B)=3,977, intervalo de confiança de 95% (95%CI) 1,507–10,494; p=0,013]. **Conclusões:** A expressão diminuída de SESN2 pode desempenhar um papel na patogênese da EM, e SESN2 poderia ser usado como um biomarcador para EM e como agente imunoterapêutico para o tratamento de EM.

Palavras-chave: Esclerose Múltipla; Sestrinas; Apoptose; Biomarcadores; Inflamação; Estresse Oxidativo.

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INTRODUCTION

Multiple sclerosis (MS) is one of the most common diseases of the central nervous system (CNS) led by the immune system and is known to cause demyelination, inflammation, and axonal damage[1]. Whether or not inflammation and neurodegeneration are causally associated with MS remains unclear. The sequence of a potential causal correlation is also unknown. The observations obtained in most experimental studies seem to support a pathogenesis in which the inflammation precedes neurodegeneration[2]. The accumulation of inflammatory cells in the CNS is a critical step in the development of demyelination in MS. The migration of inflammatory cells into the CNS may occur through the synthesis of members of many chemokine families in CNS[3]. In addition, the activation of myelin-specific T cells can cross the blood-brain barrier, and the proliferation of these cells occurs. After proliferation, myelin-specific T cells release proinflammatory cytokines, which in turn stimulate microglia, macrophages, and astrocytes[4].

The diagnosis of MS is currently based on clinical evaluations. Molecular biomarkers of MS have been mainly restricted to measurement in cerebrospinal fluid. Although the clinical utility of conventional magnetic resonance imaging (MRI) in diagnosis and treatment of MS is clear in daily practice, MRI has numerous limitations[5]. In recent studies, it was revealed that MS is a commonly misdiagnosed disorder, even among scholars with expertise[6]. There is an urgent and obvious need for improved methods to diagnose MS and follow-up the prognosis. New approaches to improving diagnostic accuracy of MS could prevent the unnecessary risks and morbidity associated with misdiagnosis, as well as the disabilities that will be experienced by MS patients[5].

In recent studies, it has been shown that newly identified cytokines and proteins can make important clinical contributions to the diagnosis and treatment of diseases. Nowadays, the roles of sestrin molecules (SESNs) have been well-established in various disorders, including neurological diseases. Sestrin2 (SESN2) is an important member of the SESN family (SESN1, SESN2 and SESN3), a set of highly conserved proteins induced by environmental stresses such as DNA damage, inflammation, autophagy, oxidative stress, and hypoxia[7-9]. SESN2 has also been shown to be responsible for free radicals scavenging and autophagy, which initiate cell protection activities[8]. Additionally, SESN2 is crucial for antioxidant defense through the regeneration of peroxiredoxins by regulating the adenosine monophosphate-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) pathway, thereby controlling cell growth and metabolism[10]. Developing sensitive and specific biomarkers to accurately differentiate MS from other disorders still remains a pressing and unmet need in the field. Although the association between SESN2 and several other neurological diseases has been investigated in various studies[11,12], there are no data related to the connection between SESN2 and MS. The aim of this study was to contribute to the literature by assessing SESN2 levels to determine if SESN2 may be used as a biomarker for MS and to evaluate its relationship to clinical outcomes.

METHODS

This study was approved by the ethics committee of our institution, and a written informed consent was obtained from all participants. The present study was conducted under the Good Clinical Practice guidelines of the Declaration of Helsinki and its later amendments.

Participants

MS patients admitted to the outpatient clinic for control purposes between June 2020 and March 2021 constituted the study population. Forty individuals with relapsing-remitting multiple sclerosis (RRMS) were consecutively defined to be included and excluded from the study. The controls were composed of 45 healthy volunteers having no known medical disorders and matched in terms of age and gender. The 40 patients in the MS group were receiving disease modifying therapy (DMT) including interferon beta-1a (8 patients), interferon beta-1b (5 patients), glatiramer acetate (6 patients), teriflunomide (5 patients), dimethyl fumarate (3 patients), and fingolimod (13 patients).

Inclusion criteria for the patient group were: voluntary participation; individuals aged 18 to 55 years; individuals meeting the McDonald's criteria for RRMS diagnosis in terms of time and space dissemination according to the 2010 version; individuals with an Expanded Disability Status Scale (EDSS) score below 5.5; and individuals with no acute or chronic disease detected other than MS.

The exclusion criteria for the patient group were: individuals with diagnosis of radiologically isolated syndrome, clinically isolated syndrome, primary/secondary MS, and RRMS who had an attack in the past 3 months; patients with a history of drug or substance addiction/abuse; and patients who were using oral or pulse corticosteroids, anticoagulants, selective serotonin reuptake inhibitors, and antipsychotic drugs.

Measurement of sestrin2

Blood samples drawn from each participant within 30 minutes' time were centrifuged at 3000 rpm for 15 minutes, and then the obtained sera were kept at -80°C until analysis. Serum levels of SESN2 were determined by the enzyme-linked immunosorbent assay (ELISA) technique. The serum concentrations of SESN2 were analyzed by Human SESN2 ELISA kits (Bioassay Technology Laboratory, Shanghai, China; catalog number, E3437Hu). The sensitivity was 0.01 ng/mL and the standard curve range was 0.05–15 ng/mL, with intra- and

inter-assays of <8 and <10%, respectively. The manufacturer's instructions were followed. The absorbances of the specimens were measured at 450 nm using the absorbance microtiter plate reader with a double-blind procedure (ELx800™, Bio-Tech Instruments, USA).

Statistical analysis

The statistical analyses were conducted using the *Standard Package for the Social Sciences* for Windows, version 15.0 (SPSS, Chicago, IL, USA). Data are reported as mean values and standard deviations (±SD) or medians and percentiles with a 25–75% quartiles. The Kolmogorov Smirnov test was used for normally distributed variables. For parametric comparisons between the two groups, the Student's *t*-test was used, while the Mann-Whitney U test was used for non-parametric comparisons. The chi-square test was also used for the comparison of the categorical data.

The receiver operating characteristic (ROC) was used to analyze the areas under the curve (AUC), sensitivity, specificity, and positive and negative predictive values. In addition, the binary logistic regression analysis was performed to determine the independent predictive risk factors for MS. P values less than 0.05 were accepted as statistically significant.

RESULTS

Eighty-five volunteers (40 in the patient group and 45 in the control group) with a mean age of 38.22±8.75 were included in the study. The demographic and clinical characteristics of the patients and controls are shown in Table 1.

No significant difference was detected between the levels of SESN2 in terms of gender (p=0.299). There was also no significant difference between levels of SESN2 and drug therapies used by MS patients (chi-square=4.608; p=0.595). Levels of SESN2 were significantly lower in patients with MS, compared with those in the controls (z=-3.06; p=0.002), and the findings are presented in Figure 1.

As shown in Figure 2, the predictive level of SESN2 for MS in ROC analysis was 2.36 ng/mL [sensitivity, 72.50%; specificity, 55.56%, positive predictive value (PPV), 59.18%; negative predictive value (NPV), 69.44%; p=0.002; and AUC=0.693 (0.582–0.804)]. The cut-off value of 2.36 ng/mL for SESN2 was the statistically significant explanatory variable for the dependent variables (p<0.001). Values lower than 2.36 ng/mL were seen 3.9 times more often in patients. The overall corrected percentage was 63.5% (Table 2).

No correlation was found between levels of SESN2 and number of MS attacks (p>0.05) and between levels of SESN2 and age (p>0.05). In addition, no correlations were found between SESN2 levels and EDSS (p>0.05) and between SESN2 levels and disease duration (p>0.05). Likewise, no significant difference was found between various DMT regarding SESN2 levels (p>0.05).

DISCUSSION

To the best of our knowledge, our study was the first to evaluate SESN2 levels in MS. In our study, the levels of serum SESN2 were found to be significantly decreased in the MS group compared with the controls. On the other hand, no correlation between SESN2 and age, sex, disease duration, clinical severity measured by EDSS, number of attacks and DMT was found. This might indicate that the molecular difference in SESN2 levels between both groups began probably in the early stages of the disease. Given the inflammatory nature of MS,

Table 1. The demographic and clinical characteristics of patients and controls.

	RRMS			
	Patients (n=40)		Healthy controls (n=45)	
	Mean	Quartile (25–75%)	Mean	Quartile (25–75%)
Age (years) (mean±SD)	–	38.7 (±8.6)	–	37.6 (±8.9)
Sex (female)	25 (62.5%)	–	26 (57.8%)	–
Disease duration (years)	7.5	5.0–12.0	–	–
Number of MS attacks	4.0	2.0–5.0	–	–
EDSS	1.5	1.0–2.0	–	–
SESN2 (ng/mL)	1.64	0.91–2.47	2.54	1.36–9.52
	DMT use	DMT use duration (years-mean)		
Interferon beta-1a, n (%)	8 (20%)	3.6	–	–
Interferon beta-1b, n (%)	5 (12.5%)	3.8	–	–
Glatiramer acetate, n (%)	6 (15%)	3.5	–	–
Teriflunomide, n (%)	5 (12.5%)	2.4	–	–
Dimethyl fumarate, n (%)	3 (7.5%)	2.3	–	–
Fingolimod, n (%)	13 (32.5%)	3.1	–	–

DMT: disease modifying therapy; EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; RRMS: relapsing remitting multiple sclerosis; SD: standard deviation.

it was intriguing to observe lower serum SESN2 levels in our MS patients. However, we believe that more comprehensive studies are needed to investigate the cause of such a situation.

Recent evidence has revealed that three different types of SESN are responsible for performing diverse functions.

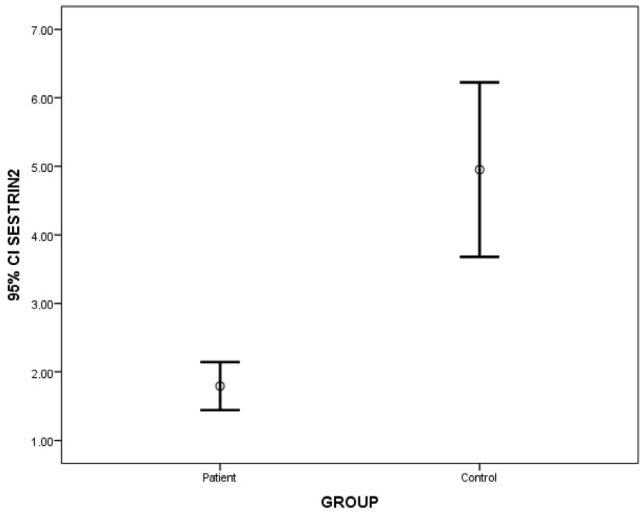

Figure 1. Mean levels of sestrin2 in patient and control groups.

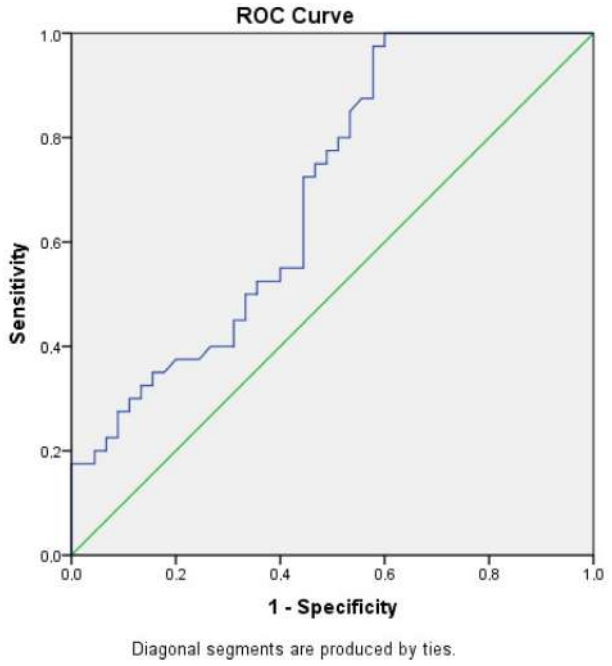

Figure 2. Receiving operating characteristics curve of sestrin2 for the prediction of multiple sclerosis in the patient group.

Specifically, SESNs have a protective effect on lymphocytes by diminishing reactive oxygen species (ROS) levels arising from oxidative and genotoxic stresses[13]. Of the three types of SESNs, SESN2 is the one that has been most extensively investigated in many studies since 2002, the year of its discovery[14]. The number of studies assessing the other types of SESNs is restricted. Recognized as a p53-activated gene 26 (PA26) due to its regulation by tumor-suppressor protein (p53), SESN1 has been accepted as one of the genes stopping tumor growth and leading to the impairment of DNA structure[13]. However, SESN2, a homolog of PA26, can also lead to hypoxia of gene 95 on account of its induction under hypoxic situations, although other cytotoxic events such as oxidative stress and DNA damage also induce SESN2[13,15,16]. SESN3 is also accepted as a new gene associated with PA26, led by the forkhead box O (FoxO) family of transcription factors[17].

In many studies, SESN2 has been shown to have significant influences on immune cells. SESN2 is likely to play a part in innate and acquired cells of the immune system, such as monocytes, macrophages, natural killer, and T cells[18,19]. Various stress-originated problems elevate the level of SESN2 by regulating various crucial transcription factors. Processes such as the concentration of ROS, protein synthesis, lipogenesis, regeneration of cells and detrimental effects on DNA are suppressed by the upregulation of SESN2, which decreases the levels oxidative stress in endoplasmic reticulum (ER), activating autophagy or relieving inflammasome activation[14,18,20-22]. Through these regulatory roles, SESN2 could be used in the treatment of some inflammatory diseases[7].

Some studies have reported that SESNs are of a vital role in various disorders, including neurological diseases[7,11,12]. The levels of SESN2 were found to be increased in individuals with various diseases, and the plasma levels were stated to have positive effects in decreasing disease severity[23,24]. Sepsis, liver diseases, ischemia-reperfusion (I/R) injury (myocardial and cerebral I/R injury), cardiovascular diseases such as chronic heart failure, coronary artery diseases, aortic dissection and atrial fibrillation, chronic obstructive pulmonary disease, metabolism-related diseases including diabetes mellitus, obesity, cancer and aging are among the disorders influenced by SESN2[11]. The effects of SESNs on neurological ailments have yet to be precisely revealed. However, SESNs have drawn increasing attention in seizures, neuropathy-related pain, ischemic stroke, Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, and amyotrophic lateral sclerosis[7,11,12]. Excessive oxidative stress and autophagy have

Table 2. Binary logistic regression analysis for sestrin2.

	Exp (B) p-value	95%CI for Exp (B) p-value	Lower	Upper
Age	0.321	0.974	0.924	1.026
Sex	0.255	0.573	0.220	1.494
SESN2<2.36 (ng/mL)	0.013	3.977	1.507	10.494
Constant	0.409	2.461	–	–

R^2: 13.6 %; 95%CI: 95% confidence interval; SESN2: sestrin2.

important effects on the pathogenesis of neurological diseases related to advanced age, especially degenerative disorders[7,12]. For example, an upregulated serum SESN2 level was observed in PD group compared to control group[25]. Another study showed significant overexpression of serum SESN2 protein and mRNA levels in the AD group compared to mild cognitive impairment patients and elderly control groups[26]. SESN2-knockdown was also shown to strongly increase lipopolysaccharide (LPS)-mediated nuclear factor-κB phosphorylation by decreasing AMPK phosphorylation and thus leading to the up-regulation of several adhesion molecules in the endothelium and expression of proinflammatory cytokines[27]. As a result, SESN2-knockdown increased the production of LPS-induced ROS, ER stress, and cell death. In several studies, it was shown that SESN2 inhibits the inflammatory pathway and decreases the extent of inflammation in macrophages, which is a significant mediator for the formation of atherosclerosis[19,28,29].

Through the genetic deletion of SESNs in animal models, especially mice, valuable information has been revealed on the vital effects of such proteins. Deprived of three types of SESNs, mice had reduced rates of postnatal survival associated with defective mTORC1 inactivation in multiple organs during neonatal fasting. In these animals, a non-redundant mechanism has been revealed, by which the sestrin family of guanine nucleotide dissociation inhibitors regulates the nutrient-sensing Rag GTPases to control the signals of mTORC1[30]. SESN2-knocked-out mice have shown proliferation of pro-inflammation genes and the activation of basilar membrane macrophages. Based on these results, SESN2 is suggested to have significant effects on cochlear homeostasis and immune responses as components of stress[31]. Other phenotypes of SESN2-knocked out mice involved the impaired hair cells in cochlear explants administered with gentamicin. In this trial, mice also displayed elevated neuropathy-related pain due to increased ROS levels in the late phase[32]. The loss of SESN2 activity is likely to contribute to the cellular accumulation of ROS, which can promote DNA damage and genomic mutations facilitating the development of tumors[33]. In previous studies, the down-regulation of SESN2 was shown to accelerate both colitis and colon carcinogenesis, while SESN1 and SESN3 were found to be strongly down-regulated in various types of cancer tissues, such as lung cancers and lymphomas[34].

The specific elements causing the pathogenesis of MS remain unknown. Recent evidence has suggested that inflammation, apoptosis, and oxidative/nitroxidative stress are important contributors to etiology, progression and clinical symptoms of MS[1]. In our study, values below the cut off value of 2.36 ng/mL for SESN2 was observed at a higher rate among MS patients (3,977 times higher), compared to the controls. In other words, significantly down-regulated levels of serum SESN2 were observed in patients with MS compared to controls. The data obtained in our study indicate that SESN2 levels were able to differentiate between patient and control groups. The above information in the literature suggests that lower levels of SESN2 may play a very important role in the development of MS by triggering inflammatory processes. In addition, the lack of a statistical significance between levels of SESN2 and age of MS patients suggests that low levels of SESN2 occur at the onset of MS. Future studies should determine the levels of SESN2 in individuals followed-up due to diagnosis of radiologically isolated syndrome (RIS) and confirm such a hypothesis. Studies on the up-regulation of SESN2 levels in MS patients and evaluating other members of the SESNs family in MS patients can help us to better understand the disease and develop treatment strategies. Therefore, we consider that SESN2 could have a significant effect as a biomarker of immunity in diagnosing MS and as an MS treatment.

However, our study has some limitations. First, the sample size was relatively small. Secondly, we evaluated only individuals with no MS attacks in the RRMS group. Thus, our results should be verified by further studies to be conducted in those with RIS, clinically isolated syndrome, progressive MS and MS attacks. Further studies with larger sample sizes, longitudinal evaluation and assessment of post-treatment levels will be more comprehensive in revealing the cause-effect relationship between SESN2 and MS.

In conclusion, we found that SESN2, an acute-stress responsive protein, was decreased in MS. Our findings also suggest that decreased SESN2 levels may cause demyelination and axonal damage in MS through inflammation, oxidative stress, and apoptosis. Our study might lead to further studies on this molecule and to the investigation of its use as a treatment option, as it is likely to prevent or slow down disease progression. SESN2 could play a part as a biomarker for MS diagnosis and as immunotherapy to treat MS.

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ARTICLE

"Stable" vs. "silent progressive multiple sclerosis": a real-world retrospective clinical imaging Brazilian study

Esclerose múltipla "estável" *vs.* "silenciosamente progressiva": um estudo brasileiro retrospectivo de correlatos clínicos e imagem

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ABSTRACT

Background: Clinical and imaging are required to characterize activity and progression in MS. The parameters for activity are well defined but not those for progression. The ideal aim for long-term treatment is that neither clinical nor imaging signs of disease should be present, and also no brain atrophy. **Objectives:** To conduct a comparative clinical-imaging study focusing on MRI brain volumetry. **Methods:** 174 consecutive relapsing-remitting MS patients (McDonald 2001) were studied, focusing on activity and progression. Annual clinical evaluations (relapse rate and EDSS) and MRI data, along with the annualized evolution of the corpus callosum index (CCI), were compared. **Results:** Out of 174 patients, 148 were considered clinically "stable" based on EDSS. However, 33 (22.2%) out of this group showed annualized reductions in CCI of more than 0.5%, which was the cutoff for defining significant brain atrophy. **Conclusions:** Among apparently "stable" relapsing-remitting MS patients, 1/5 showed significant brain atrophy over a follow-up period of at least 7 years. We consider it reasonable to suggest that MRI volume sequences should be included in follow-up protocols, so as to provide information on the real treatment response status.

Keywords: Multiple Sclerosis; Neuroimaging; Corpus Callosum.

RESUMO

Antecedentes: Critérios clínicos e de imagem são necessários para caracterizar atividade e progressão em esclerose múltipla (EM). Os parâmetros para a atividade são bem definidos, o que não ocorre com a progressão. O objetivo ideal para tratamento em longo prazo inclui ausência de sinais clínicos e de imagem, assim como inexistência de atrofia cerebral. **Objetivos:** Estudo comparativo de aspectos clínicos e correlatos de imagem, com foco em volumetria cerebral. **Métodos:** Foram avaliados 174 pacientes consecutivos com o diagnóstico de EM surto-remissiva (McDonald 2001), com foco em dados de atividade e progressão. A avaliação clínica anual (taxa de surtos e escala expandida do estado de incapacidade — EDSS) e dados de imagem, assim como a evolução anualizada do Índice de Corpo Caloso (CCI), foram comparados. **Resultados:** Da amostra inicial de 174 pacientes, 148 foram considerados "clinicamente estáveis" com base na EDSS. Todavia, 33 (22,2%) pacientes desse grupo mostraram redução volumétrica anualizada no índice de corpo caloso acima de 0,5%, nível de corte para definir a atrofia cerebral significativa. **Conclusões:** Entre pacientes de EM surto-remissiva aparentemente estáveis, cerca de 1/5 apresentou sinais de atrofia cerebral significativa em sete anos de seguimento. Consideramos razoável sugerir que sequências de volumetria deveriam ser incluídas nos protocolos de seguimento, fornecendo informação quanto ao real estado da resposta ao tratamento.

Palavras-chave: Esclerose Múltipla; Neuroimagem; Corpo Caloso.

INTRODUCTION

Relapses and remissions are clinical hallmarks of multiple sclerosis (MS) and were the basis for the original Lublin et al. classical phenotypes of the disease[1]. Since the 1990s, neurologists worldwide have recognized relapsing-remitting, primary and secondary progressive MS as the prototypes for classifying their patients using exclusively clinical evidence of relapses and measurements of progression, using scales such as John Kurtzke's Expanded Disability Scale Score (EDSS)[2].

However, new phenotypes were required. The development of new drugs has created more aggressive options for use as early as possible on non-responders or therapeutic

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Conflict of interest: There is no conflict of interest to declare.

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failures. These new options, in association with the inclusion of imaging data to demonstrate active lesions, even if asymptomatic, have brought a new approach. Clinical and imaging information about these phenotypes has been gathered (Figure 1), and this has led to earlier and more sensitive characterization of activity and progression in MS patients[3].

Clinical relapses and their magnetic resonance imaging (MRI) correlates are well-defined and accepted parameters for demonstrating the inflammatory activity in MS. On the other hand, the progressive component of the disease is a more subtle and insidious process, for which clear-cut, practical and sensitive markers are still far from being reached.

The aim of this study was to analyze the impact of a practical imaging method for measuring axonal loss and corpus callosum atrophy among a real-world sample of apparently clinically stable MS patients, and its implications for clinical practice.

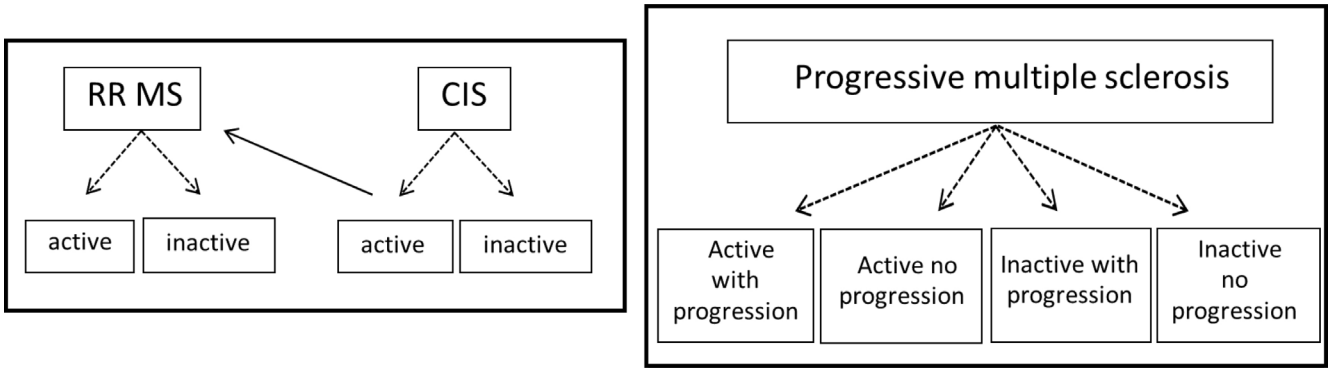
METHODS

We included patients from retrospectively analyzed files on 185 consecutive non-selected cases from our program for treating patients with diagnoses of relapsing-remitting MS (in accordance with the McDonald 2001 criteria). These patients were seen between 2001 and 2012; they were all on regular treatment, with self-reported full adherence. At least three MRI studies were available for each patient, all analyzed by the same observer (F.F.A.F.), at the baseline, an intermediate time (at variable times) and at the end of the follow-up period, with a proper protocol, which thus led to reliable evaluation of activity and progression over at least a 7-year period.

Conventional MRI studies were acquired using a Siemens 1.5T scan device, in slices of 3 mm with no gap. The scans consisted of at least an axial T1W pre and post-gadolinium injection, axial T2W/FLAIR and sagittal T1W, among other sequences, according to the indications, which were established in case-by-case evaluations.

All the patients gave their informed consent, and the study protocol was approved by the Ethics and Humanity Committee of our institution. Eleven files were excluded: 3 cases due to lost follow-up and 8 due to insufficient data, thus resulting in a study group of 174 patients. As a real-world sample, both routine clinical and imaging evaluations were performed by the same two observers (G.M.A.F. and F.F.A.F.), which was a possible limitation of our study. The evaluations included the relapse rate and EDSS, measured at least annually, for no less than 7 years (mean, 8.4). All patients with no evidence of incapacity progression over this period, based on an increase in EDSS of 0.5 points or more, were considered "clinically stable". MRI activity data included the presence of gadolinium-positive lesions or new/enlarging T2W lesions, as originally defined by Barkhof and Tintoré[4,5] and adopted by McDonald and the International Panel[6]. Corpus callosum atrophy was evaluated in terms of the annualized evolution of the corpus callosum index (CCI), as previously described by our group[7].

On the other hand, we determined the burden of disease by manually measuring T2W lesion counts on axial FLAIR sequences, and this was significantly greater in "progressive" patients (8.7 vs. 5.2; p=0.001, Fisher). For methodological reasons, we did not take into account enlarging lesions.



Current markers	
Activity	Clinical: relapses
	MRI: Gd+or new/enlarging T2W
Progression	Clinical: increasing dysfunction/disability (EDSS)
	MRI: not yet established*

*The following are under consideration: increasing number and volume of T1W hypointense lesions, brain volume loss, magnetization transfer ratio (MTR) and diffusion tensor imaging (DTI).

Figure 1. Clinical and imaging information on new phenotypes has been gathered, thus leading to earlier and more sensitive characterization of activity and progression in multiple sclerosis patients.

RESULTS

The demographic data matched with the population of our treatment program. After a 7-year follow-up, 148 out of 174 showed no evidence of progression on EDSS and were considered "clinically stable" (Table 1). Nevertheless, in this "stable" group, 33/148 (22.2%) showed an annualized reduction in CCI of more than 0.5% (Figure 2), a score that our original study showed to be the cutoff for distinguishing a significant loss of brain volume, compared with the controls[7]. As expected, the "progressive" patients were older (37.3 vs. 32.4 years old), had had more time since the disease diagnosis (8.7 vs. 6.6 years), higher disability scores on EDSS (3.9 vs. 3.1) and higher annualized relapse rates (0.22 vs. 0.18) than the "stable" ones, but none of these variables were statistically significant (Table 2). For methodological reasons, we did not take into account enlarging lesions.

Also of note, the gender prevalence ratio of the "progressive" group showed a shift compared with the "stable" ones and to the whole sample (female 45.5% vs. 61.7% and 58.1% respectively; Table 1). These are interesting data to be studied, but far beyond the scope of this paper.

Table 1. After a 7-year follow-up, 148 out of 174 patients showed no evidence of progression in Expanded Disability Scale Score and were considered "clinically stable"

"Clinically stable" group characteristics	
N	148
Mean age (range)	36.6 (17–61)
Male/Female	62/86
Years of disease (mean)	8.4 (3.7–11.7)
Mean EDSS (range)	3.7 (1–5.5)
ARR	0.21
Mean T2W lesions (range)	7.3 (4–17)
Annualized nCCI (range)	0.331 (0.28–0.583)

EDSS: Expanded Disability Scale Score; ARR: Annualized Relapse Rate; T2W: Magnetic Resonance Imaging T2-weighted image; nCCI: normalized corpus callosum index.

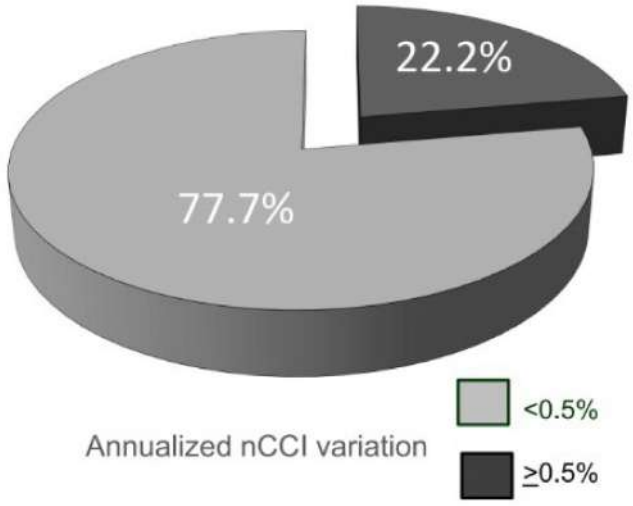


Figure 2. In this "stable" group, 33/148 (22.2%) showed an annualized reduction in CCI of more than 0.5%.

DISCUSSION

In a pivotal study on monoclonal antibodies, it was proposed that the ideal aim for long-term optimal treatment would be to reach an absence of clinical and MRI correlates of acute relapses, together with no progression of disability, i.e. the so-called "no evidence of disease activity" or NEDA 3[8]. This concept was stringently enriched through inclusion of volumetric data showing absence of brain atrophy on MRI longitudinal studies, defined as the so-called NEDA 4[9]. Moreover, recent data have suggested that axonal loss may be clinically "silent", in spite of unequivocal imaging evidence[10]. Nevertheless, imaging methodologies for measuring axonal loss and brain atrophy still demand validation, use non-conventional MRI sequences and require expertise that is not always available in most treatment centers.

The current criteria for phenotypes of evolution in MS define *worsening* disease as increasing disability due to disease activity, both from clinical and/or imaging data. These are clear and useful markers, especially for optimal treatment follow-up. Otherwise, *progression* refers to an increase in disability that is not related to relapses or active lesions on MRI. Progression might be related to a degenerative component of the disease, hallmarked by axonal loss and brain atrophy, but which is not always clinically apparent[3]. While activity is a concept that is easy to determine in daily practice, progression is not at all. In spite of the widespread use of clinical standards of evaluation, such as EDSS and MSFC, these lack enough sensitivity to be used

Table 2. Considering the normalized corpus callosum index cutoff of 0.5%, a subgroup of the "clinically stable" patients seemed to behave as "progressive"

	"Stable" patients	"Progressive" patients
N	115 (77.7%)	33 (22.2%)
Mean age (range)	32.4 (17–44)	37.3 (27–61)
Male/Female	44/71	18/15
Years of disease (mean)	6.3 (3.7–8.8)	8.6 (7.1–11.7)
Mean EDSS (range)	3.1 (1–4)	3.9 (2.5–5-5)
ARR	0.18	0.22
Mean T2W lesions (range)	5.2 (4–9)	8.7 (6–17)
Annualized nCCI (range)	0.317 (0.28–0.433)	0.541 (0.508–0.583)

EDSS: Expanded Disability Scale Score; ARR: annualized relapse rate; T2W: Magnetic Resonance Imaging T2-weighted image; nCCI: normalized corpus callosum index.

as a parameter for progressive disease, especially over the short term. Cognitive batteries are usually complex and time consuming[11]. Similarly, imaging markers of axonal loss that use non-conventional sequences require expertise for their interpretation, which is not always available in most treatment centers[12,13].

The corpus callosum is the largest axonal interhemispheric brain connection. It seems reasonable to infer that diffuse axonal loss may be expressed through its morphological changes. The CCI is a simple and feasible index that is obtained from two-dimensional measurement of the corpus callosum using an orthogonal semi-automated linear model applied to a conventional mid-sagittal T1W MRI sequence (Figure 3). It was recently replicated in several centers and a normalized CCI was shown to be a reliable marker for brain atrophy, with good intra and inter-observer ratings, and with correlations with brain parenchymal fraction, EDSS and the speed of information processing measured through the Paced Auditory Serial Addiction Test (PASAT)[7,14,15,16]. Compared with a blinded radiologist, CCI determination showed interobserver disagreement of 0.92% (SD=0.32; p=0.003)[17].

In this study, "progressive" patients had higher lesion counts on T2W/FLAIR sequences at baseline than "stable" ones, thus suggesting that more active disease should be a predictive factor for axonal loss and callosal atrophy in late stages[13]. Also for methodological purposes, we did not take into account infratentorial and spinal cord lesions, which are both relevant to disability but were beyond the scope of our paper.

Burden of disease, as expressed through higher T2W hyperintense lesion counts, is not an easy parameter for clinical practice, but in our sample high scores correlated with more clinically active disease and more axonal loss. Its correlation with CCI points towards a reasonable association between aggressiveness of disease and progression.

MS is a multifaceted disease: inflammation and neurodegeneration evolve together. Over recent years, use of MRI has dramatically changed the approaches to MS. Imaging technologies are continuing to emerge, with improvements in diagnostic sensitivity and specificity and optimization of follow-up, and these are also providing new information on the pathophysiology of this disease[17]. They are welcome, but still far from being available in most centers.

In this real-world proof-of-concept study, we randomly enrolled patients who were in a regular program of treatment, and these patients were followed for 7 year. Data were collected using conventional daily-practice methodology for diagnosis and follow-up.

Among 148 apparently "clinically stable" MS patients on regular treatment schedules and fulfilling the criteria for NEDA-3 over a period of at least 7 years, more than

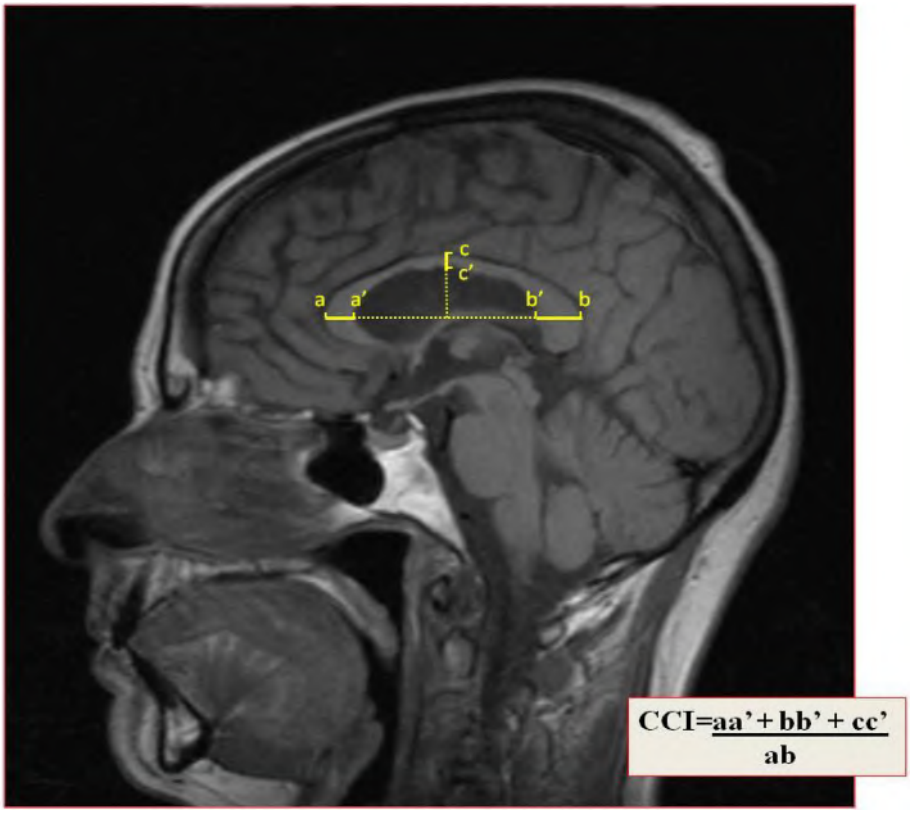


Figure 3. The corpus callosum index is a simple and feasible tool obtained from two-dimensional measurement of the corpus callosum using an orthogonal semi-automated linear model, applied to a conventional mid-sagittal T1-Weighted Magnetic Resonance Imaging sequence.

20% had significant progressive callosal atrophy. Thus, less than 80% achieved the criteria for NEDA-4, which therefore raises questions regarding the optimal treatment response: is NEDA-3 enough? Or should cell loss and brain atrophy be a target, even if "clinically silent"?

Limitations and strengths

Our patients were enrolled in a real-world scenario: using serial clinical examination as well as conventional imaging analysis, always by the same staff observers (G.M.A.F and F.F.A.F), as part of a regular program of treatment in our hospital. This can be considered to be a weakness in our study, academically, but it reflects the daily-practice approach.

In spite of the low number of patients enrolled, it seems reasonable to conclude that a regular and practical brain volumetry technique can provide valuable information about the real state of the treatment response. In this manner, these "silent progressive" patients that are candidates for a switch to more active therapeutic strategies can be selected. Given that this was a proof-of-concept study, our data need to be replicated by other Centers, maybe with more robust numbers of patients.

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VIEW AND REVIEW

Traumatic brain injury in Brazil: an epidemiological study and systematic review of the literature

Traumatismo cranioencefálico no Brasil: um estudo epidemiológico e uma revisão sistemática da literatura

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ABSTRACT

Background: Traumatic brain injury (TBI) is a serious public health problem worldwide. Although TBI is common in developing countries, there are few epidemiological studies. **Objective:** To investigate the sociodemographic and clinical features of patients with TBI at the Hospital João XXIII, a public reference center for trauma in Belo Horizonte, Brazil, and to systematically review the available literature on TBI in Brazil. **Methods:** Clinical and sociodemographic data were collected from electronic medical records for the entire month of July 2016. The literature on epidemiology of TBI in Brazil was systematically reviewed using MeSH/DeCS descriptors in the PubMed and Lilacs databases. **Results:** Most patients admitted with TBI were male and under 60 years of age. Mild TBI was the most prevalent form and the most common cause of TBI was falls. A Glasgow Coma Scale score below 12, neuroimaging changes on computer tomography, and presence of any medical conditions were significantly associated with longer hospital stay. Brazilian studies showed that TBI affected mainly men and young adults. In addition, mild TBI was the most common TBI severity reported and the most common causes were motor vehicle accidents and falls. **Conclusions:** Overall, the profile of TBI in this center reflects the data from other Brazilian studies.

Keywords: Brain Injuries, Traumatic; Brain Concussion; Epidemiology; Brazil.

RESUMO

Antecedentes: O traumatismo cranioencefálico (TCE) representa, mundialmente, um problema sério de saúde pública. Apesar de o TCE ser prevalente em países em desenvolvimento, estudos epidemiológicos permanecem escassos. **Objetivo:** Investigar as características sociodemográficas e clínicas de pacientes acometidos por TCE no Hospital João XXIII — centro de referência em trauma situado em Belo Horizonte, Brasil — e revisar sistematicamente toda a literatura disponível sobre o TCE no Brasil. **Métodos:** Os dados clínicos e sociodemográficos foram coletados apenas para o mês de julho, 2016, por meio de prontuários eletrônicos. A literatura sobre a epidemiologia do TCE no Brasil foi sistematicamente revisada usando descritores *Medical Subject Headings* (MeSH)/Descritores em Ciências da Saúde (DeCS) nos bancos de dados PubMed e Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs). **Resultados:** Os pacientes acometidos por TCE eram em sua maioria homens com menos de 60 anos. O TCE leve foi a gravidade mais prevalente entre os casos. O TCE foi causado principalmente por quedas. Escores menores que 12 na escala de Coma de Glasgow mais alterações de neuroimagem em tomografia computadorizada e a presença de qualquer comorbidade médica estão significativamente associados à maior estadia hospitalar. Estudos brasileiros demonstraram que o TCE acomete principalmente homens e adultos jovens. Além disso, o TCE leve foi a gravidade mais comum reportada, e os mecanismos de TCE mais comuns foram acidentes automobilísticos e quedas. **Conclusões:** O perfil de pacientes acometidos por TCE no centro de referência em questão reflete os dados de outros estudos brasileiros.

Palavras-chave: Lesões Encefálicas Traumáticas; Concussão Encefálica; Epidemiologia; Brasil.

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INTRODUCTION

Traumatic brain injury (TBI) is defined as an injury caused by external force to the head that results in an anatomical lesion or functional impairment of cranial or encephalic structures. TBI is the leading cause of morbidity and mortality in polytrauma patients and is one of the main causes of death in individuals under 45 years of age[1-3]. TBI can have a variety of causes, from falls to car accidents.

Because of its medical and socioeconomic burden, TBI is a major public health problem worldwide. In the United States, 2.8 million emergency department visits were due to TBI and approximately 124,000 of the most severe cases develop long-term impairment[4,5]. In a single North American state, the annual direct medical cost of TBI was estimated at $95 million, or $1.67 million per 100,000 people[6]. Although lifetime costs for patients with TBI vary according to their demographic characteristics, the costs in Canadian dollars (CAD) for non-fatal cases was estimated at $2,318 for males and $2,200 for females[6]. In Europe, TBI accounted for 37% of all injury-related deaths and was estimated to cost a total of €22,907 million in 2010[7,8]. Limited demographic and socioeconomic information on TBI is available from developing countries[9].

Although TBI is widespread in Brazil and seems to have an economic and social impact, there are very few epidemiological studies [10,11]. A previous study reported that 40% of deaths in patients aged 5 to 9 years in Brazil are due to TBI and that for every patient who dies, there are at least another three more patients with long-term sequelae[12]. In addition, the annual cost of hospitalizations due to TBI has been estimated at approximately R$ 156,300,000 (US$ 70,960,000)[11]. Unfortunately, these estimates may not reflect the actual Brazilian reality, due in part to a high rate of unreported cases associated with immediate death and the absence of a nearby emergency unit[11,13,14]. Furthermore, reliable quantification of the impact caused by TBI is usually not accurate because measurements are not standardized and data collection on the incidence and outcome of brain injury is incomplete. Therefore, clinical-epidemiological studies are urgently needed to systematically investigate TBI in Brazil.

The current study aimed to investigate sociodemographic and clinical characteristics of patients admitted to João XXIII Hospital with TBI and to identify factors that may influence TBI morbidity and mortality. Also, the epidemiological data available on TBI in Brazil was systematically review.

METHODS

Original report

This was an observational study conducted at the Joao XXIII Hospital. This hospital is the main trauma center in the Metropolitan region of Belo Horizonte, the third largest metropolitan region in Brazil with more than five million inhabitants. The study was approved by the Human Research Ethics Committee of the Federal University of Minas Gerais (COEP-UFMG).

All records of patients admitted to the Emergency Department of the Joao XXIII Hospital within one month (July 2016) were evaluated using a structured protocol to obtain sociodemographic and clinical information. The sociodemographic data included: (i) sex, (ii) ethnicity, (iii) marital status, (iv) place of residence (Belo Horizonte, metropolitan area, rural area), and (v) educational level. Clinical variables included TBI features (Glasgow Coma Scale Score [GCS], CT neuroimaging changes, hemodynamic instability, and ventilatory support) and hospital outcome. The following premorbid variables were also recorded: (i) clinical comorbidities (any medical conditions that were either secondary to the TBI or that the patient already had on admission) and (ii) alcohol or illicit drug use (assessed via medical record). The causes, severity, and type of TBI were also recorded. Neuroimaging results were included when available.

Exclusion criteria included: (i) follow-up patients, (ii) non-TBI patients (evaluated via the absence of a TBI diagnosis on record), (iii) burn victims, (iv) exogenous intoxications, (v) venomous animal bites, (vi) trauma patients without TBI, and (vii) patients admitted 24 hours after TBI.

Statistical analyses were conducted with *Statistical Package for the Social Sciences* (SPSS) software, version 17.0. Chi-squared analyses were performed to determine statistically significant frequencies of specific events in subgroups. Binary logistic regression using a backward elimination approach was performed to determine which variables were significantly associated with a longer hospital stay, defined as more than 24 hours, as opposed to patients discharged within 24 hours after hospital admission. At the João XXIII Hospital, patients whose state of consciousness remained stable for 24 hours were discharged. The following variables were included in the initial model: age, sex, GCS score (greater than or equal to 13 or less than 12), comorbidity (presence or absence), neuroimaging changes in computed tomography, and alcohol and drug use. Stepwise backward selection was performed automatically using the SPSS software, version 17.0 (SPSS Inc., Chicago, IL, USA), and exclusion testing was done with the likelihood ratio based on the conditional parameter estimates. The goodness of fit of the logistic regression model was assessed using the Hosmer-Lemeshow test and a Receiver Operating Characteristic (ROC) curve.

Systematic review

A systematic search for TBI studies in Brazil was performed independently by two authors (JLVMB and ASM) in the PubMED and Lilacs databases using the MeSH/DeCS descriptors for *traumatic brain injury, *epidemiology, and *Brazil. The inclusion criteria were as follows: (i) studies evaluating sociodemographic and clinical information on TBI cases in Brazil, (ii) original articles, and (iii) articles in Portuguese, Spanish, or English.

RESULTS

In July 2016, 6,184 patients were admitted to the hospital, with 490 individuals diagnosed with TBI. These 490 individuals accounted for 7.92% of the total admissions during the research period. Four hundred seventy-seven records had enough information to determine clinical outcome by age, while 436 records contained all information required by our research protocol (data not shown).

Male patients formed the majority of our sample (n=324, 66.1%). Most TBI occurred in adults (n=259, 52.9%). The most common mechanism for TBI was an unspecified fall (n=124, 25.3%), followed by a fall from one's own height (n=118, 24.1%) (Table 1).

Table 1. Sociodemographic data of the 490 available traumatic brain injury records.

		n	%
Sex	Male	324	66.1
	Female	166	33.9
Origin	Belo Horizonte	341	69.9
	Metropolitan region	107	21.8
	Metropolitan region outskirts	4	0.8
	Outside metropolitan region (but still within the state of Minas Gerais)	29	5.9
	Different State	2	0.4
	Not informed	7	1.4
Age	0-18 years	149	30.4
	19-59 years	259	52.9
	60 years or more	82	16.7
Race	Brown	336	68.6
	White	114	23.3
	Black	32	6.5
	Not informed	8	1.6
Outcome	Death	15	3.1
	Discharge<24h	367	74.9
	Discharge >24h	95	19.4
	Hospitalized	7	1.4
	Not informed	6	1.2
TBI mechanism	Unspecified fall	124	25.3
	Fall from own height	118	24.1
	Fall from superior height	43	8.8
	Aggression	61	12.4
	Firearm	6	1.2
	Hit or struck by a car	45	9.2
	Traffic collision	66	13.5
	Non-traffic-related collision	16	3.3
	Repetitive TBI	4	0.8
	Not informed	7	1.4

TBI: traumatic brain injury.

The consequences of TBI differed considerably between age ranges (p=0.031). Deaths by age range were: (i) ≤18 years old, 1 death/112 individuals (0.89%), (ii) 19–59 years old, 7 deaths/245 individuals (2.9%), and (iii) ≥60 years old, 6 deaths/79 individuals, (7.6%). For the latter analysis, we considered only the 436 records that contained all the data required by our research protocol.

Patients with TBI were divided into three groups based on their GCS score on hospital admission. Patients who had GSC scores of 13–15 on hospital admission were classified as "mild TBI". Patients with GSC scores of 9–12 and 3–8 were classified as "moderate TBI" and "severe TBI", respectively[11,13]. Patients with mild TBI accounted for the majority of TBI-related admissions and comprised 87.4% of the total number of TBI cases. Moderate and severe TBI cases accounted for 5.5 and 7.1% of TBI cases, respectively.

Next, we analyzed the mechanisms involved in TBI. The mechanisms of TBI were differed significantly between the different severity categories of TBI. Unspecified fall and traffic accident were the most frequent mechanisms for mild and severe TBI, respectively (data not shown).

Male patients were the most affected by TBI across severity levels (p=0.022). We also analyzed the incidence of comorbidities, CT neuroimaging changes, hemodynamic instability, ventilatory support, and death across TBI severity levels (Table 2). Severe TBI accounted for the majority of deaths (57.1%), whereas mild and moderate TBI accounted for 21.4% each. These deaths were related to TBI or TBI-associated injuries.

In multivariate analysis, CT neuroimaging changes, the presence of medical comorbidities, and a GCS score of 12 or less remained as significant factors associated with longer hospital stay (>24h). The results are presented in Table 3. The logistic regression model was significant [Hosmer-Lemeshow goodness of fit test (step 5): chi-square=3.177; p=0.204] and predicted variability yielded an area under the curve (AUC) of 0.819 in the ROC analysis (Figure 1).

In our systematic review, we first identified 148 possible titles in the PubMED and Lilacs databases. Four articles were duplicates, and 114 studies were excluded after title/abstract screening. Of these 114 articles, we set aside one review for further reference screening. Thirty articles were fully analyzed, and 10 of these either did not meet our inclusion criteria or did not contain the required information. Two additional articles were identified in the references of review studies. Also, five additional articles were identified while reading the selected manuscripts, giving us a total of 27 eligible articles (Figure 2).

Most studies were conducted in cities in the state of São Paulo (n=6)[15-20]. Three studies dealt exclusively with epidemiological data on patients who developed specific sequelae as a result of TBI, including diffuse axonal injury, intracranial hypertension, and hypoxic brain damage[15,21,22]. Two studies addressed epidemiological data on patients affected by

Table 2. Clinical variables across different traumatic brain injury severities.

		GCS Score			p-value
		Mild (13 to 15)	Moderate (12 to 9)	Severe (8 to 3)	
Sex	Male	240 (63%)	19 (20.1%)	5 (16.1%)	0.022
	Female	141 (37%)	5 (79.2%)	26 (83.9%)	
Use of drugs		12 (3.1%)	2 (8.7%)	1 (3.2%)	0.36
Alcohol		71 (18.6%)	9 (37.5%)	3 (9.7%)	0.029
Comorbidity		95 (25%)	6 (25%)	2 (6.5%)	0.065
CT neuroimaging findings		39 (11.7%)	13 (54.2%)	24 (77.4%)	<0.001
Hemodynamic instability		0 (0%)	2 (8.3%)	4 (13.8%)	<0.001
Ventilation Support		4 (1.1%)	6 (25%)	24 (80%)	<0.001
Outcome	Death	3 (0.8%)	3 (13.6%)	8 (29.6%)	<0.001
	Discharge>24h	61 (16.3%)	12 (54.5%)	16 (59.3%)	
	Discharge<24h	311 (82.9%)	7 (31.8%)	3(11.1%)	

GCS: Glasgow coma scale; TBI: traumatic brain injury; CT: computed tomography.

Table 3. Logistic model analysis to predict hospital admission for more than 24 hours.

Predictive variable	B	SE	Wald	df	p-value	OR	95%CI for OR	
							Lower	Upper
CT neuroimaging changes	-2.909	0.378	59.220	1	0.000	0.055	0.026	0.114
Medical comorbidity	-0.703	0.347	4.115	1	0.043	0.495	0.251	0.977
GCS score	-1.838	0.491	13.998	1	0.000	0.159	0.061	0.417

CT: computed tomography; GCS: Glasgow coma scale; B: beta coefficient; SE: standard error; df: degrees of freedom; OR: *Odds Ratio*; 95%CI: 95% confidence interval.

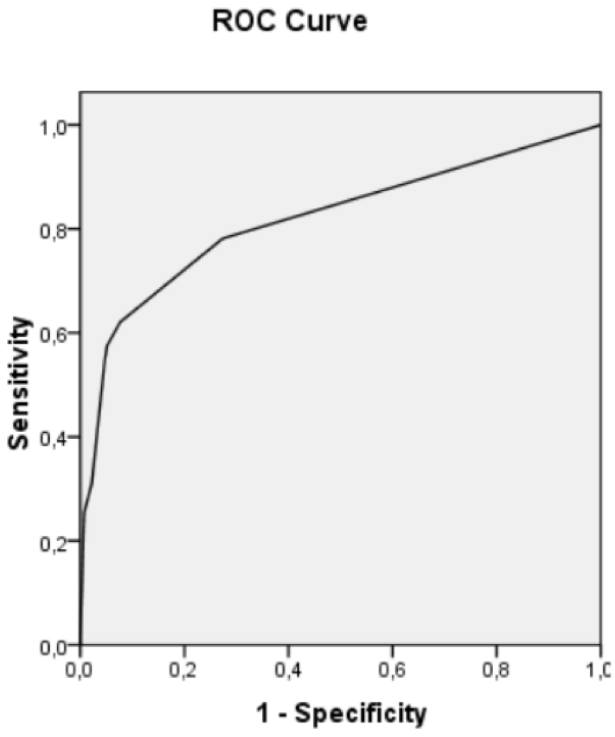


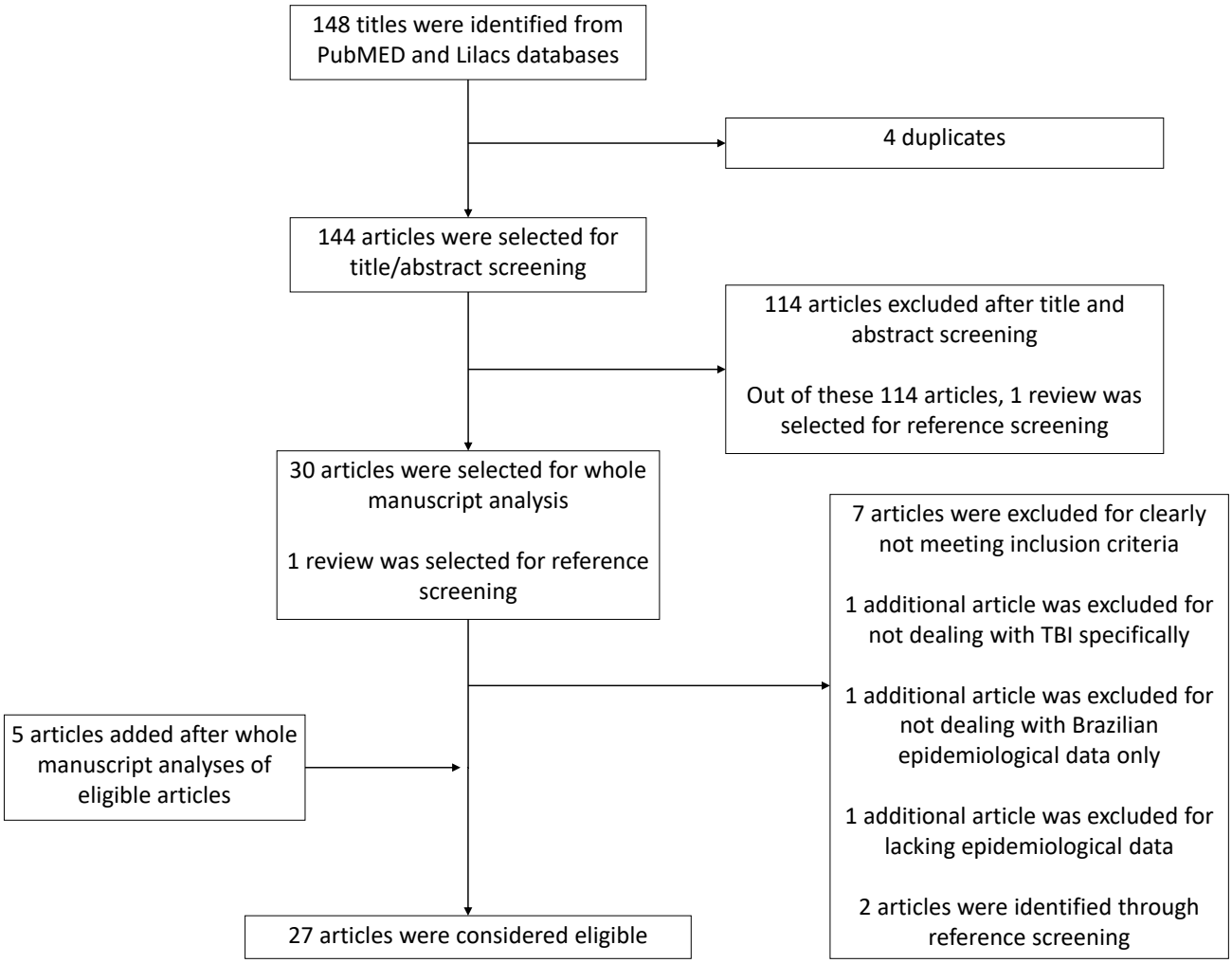
Figure 1. ROC curve of the logistic regression model (AUC=0.819).

specific TBI mechanisms, such as falls from their own height and firearm bullets[19,23]. In most studies, mild TBI was found to be the most prevalent type (n=10)[16,17,23-30]. Additionally, young men were most commonly affected in all studies[11,15-40]. There was limited information on ethnicity, with only three studies providing this information[11,15,35]. Traffic/vehicle accidents were the most common mechanism for TBI, followed by falls[15-17,19,21,24-31,33-40]. This information is presented in Table 4.

We also extracted information on the consequences of TBI, patients' clinical comorbidities, length of hospital stay, and alcohol consumption (Table 5). Surprisingly, many studies did not collect any neuroimaging findings, probably because neuroimaging is often not performed in mild TBI cases.[11,17,18,23,25,28,29,31,34,38]. In relation to other clinical findings, TBI was often accompanied by other soft tissue lesions and limb fractures[16,21,22,29,35-37]. Alcohol consumption ranged from 11.7 to 42.3%[15,16,23,24,29,36].

DISCUSSION

In the present study, we evaluated the sociodemographic and clinical characteristics of patients with TBI admitted to a public reference trauma center in Minas



TBI: traumatic brain injury.

Figure 2. Flowchart of study selection process.

Gerais, Brazil. This is the first study to perform such evaluation in the state of Minas Gerais, specifically at one of the largest reference trauma centers in Brazil. It is worth highlighting the large number of patients admitted to this center in a short period of time. The hospital admitted almost 17 patients with TBI every day. Young men were most commonly affected, and unspecific falls were the most common cause of TBI. Overall, these findings are consistent with the results of other Brazilian studies, as shown in our systematic literature review [11,15-40].

The higher vulnerability of men can be explained by sociocultural and behavioral factors, such as higher exposure to urban violence than women[25]. A European systematic review found a preponderance of men in 28 studies in which the male-to-female ratio ranged from 1.2:1.0 to 4.6:1.0[41]. Accordingly, men in the United States have higher age-adjusted rates of emergency department visits and deaths related to TBI[4]. In our sample, TBI occurred more frequently in young adults, with mean ages ranging from 22 to 49 years in different studies[25,41,42].

In contrast to most Brazilian reports, the current study found that falls were the main cause of TBI, but not traffic accidents[29,43]. One of the largest epidemiological studies conducted in the Brazilian population found that falls were the most common TBI mechanism, similar to our findings[33]. Falls were also the most common cause of TBI in European countries and in the USA[4,41].

Approximately 19% of our sample reported having consumed alcohol prior to the traumatic event. Our results show that falls, followed by traffic accidents, were the main causes of TBI in patients under the influence of alcohol. Falls were also the main cause of TBI in patients under the influence of illicit drugs (mainly marijuana and crack), but here traffic accident was followed by physical aggression. It is known that the use of alcohol and illicit drugs favors the occurrence of risky situations[29]. In an American study, it was found that both alcohol and illicit drug use were common before a TBI[43]. In Brazil, it is still unclear what role alcohol and other drugs play in TBI[36]. Most of the studies included in our review did not evaluate alcohol status of patients, and those that did had missing data on such information[15,16,23,29,36].

Table 4. Sociodemographic characteristics of Brazilian epidemiological studies on traumatic brain injury.

Reference	Location	Study design	TBI severity/type	Most Common TBI severity (if applicable)	Male		Female		Most afflicted age group	Most afflicted ethnicity	Death	Most common TBI mechanism
					n	%	n	%				
Melo et al., 2019[24]	Parnaíba, Piauí, Brazil	Retrospective and Descriptive	General	Mild, n=50 (42.7%)	94	80.3%	23	19.7%	Mean age: 33.17 years (SD±17.2)	Not informed	Not informed	Automobile accidents, n=96 (82.1%)
Marinho et al., 2017[31]	Natal, Rio Grande do Norte, Brazil	Cross-sectional	General	Moderate, n=228 (61.3%)	317	85.2%	55	14.8%	18–30 years old, n=209 (56.2%)	Not informed	Not informed	Automobile accidents, n=95 (25.6%)
De Almeida et al., 2016[11]	Not applicable	Cross-sectional	General	Not informed	97,552 (mean per year)	77.7% (mean per year)	28,017 (mean per year)	22.3 (mean per year)	20–29 years old, n=28,905.4 (mean per year)	Mixed race, n=3,142,782.4* (mean per year) *Greater number of cases because data were missing	n=9,714 (7.7%)(mean per year)	Not informed
Vieira et al., 2016[15]	São Paulo, São Paulo, Brazil	Prospective Cohort Study	Severe TBI with diffuse axonal injury	Not applicable	70	89.7%	8	10.3%	18–28 years old, n=34 (43.6%)	White, n=51 (65.4%)	n=24 (30.8%)	Traffic accidents, n=65 (83.3%)
Tavares et al., 2014[32]	Distrito Federal, Brasília, Brazil	Cross-sectional	General	Severe, n=108 (55.7%)	161	82.99%	33	17.01%	21–40 years old, n=67 (34.5%)	Not informed	Not informed	Physical aggression, n=57 (29.4%)
De Souza et al., 2013[19]	São Paulo, São Paulo, Brazil	Cross-sectional	General TBI caused by firearm projectiles	Severe, n=68 (37.6%)	154	85%	27	15%	21–30 years old, (47%)	Not informed	Not informed	Not applicable
Santos et al., 2013[25]	Pelotas, Rio Grande do Sul, Brazil	Epidemiological, Descriptive, and Retrospective	General	Mild, n=202 (40.7%)	314	63.3%	182	36.7%	0–15 years old, n=220 (44.3%)	Not informed	n=2 (0.4%)	Falls, n=233 (47.0%)
Fernandes et al., 2013[33]	Not applicable	Cross-sectional, descriptive	General	Not informed	358,780	81.5%	81,706	18.5%	14–34 years old, n=231,827 (53.0%)	Not informed	n=52,087 (12.0%)	Falls, n=154,170 (35.0%)
Carvalho Viégas et al., 2013[34]	Ananindeua, Pará, Brazil	Epidemiological, Cross-sectional, observational	General	Not informed	220	88%	30	12%	20–30 years old, n=81 (32.4%)	Not informed	n=55 (22%)	Traffic accidents, n=91 (36.4%)
Ruy and Rosa, 2011[35]	Criciúma, Santa Catarina, Brazil	Cross-sectional, descriptive, retrospective	General	Severe, n=63 (67.7%)	82	88.2%	11	11.8%	Mean age: 34.6 years (SD±16.7)	White n=84 (90.3%)	n=25 (26.9%)	Automobile accidents, n=52 (55.9%)
Moura et al., 2011[26]	Petrolina, Pernambuco, Brazil	Cross-sectional, epidemiological	General	Mild, n=54 (53.47%)	87	86.14%	14	13.86%	21–40 years old, n=52 (51.49%)	Not informed	n=8 (7.92%)	Motorcycle accident, n=45 (44.55%)
Ramos et al., 2010[36]	Caruaru, Pernambuco, Brazil	Document-based	General	Not informed	139	81.2%	32	18.7%	25–49 years old, n=56 (29.9%)	Not informed	Not informed	Motorcycle accident, n=34 (19.9%)
Guerra et al., 2010[21]	Belo Horizonte, Minas Gerais, Brazil	Retrospective cohort study	General TBI patients who developed intracranial hypertension	Severe, n=132 (100%)	89	67.4%	43	32.6%	7–9 years old	Not informed	n=68 (51.5%)	Getting hit by a vehicle, n=68 (51.5%)
Martins et al., 2009[37]	Florianópolis, Santa Catarina, Brazil	Prospective	Severe	Not applicable	631	84%	117	15.6%	Mean age: 34.8 years old (SD±16.3)	Not informed	n=249 (33.3%)	Road accident, n=225 (30.1%)

Continue...

Table 4. Continuation.

Reference	Location	Study design	TBI severity/type	Most Common TBI severity (if applicable)	Male		Female		Most afflicted age group	Most afflicted ethnicity	Death	Most common TBI mechanism
					n	%	n	%				
Braga et al., 2008[23]	Florianópolis, Santa Catarina, Brazil	Prospective	General TBI caused by one's own height	Mild, n=69 (90.7%)	44	57.9%	32	42.1%	Mean age for men: 44.7 years Mean age for women: 47.2	Not informed	Not informed	Not applicable
Faria et al., 2008[38]	Uberlândia, Minas Gerais, Brazil	Epidemiological, Prospective	General (Severe and moderate were grouped together)	Severe and moderate (grouped together), n=56 (66.7%)	68	80.9%	16	19.1%	Mean age for severe and moderate: 40.6 years Mean age for mild: 34.8	Not informed	Not informed	Transport accidents, n=54 (64.74%)
Pereira et al., 2006[27]	Aracaju, Sergipe, Brazil	Longitudinal Prospective	General	Mild, n=422 (89%)	344	73%	126	27%	10–29 years old	Not informed	n=3 (0.6%)	Accidental fall, n=148 (31.5%)
Melo et al., 2006[28]	Salvador, Bahia, Brazil	Cross-sectional descriptive	General	Mild, n=249 (63.8%)	280	71.8%	110	28.2%	Not applicable (Study conducted on a specific group age (0–19 years old)	Not informed	Not informed	Fall from height, n=134 (34.4%)
Melo et al., 2004[29]	Salvador, Bahia, Brazil	Cross-sectional	General	Mild, n=146 (38.4%)	460	82.9%	95	17.1%	21–30 years old, n=128 (23.2%)	Not informed	n=127 (22.9%)	Traffic accidents, n=226 (40.7%)
Dantas Filho et al., 2004[39]	Campinas, São Paulo, Brazil	Cross-sectional	Severe	Not applicable	166	80.58%	40	19.42%	Mean age: 29.21 years old	Not informed	n=75 (36.40%)	Traffic accidents, n=147 (71.36%)
Gusmão et al., 2002[22]	Belo Horizonte, Minas Gerais, Brazil	Prospective	Fatal TBI victims	Not applicable	90	75.0%	30	25.0%	Mean age: 37.5 years old (SD±18.3)	Not informed	Not applicable (Post-mortem study)	Not applicable (all patients came from traffic accidents)
Koizumi et al., 2001[40]	Not applicable	Cross-sectional	General	Not informed	10,251	62.6%	6,125	37.4%	(Study conducted on children who were ≥ 10 years old) 0–4 years old, n=9,302 (56.8%)	Not informed	n=332 (2.0%)	Falls, n=10,022 (61.2%)
Koizumi et al., 2000[20]	São Paulo, São Paulo, Brazil	Cross-sectional, retrospective	General	Not informed	2784	76.6%	851	23.41%	≤10 years old (20.3%)	Not informed	n=371 (10.2%)	Aggression, n=1,767 (48.6%)
Colli et al., 1997[16]	Ribeirão Preto, São Paulo, Brazil	Cross-sectional	General	Mild, n=2,584 (74.5%)	2476	71.4%	992	28.6%	0–10 years old (about 30% of all men about 10% of all women)	Not informed	n=209 (6%)	Traffic accidents, n=1,241(35.8%)
Gennari et al., 1995[17]	São Paulo, Brazil	Prospective	General	Mild, n=47 (47%)	85	85%	15	15%	Closed head injury patients' mean age: 35.4 years old Penetrating head injury patients' mean age: 27.2 years old	Not informed	n=12 (12%)	Traffic accidents, n=40 (40%)
Masini et al., 1994[30]	Distrito Federal, Brazil	Retrospective	General	Mild, n=76 (76%) (Independent 100 people sample)	65 (Independent 100 people sample)	65% (Independent 100 people sample)	35 (Independent 100 people sample)	35% (Independent 100 people sample)	1–30 years old, n=72 (72%) (Independent 100 people sample)	Not informed	n=797 (14.7%)	Traffic accident, n=2391 (44%)
Maset et al., 1993[18]	Sao Jose do Rio Preto, São Paulo, Brazil	Cross-sectional	General	Not informed	759	70.0%	325	30.0%	20–29 years old, n=303 (28.0%)	Not informed	Full text was not retrievable	Full text was not retrievable

Table 5. Traumatic brain injury-related consequences, clinical comorbidities, length of hospital stay, and alcohol intake information in epidemiological studies on traumatic brain injury.

Reference	Neuroimaging findings	Other clinical comorbidities/findings	Hospital stay length	Alcohol intake
Melo et al., 2019[24]	Computerized tomography, n=83 (70.9%) reported no encephalic lesions. From the remaining patients: (i), n=18 (15.4%) presented frontal lobe lesions; (ii), n=12 (10.3%) presented parietal lobe lesions; (iii), n=7 (6%) presented temporal lobe lesions; (iv), n=4 (3.4%) presented occipital lobe lesions.	Not informed	Not informed	19.7% (n=23) of patients displayed intoxication signs, according to their records. The remaining records did not include any information on patients' alcoholic statuses.
Marinho et al., 2017[31]	Not informed	Not informed	Not informed	Not informed
De Almeida et al., 2016[11]	Not informed	Not informed	Mean hospital stay length for: (i) 2008: 5.4 days; (ii) 2009: 5.3 days; (iii) 2010: 5.5 days; (iv) 2011: 5.6 days; (v) 2012: 5.8 days. Overall mean length of hospital stays: 5.5 days.	Not informed
Vieira et al., 2016[15]	Early diffuse axonal injury and intracranial hypertension signs in computerized tomography are associated with greater mortality	Hypotension, hypertension, hypothermia, hyperthermia, hypoglycemia, hyperglicemia, bradycardia, tachycardia, and hypoxia.	Not informed	n=33 (42.3%) patients reported alcohol intake prior the trauma event.
Tavares et al., 2014[32]	Chronic subdural hematoma, n=63 (32.5%) Acute extradural hematoma, n=49 (25.3%) Acute subdural hematoma, n=30(15.5%) Cerebral edema, n=2 (1.0%) Firearm projectile, n=7 (3.6%) Depressed skull fracture, n=38 (19.6%) Intraparenchymal hematoma, n=5 (2.6%)	Not informed	Not informed	Not informed
De Souza et al., 2013[19]	Study conducted on TBI caused by projectile firearms Frontal lobe lesion, n=49 (27%) Temporal lobe lesion, n=45 (25%) Parietal lobe lesion, n=25 (14%) Occipital lobe lesion, n=31 (17%) Facial lesion, n=20 (11%) Multiple lesions, n=11 (6%)	Tangential TBI, n=29 (16%) Penetrating TBI, n=152 (84%)	Not informed	Not informed
Santos et al., 2013[25]	Not informed	Not informed	Not informed	Not informed
Fernandes et al., 2013[33]	Study did not specify whether lesions were chronic or acute. Fractures, n=11,125 (2.5%) Extradural hematoma, n=20,923 (4.8%) Subdural hematoma, n=27,447 (6.3%) Focal lesions, n=31,644 (7.2%) Diffuse lesions, n=159,241 (36.3%) Subarachnoid hemorrhage, n=1,856 (0.4%) Non-specified lesions, n=186,742 (42.5%)	Not informed	Not informed	Not informed

Continue...

Table 5. Continuation.

Reference	Neuroimaging findings	Other clinical comorbidities/findings	Hospital stay length	Alcohol intake
Carvalho Viégas et al., 2013[34]	Not informed	Not informed	Not informed	Not informed
Ruy and Rosa, 2011[35]	Not informed	Sensory reduction, n=45 (48.5%) Anisocoria, n=15 (16.3%) Mental confusion, n=11 (12.1%) Psychomotor agitation, n=10 (10.9%) Cardiopulmonary arrest, n=10 (10.9%) Respiratory failure, n=9 (9.8%) Seizures, n=6 (6.7%) ICU clinical complications: Pneumonia, n=16 (17.3%) Sepsis, n=2 (2.2%) Acute renal failure, n=2 (2.2%) Cerebral hemorrhage, n=36 (38.9%) Cerebral contusion, n=36 (38.5%) Cerebral edema, n=23 (24.9%) Bone fracture of any kind, n=18 (19.6%) Pneumocephalus, n=12 (12.9%)	Not informed	Not informed
Moura et al., 2011[26]	Study did not specify whether lesions were acute or chronic. Diffuse axonal injury, n=1 (0.99%) Extradural hematoma, n=20 (19.82%) Cerebral contusion, n=18 (17.82%) Subarachnoid hemorrhage, n=10 (9.9%) Subdural hematoma, n=6 (5.94%) Most afflicted cranial sites: Frontal, n=25 (24.75%) Temporal, n=12 (11.88%) Temporoparietal, n=12 (11.88%) Parietal, n=9 (8.91%) Occipital, n=6 (5.94%) Parietofrontal, n=6 (5.94%) Frontotemporal, n=4 (3.96%) Temporooccipital, n=2 (1.98%) Basilar skull fracture, n=2 (1.98%)	At admission: Headache, n=17 (16.83%) Vomiting, n=16 (15.84%) Otorrhagia, n=9 (8.91%) Coma, n=6 (5.94%)	Not informed	Not informed
Ramos et al., 2010[36]	General nervous system lesion, n=34 (19.9%)	Bone lesion, n=39 (22.8%) Vascular lesion, n=55 (32.2%) Multiple lesions, n=26 (15.2%) Soft tissues, n=7 (4.1%)	Not informed	n=20 (11.7%)
Guerra et al., 2010[21] *(Only severe TBI) cases were analyzed)*	Diffuse Axonal Injury, n=56 (42.4%) Swelling, n=74 (56.1%) Intraparenchymal hemorrhage, n=46 (34.8%) Subarachnoid hemorrhage, n=41 (31.1%) Study did not specify whether lesions were acute or chronic: Subdural hematoma, n=20 (15.2%) Intraventricular hemorrhage, n=15 (11.4%) Extradural hematoma, n=14 (10.6%)	Thoracic lesion, n=48 (36.4%) Skeletal muscle lesion, n=37 (28.0%) Abdomen, n=21 (15.9%) Spinal cord, n=6 (4.6%)	Not informed	Not informed

Continue...

Table 5. Continuation.

Reference	Neuroimaging findings	Other clinical comorbidities/findings	Hospital stay length	Alcohol intake
Martins et al., 2009[37] *(Only severe TBI cases were analyzed)*	Marshall type I injury, n=22 (2.9%) Marshall type II injury, n=175 (23.4%) Marshall type III injury, n=172 (23.0%) Marshall type IV injury, n=58 (7.8%) Evacuated mass lesion, n=240 (32.1%) Non-evacuated lesion, n=30 (4.0%) Brainstem lesion, n=50 (6.7%) Subarachnoid hemorrhage, n=267 (35.7%)	Face trauma, n=108 (14.4%) Cervical spine trauma, n=27 (3.6%) Dorsal-lumbar spine trauma, n=7 (0.9%) Thoracic trauma, n=141 (18.9%) Abdominal trauma, n=70 (9.4%) Limb trauma, n=204 (27.3%) (Pupil) Isochoric, n=283 (37.8%) (Pupil) Miotics, n=30 (4.0%) (Pupil) Anisocorics, n=347 (46.4%) (Pupil) Mydriatics, n=83 (11.1%)	Not informed	Not informed
Braga et al., 2008[23] *(Only TBI cases caused by falling from standing height were analyzed)*	Not informed	Systemic arterial hypertension, n=9 (11.8%) Epilepsy, n=6 (7.9%) Alcoholism, n=4 (5.3%) Diabetes mellitus, n=3 (3.9) Heart failure, n=3 (3.9%) Alzheimer's disease, n=3 (3.9%) HIV infection, n=3 (3.9%)	Not informed	n=11 (14.5%)
Faria et al., 2008[38]	Not informed	Not informed	Not informed	n=33 (39.3%)
Pereira et al., 2006[27]	Altered CT scan, n=75 (31.0%) out of 242 Altered plain radiography of the skull, n=4 (1.7%) out of 239	Altered conscious level, n=85 (18.1%) Vomiting and nausea, n=97 (20.6%) Sleepiness, n=51 (10.9%) Headache, n=40 (8.5%) Dizziness, n=18 (3.8%) Seizures, n=11 (2.3%) Otorrhagia, n=12 (2.6%) Epistaxis, n=8 (1.7%) Diplopia, n=2 (0.43%)	Not informed	Not informed
Melo et al., 2006[28] *(Study conducted on children and teenagers only)*	Not informed	Not informed	Not informed	Not applicable
Melo et al., 2004[29]	Not informed	1 lesioned organ, n=117 (66.1%) 2 lesioned organs, n=40 (22.6%) ≥3 lesioned organs, n=20 (11.3%)	Not informed	n=27 (4.9%)
Dantas Filho et al., 2004[39]	Marshall type I injury, n=15 (7.28%) Marshall type II injury, n=63 (30.58%) Marshall type III injury, n=33 (16.02%) Marshall type IV injury, n=13 (6.31%) Focal lesion (operated), n=72 (34.95%) Focal lesion (not operated), n=10 (4.85%)	Hypo-/Hypernatremia and Hypo-/hypercalcemia, n=130 (63.21%) Polyuria, n=32 (15.53%) Bronchopneumonia, n=119 (57.77%) Urinary infection, n=11 (5.34%) Sepsis, n=10 (4.85%) Sinusitis, n=6 (2.91%) Gastrointestinal bleeding, n=3 (1.46%) Hypoxia, n=81 (39.32%) Hypotension, n=39 (18.93%) Both hypoxia and hypotension, n=22 (10.68%)	Not informed	Not informed

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Table 5. Continuation.

Reference	Neuroimaging findings	Other clinical comorbidities/findings	Hospital stay length	Alcohol intake
Gusmão et al., 2002[22] (*Only evaluated fatal patients*)	Diffuse axonal injury, n=96 (80.0%) Intracranial hypertension, n=47 (39.2%) Skull fracture, n=63 (52.5%) Hypoxic brain injury: (19.2%)	Limb fractures, n=46 (38.3%) Thoracic trauma, n=42 (35%) Abdominal trauma, n=44 (36.7%) Both thoracic and abdominal trauma, n=32 (26.7%) Pneumonia, n=10 (8.3%) Purulent meningitis, n=3 (2.5%)	Not informed	Not informed
Koizumi et al., 2001[40] (*Only evaluated children*)	Skull fractures, n=1,800 (11%)	Not informed	<1 day, n=333 (2.0%) 1 to 3 days, n=12,100 (73.9%) 4 to 7 days, n=2.825 (17.3%) 8 to 29 days, n=1.023 (6.2%) ≥30 days, n=95 (0.6%)	Not applicable
Koizumi et al., 2000[20]	Fracture of skull vault, n=45 (1.2%) Basilar skull fracture, n=32 (0.9%) Other skull fractures, n=22 (0.6%) Multiple fractures of skull/face, n=4 (0.1) Brain concussion, n=1038 (28.6%) Cerebral laceration and contusion, n=192 (5.3%) Hemorrhage, n=509 (14.0%) Traumatic intracranial lesion of other types, n=1793 (49.3%)	Not informed	Most predominant hospital stay duration is of 1 to 7 days hospitalized (n=2,637; 72.5%).	Not informed
Colli et al., 1997[16]	Plain radiography of the skull: 18.0% (24% of 73%) presented fractures. CT scan: 4.2% (30% of 14%) presented brain lesions	Scalp lesion: 66.2% Headache (21.4% of children) Vomit: 17% (approximately in adult and children) Headache: 17% (approximately) Alteration of consciousness (some time after TBI): 24.4% Alteration of consciousness (immediately afterwards): 87% Soft tissue lesion: 17.9% Face lesion: 15.4%* *Full text was not retrievable. Figure 7 was missing	Not informed	17% of adults (approximately)*
Gennari et al., 1995[17]	Not informed	Penetrating trauma, n=32 (32%) Blunt trauma, n=68 (68%)	Not informed	Not informed
Masini et al., 1994[30]	Chronic subdural hematoma, n=54 (1) Acute extradural hematoma, n=40 (0.7%) Acute subdural hematoma, n=40 (0.7%) General fractures and basilar skull fracture, n=58 (1%) Cerebral contusion, n=56 (1%) Firearm projectile induced lesion: 19 (0.4%) Intracerebral hematoma: 9 (0.2%)	Not informed	n=64 (64%) were discharged <24 hours. n=16 (16%) stayed longer than 7 days.* *Independent 100 people sample 71.6% patients	Not informed
Maset et al., 1993[18]	Not informed	Not informed	Average hospital stays: 4.65 days 71.6% patients stayed for a maximum of 4 days. 24.9% patients stayed for 2 days. 1.7% patients stayed for a period greater than 20 days.	Not informed

TBI: traumatic brain injury

Regarding the severity of TBI, as determined by the GCS, the majority of our sample was diagnosed as mild (87.4%). Mild TBI was also the most common severity level in the Brazilian studies examined, but studies differed in their sample composition. For example, Marinho et al. analyzed a group of 18–30-year-old individuals — an age group more prone to riskier situations and to moderate and severe TBI[29,31,43]. Faria et al. grouped severe and moderate TBI together and yet accounted for only 52% of the total cases[38].

The clinical meaning of mild TBI should not be underestimated, as it has been associated with the development of cognitive and behavioral changes[44]. According to one scoping review, half of patients with a single episode of mild TBI develop long-term impairments in several cognitive domains, including executive functions, learning/memory, attention, processing speed, and language[45]. This review included heterogeneous studies using different cognitive batteries in mild TBI patients at different time points after the traumatic event, which may explain the high rate of cognitive deficits. For example, significant episodic memory deficits can already be observed in the acute phase of mild TBI[46].

Neuroimaging is an important tool in establishing the prognosis for TBI. Seventy-six of 436 (17.4%) patients had early tomographic/neuroimaging TBI-related alterations. It is well known that the more severe the TBI, the more likely the patient is to have neuroimaging changes[47]. Our results confirm that more than half of the patients with moderate or severe TBI had cranial CT changes. Conversely, about 10% of patients with mild TBI had neuroimaging changes. Few of the Brazilian studies reviewed included their neuroimaging findings, as neuroimaging is not considered cost-effective due to the low rate of positive neuroimaging findings in mild TBI[48].

The length of hospital stay was less than 24 hours in 73.6% of the cases, as most were mild TBI cases. Conversely, a GCS score of 12 or less on admission, as well as neuroimaging changes and medical comorbidity (i.e., both clinical and psychiatric conditions), were associated with a longer hospital stay. Similar to our results, Sorensen et al. found that lower GCS score and psychiatric comorbidity were significantly associated with delay in hospital discharge in patients with TBI[49]. The length of hospital stay in our systematic review varied widely, probably due to the heterogeneity of the sample and the different protocols for treatment and management of TBI in different clinical settings.

In the current study, 3.6% of our post-TBI patients died (n=18). Mortality rates should be interpreted with caution, considering the heterogeneity of epidemiological studies on TBI. For instance, Fernandes et al. found a mortality rate of 12.0% in a much larger sample that included over 400,000 records from a much longer time window[33]. In Europe, there is also a wide variation in post-trauma mortality rate, ranging from $3.0/10^5$ inhabitants per year in both Hannover and Münster (Germany) to $18.3/10^5$ per year in Finland and Italy[41]. In the USA, about one third of all related deaths are diagnosed with TBI[50].

There are limitations to the present study. Some variables (e.g., level of education) were not available for a significant percentage of patients, reflecting the challenges of clinical data collection in a busy trauma center, and thus preventing a more thorough analysis. Medical records also did not include categories of falls. We were only able to capture serious sequelae during hospitalization, which prevented us from exploring less severe complications, including cognitive, behavioral or motor symptoms, and the associated impact on patients' lives. In addition, the present study was conducted in a time window of one month within one year — which was one of the main reasons that led us to conduct a systematic review. From the literature review, we obtained an accurate snapshot of TBI epidemiology in one of the main trauma centers in one of the largest metropolitan regions of Brazil. We chose the month of July because of winter break — a time of year in which people are more exposed to risky situations (such as car travel) and, consequently, to TBIs.

Future studies with a comprehensive longitudinal evaluation of TBI beyond the acute phase are warranted. The investigation of regional specificities in TBI profile in other Brazilian regions and other developing countries could also provide meaningful clinical and epidemiological information. Only with robust evidence can optimal prevention and rehabilitation measures be implemented, influencing the outcome of this daunting problem.

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VIEW AND REVIEW

Sleep disorders in Down syndrome: a systematic review

Distúrbios do sono na síndrome de Down: revisão sistemática

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ABSTRACT

Background: Sleep disorders are commonly observed in children with Down syndrome (DS) and can lead to significant behavioral and cognitive morbidities in these individuals. **Objective:** To perform a systematic review evaluating sleep disorders in individuals with DS. **Methods:** Search strategies were based on combinations of keywords: "Down syndrome"; "trisomy 21"; "sleep disorders"; "dyssomnias"; "sleep apnea"; "obstructive"; "sleeplessness"; "insomnia"; "parasomnias"; and "excessive daytime sleepiness". PubMed and Science Direct were used. Only original studies and retrospective reviews in English published between January 2011 and March 2021 were included. **Results:** 52 articles were included, most of them involving children and adolescents under 18 years of age. The main sleep disorder associated with DS was obstructive sleep apnea (OSA). Some studies reported the presence of cognitive dysfunction in patients with DS and sleep-disordered breathing, and few have been found about parasomnia, insomnia, and daytime sleepiness in these patients. Movement disorders and unusual postures during sleep may be related to disordered sleep breathing in DS. The main treatment options for OSA are continuous positive airway pressure therapy (CPAP), surgery, and weight control. Computational modeling associated with MRI has been used to plan surgical interventions in these patients. **Conclusions:** Individuals with DS are at high risk of developing sleep-related breathing disorders. The main sleep disorder associated with DS was OSA. The presence of sleep-disordered breathing contributes to a worsening of cognitive function in patients with DS.

Keywords: Down Syndrome; Sleep Wake Disorders; Sleep Apnea Syndromes.

RESUMO

Antecedentes: Os distúrbios do sono são comumente observados em crianças com síndrome de Down (SD) e podem levar a morbidades comportamentais e cognitivas significativas nesses indivíduos. **Objetivo:** Realizar uma revisão sistemática para avaliar os distúrbios do sono em indivíduos com SD. **Métodos:** As estratégias de busca foram baseadas em combinações de palavras-chave: "Síndrome de Down"; "trissomia 21"; "distúrbios do sono"; "dissonias"; "apneia do sono"; "obstrutivo"; "insônia"; "insônia"; "parassonias" e "sonolência diurna excessiva". PubMed e Science Direct foram usados. Apenas estudos originais e revisão retrospectiva de prontuários escritos em inglês e publicados de janeiro de 2011 a março de 2021 foram incluídos. **Resultados:** Foram selecionados 52 artigos, a maioria com crianças e adolescentes menores de 18 anos. O principal distúrbio do sono associado à SD foi a apneia obstrutiva do sono (AOS). Alguns estudos relatam a presença de disfunção cognitiva em pacientes com SD e distúrbios respiratórios do sono, e poucos foram encontrados sobre parassonia, insônia e sonolência diurna nesses pacientes. Distúrbios do movimento e posturas incomuns durante o sono podem estar relacionados ao distúrbio respiratório do sono na SD. As principais opções de tratamento para AOS são pressão positiva contínua nas vias aéreas (CPAP), abordagem cirúrgica e controle de peso. A modelagem computacional associada à ressonância magnética tem sido usada para planejar intervenções cirúrgicas nesses pacientes. **Conclusões:** Indivíduos com SD apresentam alto risco de desenvolver distúrbios respiratórios relacionados ao sono. O principal distúrbio do sono associado à SD foi a AOS. A presença de distúrbios respiratórios do sono contribui para a piora das funções cognitivas em pacientes com SD.

Palavras-chave: Síndrome de Down; Transtornos do Sono-Vigília; Síndromes da Apneia do Sono.

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INTRODUCTION

Down syndrome (DS) was first characterized in 1866 by John Langdon Down, who described "individuals with peculiar clinical manifestations". Furthermore, in 1958, Jérôme Lejeune and Pat Jacobs stated that DS is a genetic syndrome related to a trisomy of chromosome 21. The DS prevalence in USA is around 13.56 for every 10,000 live births[1-3].

Clinical manifestations vary widely from person to person, but cognitive impairment is commonly noted in this syndrome[4,5]. Also, there are some common phenotypic features in individuals with DS, such as muscle hypotonia, macroglossia, brachycephaly, epicanthal folds, flat nasal bridge, micrognathia, low-set ears, excessive skin on the nape, single transverse palmar crease, clinodactyly of the fifth finger, and a larger gap between the first and second toes[6,7].

Sleep plays a critical role in good health and well-being. For this reason, sleep disorders in children and adolescents are associated with problems in physical, behavioral, and physiological development and pose an additional risk for obesity, endocrine disorders, depression, immunological, and heart diseases[8-10]. These disorders are commonly observed in children with DS and can lead to significant behavioral and cognitive morbidities in individuals with DS[11-13].

The aim of this study was to provide a systematic review to evaluate sleep disorders in people with Down syndrome, focusing on clinical presentation, pathophysiology, and treatment strategies.

METHODS

A systematic review of the literature, based on the PRISMA statement and the recommendations for systematic review and meta-analysis, was conducted to investigate the main sleep disorders in patients with Down syndrome and their treatment[13]. Search strategies were based on combinations of keywords "Down syndrome", "trisomy 21", "sleep disorders", "dyssomnias", "sleep apnea", "obstructive", "sleeplessness", "insomnia", "parasomnias", and "excessive daytime sleepiness", which were defined based on previous research in the Medical Subject Headings (MeSH) system. PubMed and Science Direct were used as databases, with a publication period of January 2011 to March 2021.

Researchers 1 and 2 (R.A.S and L.H.C) considered the topics covered in each article searched, in addition to the inclusion and exclusion criteria. Treatment-only studies were excluded; the focus was on studies that addressed sleep disorders in patients with DS.

Inclusion criteria were: original studies and retrospective chart reviews written in in English and with no restriction on health, age, or gender of subjects. Exclusion criteria were: papers not related to sleep disorders in DS patients after reading the full text and editorials, letters to the editor, review articles, case reports, and meeting abstracts. The collected data were compiled into a spreadsheet containing all relevant information from the studies, including authors, year of publication, journal name, sample characteristics (size, gender, age, and geographic area), data collection methods, clinical diagnosis, and assessed sleep disorder.

RESULTS

An initial search identified 3559 studies from the past 10 years. Subsequently, editorials, letters to the editor, review articles, case reports, meeting abstracts, and laboratory-based studies, including animal studies, were excluded, remaining 163 articles. After reading full-text articles, that met all predefined criteria, and excluding duplicates, 52 articles were included in this systematic review (Figure 1).

Among the selected studies were papers from 14 countries, most of them from the USA and Belgium. Regarding the population studied, most studies included children and adolescents under 18 years of age, and only 9 included the adult population. The main results are summarized in Tables 1 to 4. Almost all studies were case series, and about 50% of the manuscripts used PSG to define OSA.

DISCUSSION

Prevalence, etiology, and correlating factors for sleep disorders in individuals with Down syndrome

The main sleep disorder associated with DS in the selected articles was obstructive sleep apnea (OSA), with a prevalence ranging from 60 to 95%, depending on the criteria used for diagnosis and the age of the patients. However, the heterogeneity between the studies in terms of the method used for the diagnosis of the respiratory disorder is noteworthy: polysomnography (PSG), home polysomnography (HPSG), home night sleep records, cardiorespiratory polygraphy, housekeeping, McGill oximetry score, and actigraphy. In some cases, only questionnaires or scales were used, such as: Pittsburgh Sleep Quality Index (PSQI); Epworth Sleepiness Scale (ESS); Berlin Questionnaire (BQ); Child Sleep Habits Questionnaire (CSHQ), which may have compromised the assessment of prevalence [14-22].

We found few studies of parasomnia, insomnia, and daytime sleepiness in individuals with DS. Two studies found that some sleep problems were significantly more common in the population with DS, such as: resistance to bedtime, sleep duration, sleep anxiety, night watch, parasomnias, and daytime sleepiness[20,23,24]. However, none of the studies addressed the presence of parasomnias and their most frequent types isolated.

Maris et al. studied the occurrence of parasomnias, insomnia, and daytime sleepiness by comparing two groups

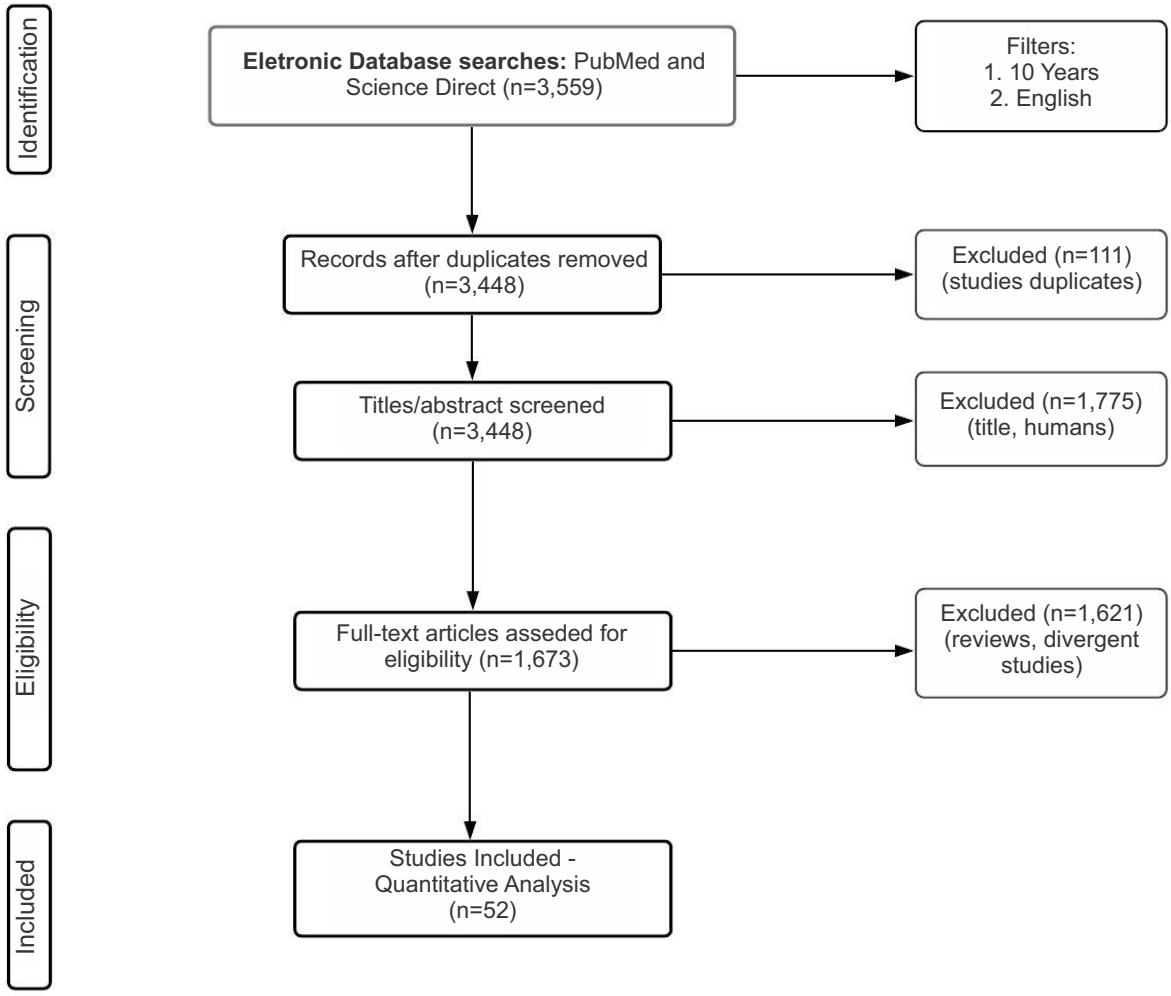

Figure 1. Flowchart of the literature search based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Table 1. Synthesis of articles selected for systematic review on prevalence, etiology, correlating factors, screening methods, and biomarkers for obstructive sleep apnea in Down syndrome patients (age>18 years).

Author/year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
Carvalho et al., 2020[49]	Case series-Questionnaires; blood county	60 (DS)	>18 years	-	Adults with DS have a very high prevalence of OSA. Hematocrit levels, STOP-Bang questionnaires (SBQ) showed a strong correlation with OSA severity. The SBQ performed well in identifying moderate to severe OSA in this population.	Considered together, these results point to the need to perform OSA screening in all adults with DS, and STOP-Bang may play a role in this screening.
Capone et al., 2013[38]	Case Control-PSG; Reiss and ABC scales	37 (9C) (28 DS)	19.8 (C) 21 (SD) years	5 years	-86% of DS cases had OSA compared with 44% of controls; -Moderate-severe OSA was present in 54% of DS compared to 11% of controls; -Intermittent sleep-associated hypoxia and REM sleep deficits were also more frequent in DS. Across all subjects, prior tonsillectomy was not related to the presence or absence of OSA.	The results of the study suggest that OSA is a common comorbidity in adolescents and young people with DS and depression.

OSA: obstructive sleep apnea; DS: Down syndrome.

Table 2. Synthesis of articles selected for systematic review on prevalence, etiology, correlating factors, screening methods, and biomarkers for obstructive sleep apnea in Down syndrome patients (age<18 years).

Author/year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
Wijayaratne et al., 2021[48]	Case series-BMIZ score; sleep symptoms questionnaires	64 (DS)	3–19 years	-	Despite not being referred for clinical sleep assessment, 42% of children with DS recruited from the community had moderate/severe OSA.	There were no differences in the quality-of-life behavior, daytime functioning, and sleep symptom questionnaires although the clinical group had a higher body mass index (BMI Z score) and overt signs of obesity. These results highlight the importance of PSG screening in all children with DS.
Caloway et al., 2020[63]	Case series (Hypoglossal nerve stimulation-HGN)	20 (DS)	10-21 years	2 months	All 20 children were implanted with no long-term complications. We report two interval adverse events, both of which were corrected with revision surgery. Twenty participants completed the 2-month polysomnogram, with median percent reduction in titration AHI of 85% (interquartile range=75–92%). The median nightly usage for these children was 9.21 hours/night. There was a median change in the OSA-18 score of 1.15, indicating a moderate, yet significant, clinical change	HGN stimulation was safe and effective in the study population. Two minor surgical complications were corrected surgically. Overall, these data suggest that pediatric HGN stimulation appears to be a safe and effective therapy for children with DS and refractory severe OSA.
Lee et al., 2020[18]	Case series-PSG and FSIQ	30 (DS)	11.3 years	-	The presence of OSA in children with DS was 80% in the 6 to 18 age group, with 62.5% in the 6 to 12 age group; In individuals aged 6 and 12 years old, both OSA and% REM were associated with lower scores on the WPPSI-R Vocabulary test;	OSA can be highly prevalent in children with DS in the community. Among children with DS 6 and 12 years of age, OSA, and % REM were associated with their language function.
Waters et al., 2020[22]	Randomized Clinical TrialPSG	152 (DS)	5.0 (1st PSG) 8.2 (2nd PSG) years	3.5 years	In a tertiary sleep unit, a full spectrum of sleep-disordered breathing in Down syndrome was seen from infancy onwards. Children having only 1 study were more likely to have a normal or mild result than those having ≥2. Studies were more often severe in children age <2 compared to those ≥2 years. After age 2 years, OSA severity increased with age. Studies evaluating the effects of surgery (most often adenotonsillectomy) showed resolution of disease to mild or normal in 53.3%.	Children having only one study were more likely to have normal results. Children with multiple studies reflected disease surveillance, including follow-up after treatment interventions.

Continue...

Table 2. Continuation.

Author/year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
Nerfeldt et al., 2020[21]	PSG before and after OSA surgical treatment	138 (DS)	6.1 years	-	The prevalence of OSA was 82.6 and 39.9% had severe OSA (AHI: 7.6); comorbidities found were ear disease (60%), circulatory disease (51%) and endocrine disease (39%); 33 patients undergoing postoperative PSG had a residual prevalence of moderate or severe OSA of 63.6%; Pre and postoperative PSG of patients with ATE and APP presented median AHI changed from 21.1 to 12.4 and median OSA-18 from 54.0 to 35.0.	Uncertain surgical efficiency was indicated and no significant difference in results for ATE and APP was demonstrated. The authors point out that the frequency of PSG in the postoperative period was low and not systematic and that the groups were uneven and small.
Anand et al., 2021[30]	PSG, Child Behavior Checklist (CBCL), developmental quotient (DQ)	53 (DS)	<18 years	-	Of 53 subjects (three to 11.8 years), 51 (96%) were found to have obstructive sleep apnea (OSA). In both three to five year and six-to-12-year age groups, there was a statistically significant positive correlation between the CBCL scores and the AHI (rho=0.77 and 0.83, respectively). There was a statistically significant negative correlation between the DQ and the AHI (rho=-0.62). In multiple linear regression, AHI was the only independent variable that was associated with CBCL and DQ.	This study provides robust evidence that OSA can negatively influence the development and behavior in children with Down syndrome as in typically developing children. Moreover, with increasing severity of OSA, children with Down syndrome have more behavioral abnormalities, especially attention deficit and hyperactivity, and also have poorer development scores.
Chamseddin et al., 2019[45]	PSG	106 (DS)	2.0-18 years	6 years	90% of children had ≥1 medical comorbidities; 95 (90%) patients had OSA; and 46 (44%) had severe OSA. Mean SaO_2 nadir was lower among obese than in nonobese children (80 vs 85%). Obese versus nonobese patients had a higher prevalence of severe OSA (56 vs 35%). The multivariable model showed that severe OSA was associated only with weight.	Obese children with DS are at a high risk for severe OSA, with weight as the sole risk factor. The results of this study show the importance of monitoring the weight of children with DS and counseling parents of children with DS about weight loss
Howard et al., 2020[61]	PSG and oAHI	24 (DS)	<18 years	5 years	There was no significant change in oAHI, oxyhemoglobin saturation nadir, $ETCO_2$, or percent TST in REM after treatment for any treatment group. There was no association between reported symptoms and AHI severity or change in AHI.	In this cohort, the resolution of mild AOS was low for all treatment groups. These findings are consistent with the current understanding that OSA in children with DS is probably the result of multiple overlapping abnormalities contributing to the obstructive pathology

Continue...

Table 2. Continuation.

Author/year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
					OSA resolved in one patient treated with observation and two treated with medication, but worsened in two each in the medication and observation groups. Resolution of OSA occurred in 20% treated with medication, 7.7% with observation, and 0% with oxygen.	and suggests that a multimodal approach may be more appropriate in this population. Prospective studies will be useful in the future to establish a better understanding of treatment outcomes in children with DS and AOS lightweight.
Joyce et al., 2020[28]	Questionnaire Behavior rating inventory of executive functionpreschool version (BRIEF-P)	202 (DS)	36–71 months	-	OSA was associated with poorer working memory, emotional control and shifting.	Findings suggest that known executive function (EF) difficulties in DS are already evident at this young age. Children with DS already have limited cognitive reserve and cannot afford additional EF deficits associated with OSA. OSA is amenable to treatment and should be actively treated in these children to promote optimal cognitive development.
von Lukowicz et al., 2019[58]	Polygraphy	18 (DS)	6.3 years	1.5 year	Eighteen recordings had ≥3 hours of artefact free recording in both the pretreatment and posttreatment sleep study and were therefore included in the analysis. Mean age was 6.3 years; 83% had OSA prior to intervention. Mean OAHI was 6.4 before and 6.4 after the intervention; the DI3 and SpO2nadir also did not change. Only the DI90 decreased significantly from 2.7 to 2.1.	The 1-week intense myofunctional training camp evaluated here in children with DS had only a marginal effect on OSA. Whether a longer follow-up period or duration of intervention would yield stronger effects remains to be determined
Hill et al., 2018[50]	Case series-HPO	161 (DS)	0.5–6.0 years	-	In this training sample, the best HPO parameter predictors of OSA were the delta 12 s index >0.555 (sensitivity 92%, specificity 65%) and 3% oxyhemoglobin (SpO2) desaturation index (3% ODI)>6.15 dips/hour (sensitivity 92%, specificity 63%). Combining variables (delta 12 s index, 3% ODI, mean and minimum SpO_2) achieved a sensitivity of 96% but reduced specificity to 52%.	HPO screening could halve the number of children with DS who require multichannel sleep studies and reduce the burden on children, families, and health services alike. This approach offers a practical universal screening approach for OSA in DS that is accessible to non-specialist pediatricians.
Beppler et al., 2018[52]	Case series-pediBand (prototype)	-	5 years	-	The potential of pediBand in measuring physiological signals that can be used in the diagnosis of OSA has been demonstrated.	It was demonstrated the potential of pediBand to successfully measure physiological signals that can be used in the diagnosis of OSA.

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Table 2. Continuation.

Author/year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
Best et al., 2018[60]	Retrospective case series	65 (DS)	4.8	8.5 years	The mean AHI was 10.7 events/hour after AT. Twenty-three patients (35.4%) underwent at least one additional surgical procedure after AT; 5 (7.7%) patients had ≥two additional procedures. The most common additional surgical procedures were revision adenoidectomies (n=8) and LT (n=13). Fifteen (23.1%) patients underwent at least one DISE to help direct selection of surgical site/s.	This retrospective case series provided the foundation for an algorithm for management of persistent OSA following primary AT in children with DS
Akkina et al., 2018[59]	PSG	24 (DS)	<18 years	3.5 years	The primary outcome was change in PSG parameters including AHI, OAHI, oxygen nadir, oxygen desaturation index, and mean carbon dioxide level. While improvement was seen in all PSG parameters, only improvement in oxygen nadir in children who had undergone prior AT was statistically significant (88.5 to 90.9%, p=04).	This study confirms a high proportion of multisite airway obstruction in DS patients with OSA. Although we observed an improvement across PSG measures, this study lacked power to detect statistically significant changes. DISE directed surgery holds promise as a beneficial tool for children with DS but a larger prospective study is needed before specific recommendations may be made on incorporating DISE into the OSA diagnostic and treatment algorithm for children with DS.
Slaats et al., 2018[65]	CT before the surgical procedure and PSG in the postoperative period	33 (DS)	4.3 years	3 years	Nineteen children underwent a second PSG after AT. Seventy-nine percent had persistent OSA (OAHI> 2 events/h). A greater than 50% decrease in OAHI was observed in 79% and these children had a significantly higher volume of the regions below the tonsils.	Children with severe OSA had a reduced air passage in the upper airway. Therefore, this study suggests that an image of the upper airway may have an influence on the choice of the text. This study is a pioneer in terms of analyzing the therapeutic response with CT analysis of upper airway.
Nehme et al., 2017[43]	Case series- PSG and sleep questionnaires	119 (DS)	6.6 years	10 years	Sleep-disordered breathing (SDB) was present in 42.9% of children, with its highest prevalence at age 8 years. Gastroesophageal reflux disease (GERD) was associated with lower odds of OAHI>5 events/hour; Presence of difficulty breathing at night, reported in the questionnaires of parents/caregivers, was significantly associated with apnea.	SDB is highly prevalent at all ages in children with Down syndrome. Symptoms did not predict SDB in this population, although GERD may mimic SDB.

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Table 2. Continuation.

Author/year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
Skotko et al., 2017[51]	Case series-PSG, Questionnaire, image exam	102 (DS)	3.0–24.0 years	6 months	The main outcome measure was the AHI. Using a Logic Learning Machine (with a questionnaire, imaging exam, and PSG) the best model had a cross-validated negative predictive value of 73% for mild OSA and 90% for moderate or severe OSA; positive predictive values were 55 and 25%, respectively.	In areas of the country where PSG is less available or affordable or when patients with DS are unable or unwilling to tolerate a sleep study, the model might offer, after validation, a viable alternative for providers looking to exclude moderate or severe OSA with a questionnaire.
Dudoignon et al., 2017[55]	Retrospective cohort	57 (DS)	5.9–6.2 years	5.5 years	33% patients required noninvasive respiratory support. Mean age at noninvasive respiratory support initiation was 7±7 years. On 11 patients with objective adherence data available, mean compliance at 2±1 years of treatment was excellent with an average use per night of 8hr46±3hr59 and 9 patient suing then on invasive respiratory support >4 hr/night. Non-invasive respiratory support was associated with an improvement of nocturnal gas exchange.	The study confirms the high prevalence and increased severity of OSA in children with DS. Upper airway surgery represents a first line treatment but has a limited efficacy. CPAP or NIV represent a very effective therapeutic option in case of persistent OSA after upper airway surgery. The major problem of CPAP/NIV is compliance but good results may be achieved by an experienced pediatric CPAP/NIV team.
Elsharkawi et al., 2017[53]	Urinary biomarkers	57 (DS)	4.0–9.1 years	-	Most night-sampled urinary biomarkers were elevated among individuals with DS relative to matched HC. No urinary biomarker levels differed between individuals with DS with vs. without OSA.	DS is associated with a different urinary biomarker profile when compared to HC. While urinary biomarkers may be predictive of OSA in the general pediatric population, a different approach is needed in interpreting urinary biomarker assays in individuals with DS.
Prosser et al., 2017[57]	PSG	21 (DS)	4.3–9.3 years	10 years	The median improvement in overall AHI and the OAHI were 5.1 events/hour and 5.3 events/hour (range, 22.9 to 41), respectively. The mean oxygen saturation nadir improved from 84 to 89%. The mean time with CO_2>50 mmHg, central index, and percentage of rapid eye movement sleep were not significantly different. After surgery, the OAHI was <5 events/hour in 61.9% and ≤1 in 19% of patients.	In children with DS, persistent OSA after AT and lingual tonsil hypertrophy, LT significantly improved AHI, OAHI, and O_2 saturation nadir. We recommend that children with DS should be evaluated for lingual tonsil hypertrophy if found to have persistent OSA following T&A.
Jayaratne et al., 2017[54]	Stereophotography 3dMDface	63 (DS)	4.86–7.49 years	-	Participants with DS had maxillomandibular hypoplasia with smaller	Anthropometric analysis of different craniofacial landmarks

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Table 2. Continuation.

Author/year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
					ear, nose, and eye measurements compared to neurotypically developing peers. We found no statistically significant differences in 3D photogrammetric measurements between participants with DS with or without OSA.	and measurements demonstrated that OSA cannot be correlated with the presence, absence, or degree of any of these structural alterations within this population
Hill et al., 2016[17]	Case series-Polygraphy	188 (DS)	0.6–6 years	-	Moderate or severe OSA, defined by an OAHI>5/ hour, was found in 14%; and mild-moderate OSA (OAHI>1<5/h) in 59% of children. Male gender and habitual snoring predicted OSA but did not have independent predictive power in the presence of the other factors. Age in months, BMI, and tonsillar size did not predict OSA.	Moderate to severe OSA is common in very young children with DS. Examination of tonsillar size did not predict OSA severity. Population-based screening for OSA is recommended in these children and domiciliary cardiorespiratory polygraphy offers an acceptable screening approach. Further research is needed to understand the natural history, associated morbidity, optimal screening methodology, and treatment modality for OSA in these children.
Maris et al., 2016[46]	Case series-PSG and questionnaire to parents/ caregivers	122 (DS)	4–18 years	5 years	The overall prevalence of OSA was 66.4%.	A significant inverse correlation was found between age and AHI
Maris et al., 2016[37]	DISE e PSG	41 (DS)	4.2 years	5.5 years	Adeno-/tonsillar obstruction was found in 75.6% of the patients, and these patients subsequently underwent UA surgery; A multilevel collapse was present in 85.4%. Tongue base obstruction was present in ten patients (24.4%) and epiglottic collapse in 48.8%; A significant improvement in oAHI from 11.4/h to 5.5/h was found, but persistent OSA was present in 52% of the children.	Most patients with DS and OSA present with multilevel collapse on DISE. Adenotonsillectomy results in a significant improvement of the oAHI; however more than half of the patients had persistent OSA, probably due to multilevel collapse.
Maris et al., 2017[44]	PSG	34 (DS)	2.7–5.8 years	5.5 years	The majority presented with severe OSA (58.9%). AT was performed in 22 children, tonsillectomy in 10 and adenoidectomy in two. Postoperatively, a significant improvement of the OAHI was measured from 11.4/hour to 3.6/hour, with a parallel increase of the minimum oxygen saturation. Children with initially more severe OSA had	AT results in a significant improvement of OSA in children with DS without a change in sleep efficiency or sleep stage distribution. Severe OSA was associated with a larger reduction of OSA severity.

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Table 2. Continuation.

Author/year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
					significantly more improvement after UA surgery. Persistent OSA was found in 47.1% of the children.	
Brockmann et al.; 2016[14]	Case Control-HPSG	44 (DS)	3.6 years	-	83% of individuals obtained HPSG results comparable to PSG; 61% of the study subjects had OSA, 18% of which were mild to moderate cases.	A portable polysomnographic home device may be helpful for diagnosing OSA in children with DS.
Diercks et al., 2016[62]	Hypoglossal nerve stimulator (HGN) Case report	1 (DS)	14 years	6 months	Hypoglossal nerve stimulator therapy was well tolerated and effective, resulting in significant improvement in the patient's OSA (overall AHI: 3.4 events/hour; AHI: 2.5–9.7 events/hour at optimal voltage settings depending on sleep stage and body position). Five months after implantation, the patient's tracheotomy was successfully removed and he continues to do well with nightly therapy.	The study demonstrated that the therapeutic measure obtained a well-tolerated and effective result, significantly reducing the patient's respiratory impairment.
Ono et al., 2015[33]	Case series-Questionnaire	90 (DS)	16.6 years	-	71% of the sample suffered from snoring, 59% had excitation, 25% apnea, and 22% nocturia; 24% had an unusual sleep posture, with the majority being from 6 to 15 years old (52%); Nocturia was the strongest predictor of unusual sleep positions for all OSA symptoms.	Symptoms related to OSA such as snoring and arousal are frequently observed in Japanese people with DS. Anatomical factors might contribute to the pathogenesis of OSA in people with DS, especially in the younger age groups. The high prevalence of unusual sleep postures may indicate a need to protect or compensate for OSA in people with DS who were less likely to be obese.
Brooks et al., 2015[26]	PSG, MSLT and neuropsychological tests	25 (DS)	7.2–18.7 years	1 year	The study demonstrated that the clinical findings were not predictive of the presence of OSA (PSG identified OSA in 10 out of 25). The author presented that there was no divergence in neuropsychological tests between children who had and did not have OSA.	Although SDB is common in children with DS, it is not a major contributor to their cognitive deficits. Cognitive function is related to the amount of sleep and particularly slow wave sleep. Successful treatment of SDB may improve their attention.
Thottam et al., 2015[39]	PSG in the pre and postoperative period of AT	36 (DS)	9.0 years	5.5 years	Children with DS who underwent surgery showed significant reductions in PSG obstructive and central AHI; 86.7% of children with DS presented a significant reduction in AHI for moderate or mild disease and 66.7% had resolution of central sleep apnea in the postoperative period.	Children with DS who underwent AT demonstrated significant reductions in both obstructive and central apneic indices on PSG. A significant number of patients with central sleep apnea demonstrated resolution postoperatively.

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Table 2. Continuation.

Author/year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
Coverstone et al.; 2014[15]	PSG and McGill oximetry score	119 (DS)	7.0 years	3.5 years	OAHI was ≥2.5 for 50% of all individuals; 36.1% had McGill equal to 2 and 14.3% equal to 3 or 4; McGill oximetry scores 3 and 4 are related to OSA and indicate clinical follow-up.	McGill oximetry scores of 3 or 4 reliably identified patients with marked OSDB. The possibility of central apneas causing hypoxemia must be considered in those with McGill Score 2.
Lin et al., 2014[19]	Case series-PSG and McGill oximetry scale	49 (C) 49 (DS)	6.3 (C) 6.2 (DS) years	-	34.69% of children with DS presented OSA; OSA in children with DS was more severe than in children in normal development; Children with DS had a higher mean of pCO_2 during sleep and worse scores on McGill oximetry.	Children with DS have more complicated OSA and more impaired gas exchange compared to children in the control group, with similar symptoms.
Breslin et al., 2014[27]	Case series-PSG and cognitive assessment	38 (DS)	9.7 years	3 months	Among children with DS, mean verbal IQ score was 9 points lower in those with comorbid OSA (AHI>1.5) than in those without OSA, and performance on measures of cognitive flexibility was poorer. Children with OSA showed increased light-stage sleep at the expense of slow-wave sleep.	The results suggest that more work is needed to understand the influence of poor sleep on learning in DS and other neurodevelopmental syndromes, many of which demonstrate disordered sleep to some extent.
Stores et al., 2014[47]	Case series-Questionnaire, Oximetry	31 (DS)	2.3–16.7 years	-	No significant association was found between objective measures of restlessness during sleep and 'snoring', nor were objective measures of restlessness related to reductions in overnight blood oxygen levels. -The objective measure of snoring was significantly associated with reductions in overnight blood oxygen levels.	The overnight measures used in the present study proved feasible and largely acceptable to the children and their families. More time spent familiarizing children with the procedure and the use of more recently developed recording systems would be likely to improve the success rate with this particular procedure.
Austeng et al., 2014[40]	Case series-PSG	29 (DS)	8.0 years	-	AHI>1.5 in 28 of 29 children and an OAI>1 in 24 of 29 children. 19 children (66%) had an AHI>5 and 17 children (59%) had an OAI>5 which indicated moderate to severe OSA. No correlation was found between OSA and obesity or gender.	The high prevalence of disease found in these previously undiagnosed 8-year-old children underlines the importance of performing OSA diagnostics in children with DS throughout childhood. These findings suggest that the prevalence of OSA remains high up to early school years.

OSA: obstructive sleep apnea; DS: Down syndrome.

of DS patients, the first with younger individuals (4 to 6.9 years) and the second with older children (over 11 years). Parasomnia was reported significantly less frequently with increasing age, which is also seen in normally developed children. In children with DS, in contrast to children with normal development, a decrease in the prevalence of sleep anxiety with increasing age was observed. Delay in falling asleep occurred more frequently in children with DS than children with normal development. Sleep onset delay in DS was significantly more common with increasing age and in children with sleep anxiety. Daytime sleepiness occurred more frequently among boys, regardless of age[20].

Gomes et al. examined the electrical activities of the masseter and temporal muscles in patients with DS.

Table 3. Synthesis of articles selected for systematic review about other sleep-related problems in Down syndrome (other than obstructive sleep apnea); (age>18 years).

Author/year	Study	Nº of patients	Mean of age (years/ months)	Time of follow up	Outcome	Conclusion
Gomes et al., 2020[25]	Case series-maximum mouth opening-MMO; maximum bite force-MBF; maximum voluntary clench-MVC	35 (C) 35 (DS)	19–40 years	-	Electrical activities of the masseter and temporal muscles (at rest and in maximum voluntary clench-MVC), maximum bite force-MBF, and maximum mouth opening-MMO were investigated.	Masseter and temporal muscle hypotonia were found in all atypical subjects with DS. This muscle dysfunction strongly was related to overweight/obesity, risks for development of cardiovascular/metabolic diseases, OSA severity, successive snoring episodes, and salivary flow reduction in DS.

OSA: obstructive sleep apnea; DS: Down syndrome.

Table 4. Synthesis of articles selected for systematic review about other sleep-related problems in Down syndrome (other than obstructive sleep apnea); (age<18 years).

Author/Year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
Chawla et al., 2021[24]	Case series-CSHQ and sleep clinic	76 (DS)	-	-	The first study to report the prevalence of sleep problems in Australian children with DS and to compare a community and referred group of children with DS directly.	This study reports a high prevalence of sleep problems in both a community and referred group of Australian children with DS, and suggests that there are many children with DS and sleep problems, particularly non-respiratory difficulties, who are potentially not receiving adequate treatment.
Santoro et al., 2021[34]	PSG	82 (DS)	<18 years	-	Reported sleep positions were skewed towards lateral/ decubitus (82.9%) compared to prone (11.0%) and supine (6.1%). This was consistent with hypnogram data where 71% of total sleep time in lateral/decubitus positions compared to prone (13%) and supine (6%). Tonsillectomy was associated with lower obstructive AHI (OAHI) Sleep position was not associated with age, gender, race, ethnicity, nor history of tonsillectomy. Preferred sleep position was not correlated with OAHI or OSA severity.	This study highlights the possibility that children with DS may have preferential sleep positions that cater to optimized airflow in the context of OSA, although further prospective study is needed.
Shaw et al., 2021[29]	DSM 5 criteria and individual medical record numbers (MRN's) Chi-square test and Fisher's exact AND Student's *t*-test	370 (DS)	2–17 years	1.5 year	Compared to typically developing children, children with DS may have more challenges with adaptive functioning in the school setting (examples include complying with directions and task persistence). Parents and teachers report higher rates of	Developmental/behavioral assessment is integral for detection of co-morbid conditions among a pediatric DS population and prevention of diagnostic overshadowing.

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Table 4. Continuation.

Author/Year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
					non-compliance in children with DS compared to those without DS secondary to their executive functioning and adaptive deficits	
Bassam et al., 2021[31]	Heart rate (HR) and pulse transit time (PTT) (a surrogate inverse measure of BP change)	19 (DS) 19 (C)	3–18 years	-	Children with DS exhibited reduced nocturnal dipping of HR during total sleep. Fewer children with DS exhibited a greater than 10% fall in HR between wake and REM sleep compared to TD+children.	Findings demonstrate significantly reduced nocturnal dipping of HR in children with DS compared to TD children matched for SDB severity, suggesting SDB has a greater cardiovascular effect in these children. Further studies are required to fully understand the mechanisms involved and to assess if treatment of SDB improves nocturnal dipping.
Siriwardhana et al., 2021[32]	PSG, nasal pressure, and transcutaneous carbon dioxide ($TcCO_2$)	14 (DS) 14 (C)	3–19 years	2.5 years	Children with Down syndrome also had significantly lower average oxygen saturation associated within each analysis window compared to typically developing children	Higher loop gain in children with Down syndrome and sleep disordered breathing indicates that these children have more unstable ventilatory control, compared to age, gender and sleep disordered breathing severity matched typically developing children. This may be due to an inherent impairment in ventilatory control in children with Down syndrome contributing to their increased risk of sleep disordered breathing, which may inform alternative treatment options for this population.
Richard et al., 2020[42]	Case series-PSG and clinical files	28 (DS) 28 (C)	<18 years	5 years	Mean transcutaneous partial pressure of carbon dioxide (PtcCO2) during sleep was significantly higher in patients with DS compared to controls.	This was the first study to compare nocturnal gas exchange in children with DS to a control group of children with similar OSA, but not DS. Data demonstrated that children with DS have increased transcutaneous partial pressure of carbon dioxide ($PtcCO_2$) regardless of the presence of OSA and its severity. This may be due to respiratory muscle hypotonia and/or ventilatory control alteration in patients with DS.
Giménez et al., 2018[16]	Case series-PSG, self-reports and, actigraphy.	35 (C) 47 (DS)	39.2 (C) 39.6(DS) years	-	Adults with DS had lower sleep efficiency, lower %REM, higher prevalence of OSA (78 *versus* 14%) and a higher AHI than patients in the control group. The DS group questionnaires (PSQI and ESS) did not reflect the sleep disorders detected in the PSG.	Adults with DS have more sleep disorders, especially OSA. Sleep disorders were not detected by self-reported sleep measures. Actigraphy, PSG and simplified devices validated for OSA screening are important tools for diagnosis.
Maris et al., 2016[20]	Case series-CSHQ and PSG	54 (DS)	8.9 (C) 7.5 (DS) years	-	According to the CSHQ, 74.1% of children with DS had sleep problems.	Children with DS have a significantly higher prevalence of sleep problems, compared to.

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Table 4. Continuation.

Author/Year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
					The general sleep problems were not related to age or gender, however, boys suffer more from daytime sleepiness. Symptoms of respiratory sleep disorders are related to parasomnias, longer sleep duration, and more daytime sleepiness.	normal developing healthy school-aged children. No correlations were found between the relative reports on sleep problems and the underlying OSA or severity of OSA.
Ong et al., 2018[56]	Case series- Retrospective cohort database analysis	51292 (DS)	0–20	15 years	Tonsillectomy with adenoidectomy was the most common procedure in both groups, but the proportion of tonsillectomy with adenoidectomy decreased over time. -The proportion of palatal surgery and tracheostomy also decreased significantly, whereas there was an increase in the proportion of lingual tonsillectomies, tongue-base reduction procedures, and supraglossoplasty performed in both groups over time. The relative rates of change in these procedures were higher in the DS population.	Tonsillectomy with adenoidectomy remains the most commonly performed procedure, although there was a significant increase in other sleep surgeries performed (LT, tongue-base reduction, and supraglossoplasty) between the two study periods, especially in children with DS.
Mylavarapu et al., 2016[64]	Computational fluid dynamics, virtual surgery, CT and MRI	10 (DS)	5 years	-	There was a reduction, in 8 out of 10 patients, of AHI and the resistance of upper airway, when compared to baseline values.	This study highlights the need for future studies, before using this technique in surgical plans.
Hoffmire et al., 2014[23]	Case series- CSHQ and PSQ	107 (DS)	7–17 years	2 years	65% of children with DS had sleep problems in the CSHQ, but these problems were not reported by their parents; In PSQ, 46% of children had sleep-related breathing problems and 21% sleep-related movement disorders; Children with asthma, autism and a history of enlarged adenoids and tonsils had more frequent sleep problems than children without these comorbidities.	Sleep disorders are important but also under-recognized problems in children with DS. It appears to be correlated with some prevalent comorbidities, which may provide guidance to augment current practice guidelines to evaluate sleep problems in this population.
Nisbet et al., 2014[36]	Case series- PSG and body posture record during sleep	76 (C) 76 (DS)	5.1 (C) 4.6 (DS) years	4.5 years	Sensor-recorded position (supine, prone, lateral) was expressed as the percentage of total sleep time. The apnea-hypopnea index (AHI) was calculated in each sleep state (NREM, REM), position, and position-sleep state combination. AHI was higher in REM than NREM; nonetheless, the NREM AHI was higher in DS than NREM AHI that controls.	In DS and non-DS children alike, respiratory events are predominantly REM-related. However, when matched for OSA severity, children with DS have a higher NREM AHI, which is worse in the supine position, perhaps indicating a positional effect compounded by underlying hypotonia inherent to DS.

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Table 4. Continuation.

Author/Year	Study	Nº of patients	Mean age (years/ months)	Time of follow up	Outcome	Conclusion
					The percentage of prone sleep was greater in DS than controls, but of supine or non-supine sleep was not different between them.	
Konstantinopoulou et al., 2016[41]	Case series-PSG, ECG and BPN	23 (DS)	2.7 months	-	At four months, there were no changes in cardiovascular outcomes or sleepiness between those on actual versus sham CPAP. Hours of actual CPAP use were associated with improved left ventricle function.	In children with DS, left ventricle diastolic function correlated with OSA severity, which improved with the use of CPAP. There was a tendency towards increased sleepiness in those with OSA, which correlated with the rate of awakening.
Senthilvel and Krishna, 2011[35]	PSG	17 (C) 17 (DS)	6 years	1.5 year	History of previous tonsillectomy (41%), congenital heart disease (of any type) (82%) and hypothyroidism (41%) of SD compared to 24%, 12 and 0%, respectively of C. SD assumed a unique body position sitting cross-legged flopped-forward with head resting on bed while asleep.	Some DS children assume a peculiar body position, sitting cross-legged flopped-forward with head resting on bed while asleep. This is absent in age and gender-matched controls showing otherwise similar PSG characteristics. The reason for this posture is unclear from this study.

OSA: obstructive sleep apnea; DS: Down syndrome.

These activities are atypical in these patients, indicating that DS patients are at greater risk for overweight/obesity, cardiovascular/metabolic diseases, OSA severity, and a salivary flow reduction [25].

Sleep disordered breathing in patients with Down syndrome and its negatives effects on cognitive function

Several studies have been done associating sleep parameters and cognitive functions. In one interesting study, neurophysiological parameters obtained in the PSG and multiple sleep latency test (MSLT) were correlated with the answers in cognitive tests, and found that shorter total sleep duration and greater sleepiness were associated with poorer cognitive function in patients with DS. Furthermore, the lowest percentage of slow-wave sleep was found to be a predictor of better adaptive behavior and academic performance in individuals with DS. Another important finding was that appropriate treatment of sleep-disordered breathing in DS patients resulted in better cognitive performance, especially in the area of attention[26].

Lee et al. compared the results of PSG studies and cognitive scales assessing language, behavior, and intellectual performance in patients with DS. They found that reduction in the percentage of REM sleep and the presence of OSA were associated with impaired language function in patients with DS[18]. Other studies with similar designs have correlated a reduction in slow-wave sleep with poorer performance in verbal learning and executive functions in patients with DS[26-30].

In addition, children with DS are at higher risk for sleep disordered breathing (SDB), which can negatively affect the cardiovascular system. Besides, the risk of future cardiovascular events is increased in these patients due to decreased nocturnal reduction in heart rate (HR) and blood pressure (BP)[31].

Another study discussed the unstable ventilatory control that is more common in children with DS. This finding indicates that these children are at greater risk for sleep disordered breathing than patients without DS[32].

Sleep related movement disorders and unusual sleep postures in Down syndrome patients

Sleep problems in children with DS go beyond OSA and other sleep-disordered breathing. Sleep-related movement disorders are also more common in individuals with DS[20,23]. Hoffmire et al. observed that 21% of children with DS were positive for sleep-related movement disorders measured with the CSHQ. Also, this risk was associated with asthma, autism, and a history of enlarged adenoids and tonsils[23].

Other previous studies applied questionnaires and found that atypical positions such as leaning forward with legs back, leaning forward with legs forward, leaning forward with legs crossed, and sitting were common and were often related to the presence of OSA diagnosis[33]. Additionally, patients

with DS commonly present the unique position of sitting with a flopped-forward body in which the head rests on the bed while asleep, which contributes to optimized airflow[34]. The reason for this position is unclear, but authors conjectured that this may be a protective mechanism for airway patency[35].

Another study used PSG and recording of body positions during sleep using sensors. Subjects with DS spent a significantly longer duration of sleep in the prone position and less in the right lateral decubitus position compared to subjects without the paired syndrome by age and sex[36].

OBSTRUCTIVE SLEEP APNEA IS THE MOST PREVALENT SLEEP DISORDER IN PATIENTS WITH DS

As previously mentioned, OSA is the most prevalent sleep disorder in these patients, and there are a few reasons for this. Maris et al. found that children with DS have anatomical narrowing of the upper airway at different levels and are more prone to collapse and thus at higher risk for OSA. Other factors contribute to explain the association between OSA and DS such as muscle hypotonia, higher incidence of congenital heart disease, hypothyroidism, lung disease, immunodeficiency, relative macroglossia (due to smaller bone framework of mandible and maxilla)[37].

Some studies have included a control group of children and adolescents without DS and found a prevalence of less than 20% of OSA, highlighting the important association between DS and OSA[16,21,22,38,39]. Some authors claim that individuals with DS have more severe OSA and greater refractoriness to treatment[16,19,39,40].

According to studies by Konstantinopoulou et al., left ventricle diastolic function correlates with the severity of OSA, which improves with the use of continuous positive airway pressure (CPAP). In addition, they noted a tendency for increased sleepiness in individuals with OSA, which was correlated with the awakening index. Further studies are needed to confirm the findings described[41].

Coverstone et al. evaluated the probability of developing OSA in DS patients with pulse oximetry and classified them according to the McGill score. Patients with McGill score 3 or 4 (more than 3 desaturations below 80–85% in one night of sleep) or McGill score 2 with increased body mass index (BMI>25 kg/m^2) were referred by an otorhinolaryngologist due to their increased risk of adenotonsillar hypertrophy. The authors suggest that patients with low McGill scores should be monitored regularly by a specialist to obtain continuous assessment[15].

Nicolas et al. conducted the first study to compare nocturnal gas exchange in children with DS with a control group of children with similar OSA. They concluded that patients with DS have respiratory muscle hypotonia and/or an alteration in ventilatory control[42].

Nisbet's study showed that children with DS and OSA had a similar dominance of rapid eye movements (REM) in breathing events compared to children with OSA and without DS, but the children with DS had a higher NREM apnea-hypopnea index (AHI), even though they were similar in terms of total AHI and had a similar percentage of sleep time in NREM. Notably, children with DS in supine position had a higher NREM AHI than in the non-supine position[36].

Obesity and other possible predictive variables for obstructive sleep apnea in patients with Down syndrome

The association between obesity and the occurrence or severity of OSA in patients with DS is controversial. Most studies included that no correlation exists between higher BMI and OSA in this population[14,17,19,33,40,43,44], but it should be noted that most of these studies included children only.

On the other hand, Chamseddin et al. correlated obesity not only with a higher occurrence of OSA in DS patients, but also with a high severity of OSA[45]. Similarly, two other studies reported that patients with DS, who had high BMI and/or hypothyroidism, had greater upper airways narrowing and consequently a higher severity of OSA. They also highlight the importance of preventing obesity in adolescence to reduce the incidence of OSA in adults with the syndrome[15,16]. Therefore, there is no consensus among researchers on the relationship between OSA and overweight/obesity.

There are some predictive variables for the occurrence of OSA in patients with DS, such as presence of parasomnias, longer total sleep time, daytime sleepiness, snoring, witnessed apnea and nocturia[18,23,27,33,43,46]. Hoffmire et al. described that the presence of asthma or allergic rhinitis is not related to an increased risk of OSA in patients with DS[23]. In addition, there is no consensus among researchers on the association between gastroesophageal reflux disease (GERD) and OSA in this population[23,43]. Nehme et al. pointed out that the symptoms of GERD may be similar to those of OSA, leading to a better performance of the PSG exam, which could contribute to a greater identification of OSA in these patients[43].

Screening methods and biomarkers for obstructive sleep apnea in patients with Down syndrome

Although PSG is considered the gold standard examination to define OSA, screening methods have been investigated to evaluate sleep disorders in this population. Considering the technical difficulties in performing PSG, the lack of availability of the exam, and its high cost, alternatives must be sought. In this manuscript, it was shown that only about 50% of selected studies used PSG to define OAS in DS patients. Although the presence of restlessness and snoring are important indicators of OSA in patients with DS, no significant association between these indicators and low oxygen saturation was found in the Stores et al. study. Therefore, the authors suggest that the presence of restlessness may be an

important clinical feature to assess the need for a PSG[47,48]. Questionnaires and clinical and laboratory data are used to identify moderate to severe OSA in this population[49].

Another alternative is screening by home pulse oximetry (HPO), which could halve the number of children with DS who need multichannel sleep studies[50]. Although these tests are useful, they cannot be used in isolation to diagnose breathing-related sleep disorders[47,50].

Two studies have used questionnaires as a tool for diagnosing OSA. In the first study, conducted by Hoffmire et al., the CSHQ and the Pediatric Sleep Questionnaire (PSQ) were applied[23]. In the second study, conducted by Maris et al., the CSHQ and the PSG were used as auxiliary tools for diagnosis[20]. Both studies concluded that a large number of children with DS had sleep behavior disorders (insomnia, parasomnias) and sleep-related breathing problems, but curiously, their caregivers did not complain of such conditions. No relationship was found between the scores obtained in the CSHQ and the OSA index[20,23]. Therefore, the isolated use of questionnaires as a screening tool for OSA does not seem to be an effective method.

In an interesting study conducted at Boston Children's Hospital, a predictive model was created to help screen for OSA in patients with DS. The variables used were age, sex, race, height, weight, BMI, sedentary behavior, blood pressure, peripheral O_2 saturation, neck circumference, macroglossia assessment, Mallampatti classification, Friedman/Brodksy scores, classification of scores, and current treatment for asthma, GERD, or thyroid disease. Results of the following scales and questionnaires were also used: PSQ, CSHQ, and Sleep Disorders Scale (SRBD), which were applied to parents and/or guardians. Using a logic learning machine, the best model had a validated negative predictive value of 73% for mild OSA and 90% for moderate or severe OSA. The final model revealed that the most relevant variables (out of 101) were certain CSHQ questions, SRBD questions, and the hypertension percentile. The study shows promising results with models using clinical data and questionnaires and may be an interesting tool for screening OSA in patients with DS[51].

Similarly, Beppler et al. have developed a prototype called PediBand to help diagnose OSA in patients with DS. PediBand assesses the following physiological parameters: heart rate and its variability, respiratory rate, and O_2 saturation. This model is a promising tool to investigate sleep disordered breathing in DS. However, as it is still a prototype, further clinical studies are needed to strengthen the evidence for its use[52].

OSA biomarkers have also been studied in individuals with DS. Elsharkawi et al. measured biomarkers such as epinephrine, norepinephrine, dopamine, serotonin, glycine, taurine, γ-aminobutyric acid (GABA), glutamate, phenylethylamine (PEA), aspartic acid, histamine, 3,4-dihydroxyphenylacetic acid (DOPAC), 5 hydroxy acid (5-HIAA), tyramine, and tryptamine in DS patients with OSA, DS patients without OSA, and in healthy controls, which were equal in age and gender. The results showed that epinephrine, norepinephrine, dopamine, and taurine were good predictors of the presence or absence of DS, but these results were not statistically significant in distinguishing the presence or absence of OSA in these patients. Thus, these urine biomarkers were ineffective tools for screening OSA in individuals with DS[53]. It should also be noted that the low availability of the tests and the technical difficulties in performing them are major obstacles to its use in clinical practice.

Jayaratne et al. conducted a 3D comparison of patients with and without OSA. An anthropometric analysis scheme was developed to quantify facial norms with well-defined reference points focusing on the soft tissues of the external morphology. Most anthropometric measures were lower in individuals with DS, indicating maxillomandibular hypoplasia and reduced measures of the nose, ears, and eyes. However, the authors compared patients with DS and OSA versus patients with DS and without OSA and found no significant differences in these measures. A limiting factor was the restriction to ethnicity (Caucasians only), which requires a more in-depth analysis of different ethnicities and a wider age range[54].

Treatment options for obstructive sleep apnea in patients with Down syndrome and new perspectives

The main treatment options for OSA in DS patients are CPAP, surgery, and weight control. Several therapeutic alternatives have been studied, considering that CPAP therapy is not always available or tolerated, that surgical intervention is not always appropriate, and that there is no consensus on whether there is a direct relationship between obesity and OSA in patients with DS.

Several studies indicate that adenotonsillectomy (AT) is still the gold standard for the treatment of OSA in patients with DS[37,39,44,55-58]. Other possible interventions include lingual tonsillectomy (LT) and supraglossoplasty (SGP). LT may be considered in the context of residual OSA after AT, despite its lower efficacy[56]. The authors emphasize the importance of surgical planning with the identification of upper airway obstruction sites and the main tool for this purpose is drug-induced sleep endoscopy (DISE)[20,59,60].

Concerning drug treatment, further studies are needed to clarify its role in the OSA in patients with DS. Intranasal corticosteroids may contribute to a local anti-inflammatory effect by reducing apnea, but the effectiveness has not been fully demonstrated. A retrospective study showed that children who underwent AT and used nasal corticosteroids had less residual OSA than children who did not undergo this drug treatment. Considering the small sample size of the study, the role of medication in the treatment of residual OSA in DS remains uncertain[60,61].

One of the new interventions that have been studied is myofunctional orofacial training (MT). MT is based on the principle of strengthening orofacial and cervical functions for muscular balance, thereby reducing the chances of recurrences due to the maintenance of inadequate functional patterns[58]. Diercks et al., on the other hand, pioneered the investigation of a hypoglossal nerve stimulation implant in the pediatric range as a prospect for treating a patient with DS associated with severe OSA. The study demonstrated that the therapeutic intervention produced a well-tolerated and effective outcome and significantly reduced the patient's respiratory impairment[62,63].

Three-dimensional reconstruction models from imaging exams — such as computer tomography (CT) and magnetic resonance imaging (MRI) — look promising, but studies with a larger sample of patients are needed to verify their real effectiveness[64,65].

In conclusion, individuals with DS are at high risk of developing sleep-related breathing disorders, mainly due to anatomical changes in the upper airway. The presence of sleep disorders contributes to the deterioration of cognitive function in patients with DS. PSG is the gold standard exam for determining OSA, but the high cost and difficulty of technical approach are pushing for better options. OSA is the most studied sleep disorder in patients with DS and its main treatment is AT. There are some emerging perspectives on OSA treatment in patients with DS, but high-quality trials of multimodal interventions are needed to provide robust evidence for the treatment of OSA in DS individuals.

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"I'm gonna lose my strength, I'm gonna seize and die, And all that Jazz"! Neurological diseases in jazz legends

"I'm gonna lose my strength, I'm gonna seize and die, And all that Jazz"!
Doenças neurológicas em lendas do jazz

Francisco Manoel Branco GERMINIANI[1], Carlos Henrique Ferreira CAMARGO[2], Léo COUTINHO[1], Hélio Afonso Ghizoni TEIVE[1,2]

ABSTRACT
Even though jazz is a musical style that excels in improvisation and virtuosity, it is not without its share of anecdotes, drama, and downright tragedy, and the biographies of jazz musicians and their demise are fraught with ominous and dire straits. Unsurprisingly, some would develop chronic and fatal diseases. The neurological diseases that afflicted the following six composers and musicians, all of whom are considered jazz legends, are briefly discussed: Charles Mingus, diagnosed with amyotrophic lateral sclerosis; Lester Young and Charlie Parker, both diagnosed with neurosyphilis; Thelonius Monk, who had possible frontotemporal dementia; George Gershwin, who died as a result of brain glioma; and Cole Porter, who developed phantom limb pain following an amputation. The association of lifestyles, with drug abuse, particularly alcohol and heroin, in addition to great sexual promiscuity factors contributed to the development of a series of diseases such as syphilis. In addition, we also described some fatalities such as neurodegenerative diseases and cerebral glioma.

Keywords: History of Medicine; Nervous System Diseases; Music.

RESUMO
Embora o *jazz* seja um estilo musical que prima pela improvisação e pelo virtuosismo, não é isento de drama e tragédia, e as biografias dos músicos de *jazz* e a sua morte estão repletas de dificuldades sinistras e terríveis. Alguns desenvolveriam doenças crônicas e fatais. São brevemente discutidas as doenças neurológicas que afligiram os seguintes seis compositores e músicos, todos eles considerados lendas do *jazz*: Charles Mingus, diagnosticado com esclerose lateral amiotrófica; Lester Young e Charlie Parker, ambos com neurosífilis; Thelonius Monk, que teve uma possível demência frontotemporal; George Gershwin, que morreu em decorrência de glioma cerebral; e Cole Porter, que desenvolveu dor de membro fantasma após uma amputação. A associação do estilo de vida com o abuso de drogas, particularmente álcool e heroína, além de promiscuidade sexual, contribuiu para o desenvolvimento de uma série de doenças, por exemplo, a sífilis. Também descrevemos algumas fatalidades, como doenças neurodegenerativas e glioma cerebral.

Palavras-chave: História da Medicina; Doenças do Sistema Nervoso; Música.

INTRODUCTION

In the 19th century *fin-de-siècle* New Orleans, a new musical manifestation emerged: jazz music. This new phenomenon had its roots in the blues, a form of folk music created by African Americans, and ragtime, a black version of European piano music[1,2].

Jazz would reach its heyday in the second half of the 20th century, initially in the USA. During this period, it existed in various forms and was being performed and written by great musicians and composers, some of whom became jazz legends[1,2,3].

The purpose of this review was to briefly discuss the neurological diseases that affected a select group of jazz musicians and composers, some due to their lifestyles and some due to fatality.

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Authors' contributions: FMBG, CHFC, LC: execution, review, and critique; HAGT: conception, organization, execution, review, and critique. The manuscript has been read and approved by all authors, and there are no other persons who satisfied the criteria for authorship and hence are not listed. The order of authors listed in the manuscript has been approved by all of us.

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CHARLES MINGUS AND AMYOTROPHIC LATERAL SCLEROSIS

Charles Mingus (1922–1979) (Figure 1A) was a jazz composer and a gifted double bassist. During his career, he received distinctions from various institutions, such as the National Endowment for the Arts, the Smithsonian Institute, the Guggenheim Foundation, and Yale University[4,5,6]. In the 1970s, Mingus experienced progressive lower limb weakness associated with muscle atrophy; in 1977, the diagnosis was done for amyotrophic lateral sclerosis (ALS)[3,4,5,6]. He worsened progressively and used a wheelchair until his death in 1979[3,4,5,6].

THE ENIGMATIC DISEASE OF THELONIUS MONK

Thelonius Sphere Monk (1917–1982) (Figure 1B) was considered an innovator and the founder of bebop, a new type of jazz[6,7]. He was a frequent consumer of alcohol and hallucinogenic drugs, particularly heroin, leading to his arrest and banishment from performing in New York City for 6 years[3,6,7]. There is clear evidence that Monk had depressive behavior, developing progressive mental confusion intermingled with episodes of intense restlessness and excitement, followed by periods of depression, apathy, and mutism; in the 1960s, he was admitted to a psychiatric hospital in San Francisco, California[3,6,7]. He was diagnosed with "unclassified schizophrenia," but his psychotic and cognitive conditions worsened, culminating in complete mutism[3,6,7]. In retrospect, the possible diagnoses could be bipolar disorder and frontotemporal dementia (FTD), starting with behavioral disorder followed by language disorder and subsequent dementia. Another possibility is cerebrovascular disease secondary to substance abuse[3,6,7]. In 1982, Monk suffered a stroke and died; the diagnosis with a ruptured cerebral aneurysm was questioned but never confirmed[3].

JAZZ MUSICIANS AND NEUROSYPHILIS

In 2017, Breitenfeld et al. retrospectively evaluated the diagnosis of neurosyphilis in about 1,500 composers and musicians, including many jazz artists.[8] The authors concluded that Lester Willis Young and Charles "Bird" Parker had neurosyphilis[8].

Extracted from Google images — (A) Newyorker.com; (B), (C) and (F) Britannica.com; (D) Alamy.com; and (E) interlud.hk.

Figure 1. (A) Charles Mingus (1922–1979); (B) Thelonious Monk (1917–1982); (C) Lester Young (1909–1959); (D) Charlie Parker (1920–1955); (E) George Gershwin (1898–1937); (F) Cole Porter (1891–1964).

Lester "Prez" Young (1909–1959) (Figure 1C) was a jazz saxophonist, who became addicted to alcohol and other drugs and developed cirrhosis, culminating in acute upper gastrointestinal bleeding and his consequent death. Young also had a history of coronary insufficiency and cognitive impairment with confirmed neurosyphilis[3,6,8,9].

Charles "Bird" Parker (1920–1955) (Figure 1D) was a jazz saxophonist who died very young as a result of acute pneumonia. He had a history of alcohol and heroin abuse with previous diagnoses of cirrhosis, upper gastrointestinal bleeding, and myocardial infarction[3,6,8,9,10]. Following a review of his medical records and based on the presence of behavioral and dementia disorders, as well as a positive Wasserman test, Parker was diagnosed with neurosyphilis[3,6,8,9,10].

GEORGE GERSHWIN AND BRAIN GLIOMA

George Gershwin (born Jakob Bruskin Gershovitz, 1898–1937) (Figure 1E) was a famous American composer[11,12,13,14,15]. In 1936, Gershwin started to present with several neurological symptoms and uncinate seizures (sudden episodes of a burning rubber smell followed by short episodes of "mental lapse")[6,11,12,13,14,15]. As his condition progressed, Gershwin experienced severe headaches associated with episodes of dizziness and behavioral disorders, developing signs and symptoms of intracranial hypertension before going into coma[6,11,12,13,14,15]. After his admittance to a hospital in 1937, ancillary tests revealed a cystic tumor with a mural nodule extending deeply into brain tissue. Despite urgent neurosurgery, he died in the immediate postoperative period; neuropathology confirmed the diagnosis with glioblastoma multiforme[6,11,12,13,14,15].

COLE PORTER AND PHANTOM LIMB PAIN

Cole Porter (1891–1964) (Figure 1F) came from a very wealthy family and studied at Yale and Harvard[13,16]. He remains one of the most outstanding composers the USA has produced[6,13,16]. In 1937, Porter fell from a horse and fractured his both femurs, leading to bacterial infection and consequent osteomyelitis; despite 33 operations, his staphylococcal osteomyelitis chronified[6,13,16]. He abused alcohol and narcotics because of the chronic pain and, in 1958, his right lower limb was amputated. He subsequently began to experience pain in the amputated limb and was diagnosed with phantom limb pain[6,13,16]. Porter died in 1964 from chronic renal failure[3,13,16].

PSYCHIATRY, NEUROLOGY, AND MUSICIANS

Psychiatry in the days of these jazzmen was mainly asylum-centered[3]. Mentally ill patients were institutionalized for life, as therapeutic prospects were neglected; the epidemics of neurosyphilis and alcoholism contributed to an increase in the number of patients locked in these facilities. Academic advancements in the field of psychiatry occurred in this period. Psychopharmacology remained incipient, but synthesis and clinical application of several compounds, such as bromides (1857), chloral (1869), barbiturates (1903), antihistamines (1942), and lithium (1948), were described until the 1950s. Other unusual treatment options of the time included infecting patients with malaria to treat neurosyphilis and inducing insulin coma to treat schizophrenia. Although substance abuse (first opium, chloral, and barbiturates, and later heroin) presented a vertiginous increase during the 19th and 20th centuries, it was not recognized as a relevant public health issue[17].

Tracing a parallel, the history of classical music presents many cases of neurological disease: neurosyphilis (Bedřich Smetana), ALS (Dmitri Shostakovich), stroke (Glenn Gould), aphasia (Vissarion Shebalin and Randall Thompson), Tourette's syndrome (Amadeus Mozart), and dystonia (Robert Schumann, Leon Fleisher, and Gary Graffman)[18,19].

It remains undisclosed if jazz musicians – or musicians in general – are more prone to neurological disease than the general population; their hedonistic lifestyle might have epigenetically contributed to genetically driven neurodegeneration.

In this historical review, the neurological diagnoses of six jazz composers and musicians were briefly discussed. The association of lifestyles, with drug abuse, particularly alcohol and heroin, in addition to great sexual promiscuity factors contributed to the development of a series of diseases, such as syphilis. In addition, we also described some fatalities: neurodegenerative diseases, such as ALS and frontotemporal dementia, and a case of cerebral glioma.

ACKNOWLEDGMENT

The title of this article was partly inspired by the song "All That Jazz," composed by John Kander and lyrics by Fred Ebb in 1975, for the musical Chicago.

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Acute hemorrhagic leukoencephalitis Associated with COVID-19

Leucoencefalite hemorrágica aguda associada à COVID-19

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A 64-year-old woman with diabetes and heart failure presented with severe coronavirus disease 2019 (COVID-19), remaining comatose after sedation withdrawal (Figure 1). Magnetic resonance imaging (MRI) showed bilateral subacute hematomas in the white matter, with significant mass effect (Figure 2). She was treated with high-dose intravenous methylprednisolone, but developed seizures, pulmonary bacterial infection, and ultimately died.

Acute hemorrhagic leukoencephalopathy has been previously reported in patients with COVID-19[1], and it is a possible diagnosis for this patient. As our patient presented larger hematomas than previously described[2] and received empirical anticoagulation due to a suspected pulmonary embolism, we speculate that an inflammatory process associated with SARS-CoV-2 could have been complicated by this therapy.

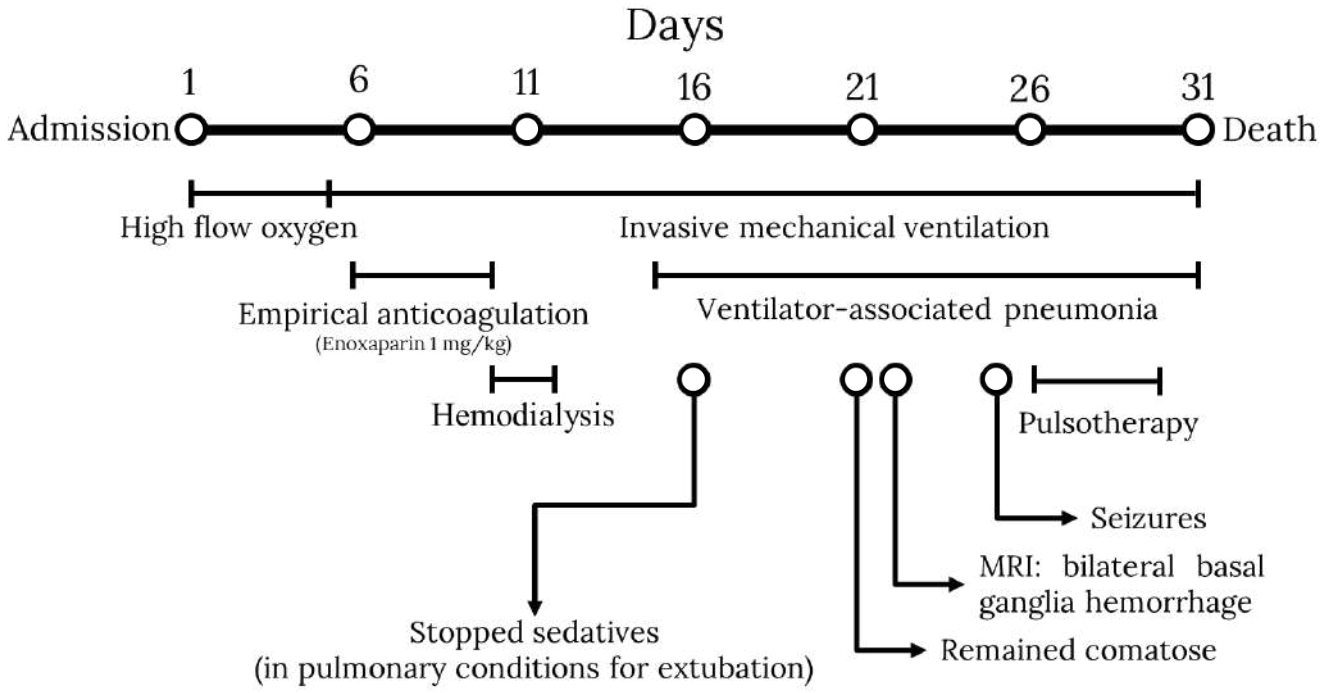

Figure 1. Hospital events timeline.

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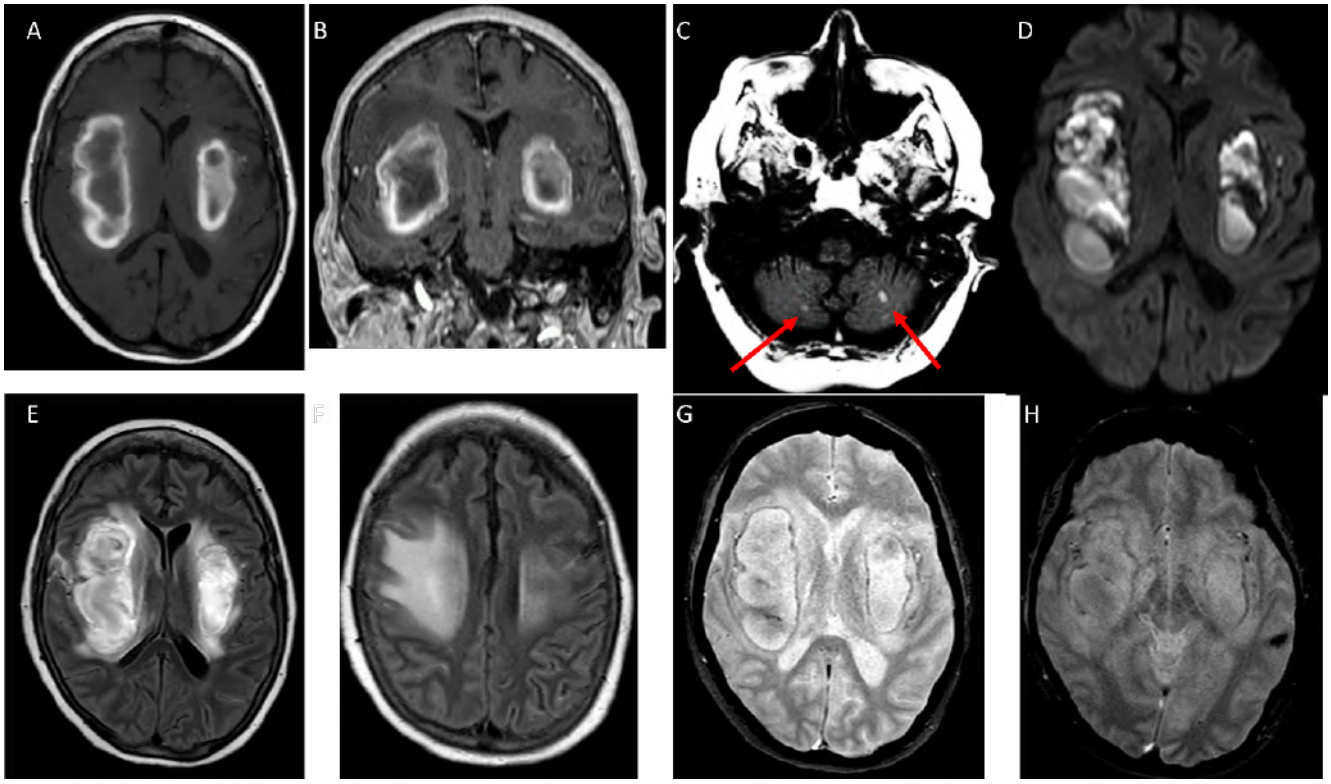

Figure 2. (A) Axial T1 spin eco (SE) showed central hypointense with peripheral hyperintense lesions on bilateral deep white matter with effacement of the lateral and third ventricles. (B) Coronal reconstruction of a volumetric T1 gradient-echo (GRE) showed central hypointense with peripheral hyperintense lesions on deep white matter. (C) Axial T1 SE showed two small hemorrhages on both cerebellar hemispheres (red arrows). (D) Diffusion-weighted imaging revealed possible restriction on bilateral deep white matter compatible with subacute hemorrhages. (E): Axial FLAIR at basal ganglia level showed hyperintensity lesions on bilateral deep white matter with surrounding edema. (F) Axial FLAIR at supraganglionic level showed extensive bilateral edema. (G): Axial T2* at basal ganglia level showed hyperintensity lesions on deep white matter with hypointensity due to subacute hemorrhages. (H) Axial T2* at lower basal ganglia level showed hyperintense lesions on bilateral deep white matter with hypointensity with blooming effect due to subacute hemorrhages and there was another small hemorrhage on the left temporal lobe.

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Atypical cutaneous presentation of tuberous sclerosis complex: Giant angiofibroma on the scalp

Apresentação cutânea atípica da esclerose tuberosa: angiofibroma gigante no couro cabeludo

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Tuberous sclerosis (TSC) is an autosomal dominant neurocutaneous syndrome characterized by several abnormalities, including benign tumors of the embryonic ectoderm in multiple organs, such as skin, eyes, and central nervous system[1]. The main dermatological manifestations of TSC are hypochromic macules (ash leaf spots), facial angiofibromas, fibrous cephalic plaques, periungual fibroids, shagreen patch, and confetti lesions[2].

A 26-year-old woman presented with a giant angiofibroma with an atypical and rare symptom of TSC, the main symptom being the skin lesions (Figures 1, 2, 3 and 4). The giant and asymmetric form is described as a rare presentation in the literature[3].

Figure 1. Massive lesion of soft parts in the occipital region presenting fibroelastic consistency, compatible with giant angiofibroma.

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Figure 2. Hyperchromic papule on the left forehead (A) and small hyperchromic papular lesions in the malar regions (B).

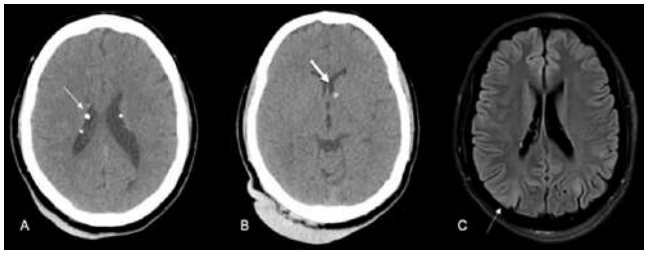

Figure 3. Typical lesions of tuberous sclerosis. In CT scans (A and B), it is possible to recognize subependymal nodules, some of which are calcified (arrow in A) and found in the topography of the left Monro foramen (arrow in B). Also, note the presence of giant occipital angiofibroma in these CT scans (A and B). FLAIR-weighted MRI image (C) showing evidence of hypersignal in the white and gray matters compatible with tubers.

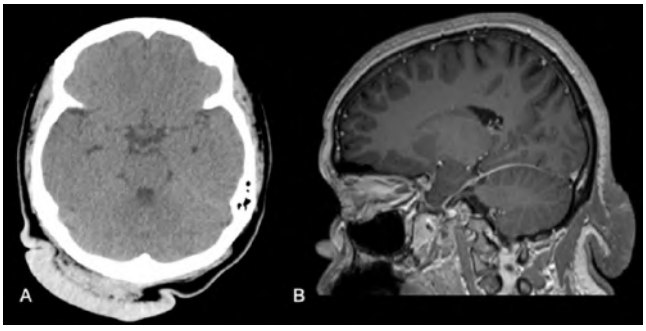

Figure 4. CT (A) and MRI scans (B) showing a soft tissue lesion characterized by marked cutaneous thickening in the occipital region.

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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.

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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. (0302040014 R4 Rev. Março 2021). www.ucb-biopharma.com.br. **Reg. MS - 1.2361.0083. 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 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. Á 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. (0302040013 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. (0302040021 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.

SAC: 0800 0166613

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