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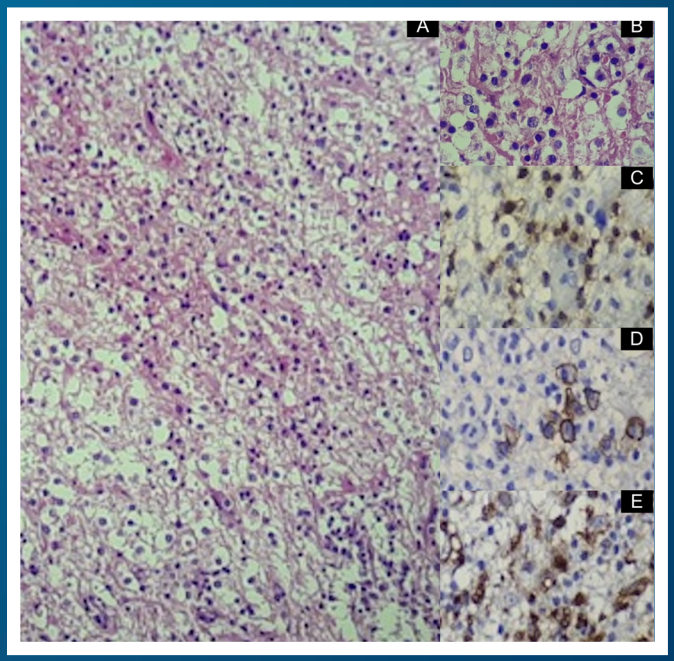

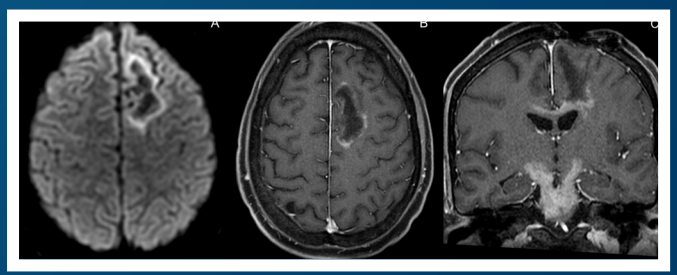

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Congresso Brasileiro de Neurologia 2022
Fortaleza.CE

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.

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EDITORIAL

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Predicting driving decline and assessing crash risk in a globally aging population

Prevendo o declínio das habilidades de direção veicular e avaliando o risco de acidentes no cenário de envelhecimento populacional global

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With the growth of the global population (7.920 billion, Jan 2022), the number of older adults (age 65 and older) will also increase when it reaches 1.5 billion by 2050. There is a parallel increase in life expectancy across many countries in the rapidly expanding older adult age stratum. Older adults are aging in place/independent residence, remaining in the workforce longer, and actively participating in their communities. In a similar vein, older drivers are one of the fastest-growing groups, representing a significant proportion of all drivers. In the United States, older adults age ≥ 65 will constitute 25% of all drivers by 2050[1]. In Europe and Japan, older drivers will make up a quarter of all drivers much earlier (2030)[2]. In Brazil, estimates of older drivers follow similar trends and range from 22-35%[3]. Conversely, motor vehicle crashes kill 1.35 million persons annually, are the eighth leading cause of death across all ages, cost $1.8 trillion (2010 USD) annually, and differentially impact low and middle income countries financially, along with a higher death rate[4]. Older adults are at the highest risk for injuries and mortality as a result of physiological decline and fragility.

Driving is a multifaceted and dynamic activity that demands instantaneous, sustained, and synchronized deployment of sensorimotor, cognitive, and affective systems. The coordination across multisystemic functions occurs in response to a rapidly changing environment with numerous stimuli (e.g., weather, road conditions, light, other drivers) while coping with internal conditions like stress, fatigue, and sleepiness. Despite driving being an overlearned task, age-related decline may moderately impact abilities (e.g., reaction time, strength, range-of-motion, sensation) that support the vehicle-driver task interface. While these modest and gradual changes may limit driving performance, they do not impact driving safety. However, chronic conditions like arthritis, cerebrovascular disease, neuropathy, cataracts, and dementia impair and increase the risk of crashes, related injury, and mortality among older drivers. As a result, significant research efforts aim to assess driving decline and identify risk factors among healthy and cognitively-normal (CN) older drivers.

Vasques and colleagues used an asymptomatic[5], healthy cadre of older adults to determine whether common neuropsychological assessments were associated with high-risk driving conditions on a driving simulator. The simulator scenarios included navigating a complex intersection, overtaking another vehicle, navigating in rain, and dealing with a vehicle malfunction. Older drivers identified as high-risk exhibited more errors (or penalties) on the intersection, overtaking, and rain performance scenarios that confirm and validate the cognitive demand of those tasks. The Rey Auditory-Verbal Learning Test (RAVLT) was able to distinguish between older drivers, and scores were significantly lower among those classified as high risk compared to those at normal risk. The RAVLT assesses attention, learning, and short-term memory (encoding, storage, retrieval). Since the simulator scenarios were novel and not experienced before, the participants had to learn and react to the new task with minimal practice. As expected, the inverse correlation between low RAVLT scores and higher errors/penalties on the simulator tasks corroborate the innate learning, memory, and attentional skills required of both tasks. Unsurprisingly, general cognitive screens like the Mini-Mental State Examination (MMSE) and Addenbrooke's Cognitive Evaluation (ACE) were not associated with any group differences.

For decades, the search has endured for a single or multidomain neuropsychological test or a composite score that may forecast or provide prescient knowledge of crash risk or driving decline. Measures of visuomotor, attentional control, and/or executive function (e.g., Trail Making Test) can predict an increased likelihood of crash risk among those with mild cognitive impairment and prodromal dementia[6]. However, this pattern does not hold for cognitively-normal older adults. In studies of CN older adults and Alzheimer's disease biomarkers, those with more abnormal biomarker levels made two-and-a-half more errors and were faster to fail a road test compared to those with normal biomarkers[7,8]. However, there no differences between independent neuropsychological measures or a composite z-score between the groups. The null findings with cognitive tasks were also found in a longitudinal study of naturalistic daily driving behavior[9] and a study of depression and driving performance[10]. General screenings like the MMSE or ACE were never designed to assess the hierarchical complexity of driving. Even multidomain measurements like the RAVLT may not capture the cognitive load and sensorimotor process integration that driving demands.

Assessment of driving decline among older adults is nuanced and can be conducted across controlled platforms like road tests and driving simulators or in daily driving via GPS dataloggers. Multimorbidity, medications, and the prescribing cascade may further obscure the sensitivity and specificity of assessing impairments. While general screens like the MMSE may not be clinically informative, multidomain measurements like the RAVLT, as shown by Vasques and colleagues, can provide insight into process-specific impairments. As a result, associations between these impairments and performance on a driving simulator may provide data on the likelihood of safe driving. Other approaches may include a combination of different risk factors like demographics (e.g., age), a composite z-score, biomarkers, self-report, and objective driving behavior to predict status and trajectory of driving decline. Driving performance (simulator, road test) and driving behavior (naturalistic) are complex sets of cognitive processes that topographically overlap, interact, and rapidly shift in response to internal and external stimuli as an individual navigates a route or trip. Assessment should be comprehensive and encompass subjective, objective, and collateral metrics of driving behavior, multidomain assessment of cognitive functioning, and the older driver's expectations about and motivation to drive[11].

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ARTICLE

Correlation between angioarchitectural characteristics of brain arteriovenous malformations and clinical presentation of 183 patients

Impacto das características angioarquiteturais das malformações arteriovenosas cerebrais na apresentaçáo clínica: análise de 183 pacientes

Ulysses Caus BATISTA[1,2], Benedito Jamilson Araujo PEREIRA[1], Andrei Fernandes JOAQUIM[2], Helder TEDESCHI[2], Ronie Leo PISKE[1]

ABSTRACT

Background: The correlation between angioarchitecture and clinical presentation of brain arteriovenous malformation (bAVM) remains a subject of debate. **Objective:** The main purpose of the present study was to assess the correlation between angioarchitectural characteristics of bAVM and clinical presentation. **Methods:** A retrospective review of all consecutive patients presenting a bAVM who underwent a cerebral angiography at Beneficencia Portuguesa Hospital in São Paulo between January 2006 and October 2016 was carried out. Patients were divided in five groups: group 1 – hemorrhage; group 2 - seizure; group 3 - headache; group 4 - progressive neurological deficits (PND); group 5 – incidental). **Results:** A total of 183 patients were included, with group 1 comprising 56 cases, group 2 49 cases, group 3 41 cases, group 4 28 cases, and group 5 9 cases. Regarding hemorrhage presentation, a statistical correlation was observed with female gender (P < 0.02), Spetzler-Martin 3B (P < .0015), and lesions with low flow (P < 0.04). A positive association was found between group 2 and age less than 36 years (P < 0.001), male sex (P < 0.018), presence of superficial lesions not classified as SM 3B (P < 0.002), presence of venous ectasia (p <0.03), and arterial steal phenomenon (P < 0.03). Group 4 was associated with older age (P < 0.01). **Conclusions:** Angioarchitectural characteristics can be correlated with some clinical presentations as well as with some clinical data, making it possible to create predictive models to differentiate clinical presentations.

Keywords: Central Nervous System Vascular Malformations; Intracranial Arteriovenous Malformations; Seizures; Stroke.

RESUMO

Antecedentes: A correlação entre a angioarquitetura e a apresentação clínica da Malformação Arteriovenosa do cérebro (MAVc) permanece um assunto de debate. **Objetivos:** Correlacionar as características angioarquiteturais das MAVc com a apresentação clínica. **Métodos:** Estudou-se pacientes consecutivos atendidos no Hospital Beneficência Portuguesa-SP, entre 2006 a 2016. Após análise geral, criaram-se cinco grupos de acordo com a apresentação clínica: 1- Hemorragia; 2 – Epilepsia; 3 – Cefaléia; 4 – Déficit Neurológico Progressivo (DNP) e 5 – Incidental. Características epidemiológicas (clínica e topografia) e angioarquiteturais (Classificação de Spetzler-Martin Modificada - SMM; Fluxo intranidal; Aneurismas arteriais, intranidais e venosos; Ectasia venosa; Congestão venosa; "Roubo" arterial; Vascularização dural; Drenagem Venosa Profunda) foram analisadas. **Resultados:** 183 pacientes foram incluídos e analisados globalmente. Após essa etapa, foram divididos nos grupos: 1 – 56 casos (30,6%); 2 – 49 casos (26,7%); 3 – 41 casos (22,4%); 4 – 28 casos (15,3%) e 5 – 9 casos (4,9%). Principais achados foram referentes a apresentação hemorrágica, na qual observamos correlação estatística positiva com o sexo feminino (P<0,02), lesões classificadas como SMM 3B (P<0,0015) e baixo fluxo (P<0,04). Relacionado à epilepsia, encontramos significância estatística que possibilitou a correlação com pacientes com idade inferior a 36 anos (P<0,001), sexo masculino (P<0,018), lesões superficiais (P<0,002), presença de ectasia venosa (P<0,003) e "roubo" arterial (P<0,01). Pacientes com DNP se apresentam com idade superior aos demais (P<0,01). **Conclusões:** Após análise multivariada, foi possível separar as MAV em grupos de acordo com as características angioarquiteturais, comprovando que algumas dessas características estão fortemente relacionadas a determinada manifestação.

Palavras-chave: Malformações Vasculares do Sistema Nervoso Central; Malformações Arteriovenosas Intracranianas; Convulsões; Acidente Vascular Cerebral.

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

Authors' contributions: UCB: Study concept and design, image analysis and acquisition of data; BJAP: Acquisition of data; AFJ: Acquisition of data and study supervision; HT: Critical revision of the manuscript for important intellectual content; RLP: Study concept and design, image analysis, study supervision and final revision.

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INTRODUCTION

Brain arteriovenous malformations (bAVM) are rare lesions, with an estimated annual incidence of 1/100,000 new cases per year, accounting for about 2% of all hemorrhagic cerebrovascular onsets[1]. According to Ondra et al[2], patients present an annual bleeding rate of 3.0%, with severe cumulative risk of morbidity (2.7%/year) and an annual mortality rate of 1%. In addition to the hemorrhage, these lesions may also cause epileptic seizures, headaches and/or progressive neurological deficits (PND). Lasjaunias et al suggested that these different forms of clinical presentations could be secondary to the location of the lesion and angioarchitectural characteristics of bAVM[3]. However, the correlation between angioarchitecture and bAVM clinical presentation remains a subject of debate[4].

The main purpose of the present study was to assess the correlation of angioarchitectural characteristics of bAVM with the clinical presentation of patients at diagnosis.

METHODS

After obtaining approval from the Institutional Review Board (No. 59830715.0.0000.5483), we conducted a retrospective database review of all consecutive patients presenting a bAVM who underwent a cerebral angiography of the six intracranial vessels following the same protocol at Beneficencia Portuguesa Hospital in Sao Paulo (Sao Paulo, Brazil) between January 2006 and October 2016. Clinical and radiological data were collected.

Inclusion criteria

Inclusion criteria were patients aged ≥18 years, with complete clinical, epidemiological, and angiographic data on hospital admission charts who were diagnosed with bAVM. All angiographies were performed by the lead author (RLP).

Exclusion criteria

Exclusion criteria were patients aged <18 years and those with incomplete data on admission charts. Other types of intracranial arteriovenous malformations (AVM) were excluded. In addition, patients who received any other prior treatment, such as surgery, embolization or radiosurgery, and therefore had alterations in the original AVM angioarchitecture, were also excluded.

Epidemiological characteristics

The following data were extracted from the database: age, sex, clinical presentation, and lesion topography.

Clinical presentation

Patients were classified into 5 groups according to the chief complaint that led to the examination: 1) intracranial hemorrhage, 2) seizures 3) persistent headache, 4) progressive neurological deficits (PND), and 5) incidental finding on image exam.

Topography

Lesions related to the cerebral cortex were classified as superficial AVMs, regardless of the lobe in which they were located or if they were corticoventricular. Malformations located in the basal ganglia (with exclusive nutrition of perforating branches) were classified as deep lesions. Those located in the cerebellum or in the brainstem were classified as posterior fossa AVMs[5].

Angioarchitectural characteristics

The following angioarchitectural characteristics (Table 1) were analyzed:

Modified Spetzler-Martin grading scale

Although the literature usually follows the Spetzler-Martin Grading Scale (S-M)[6], we considered the modifications proposed by Oliveira et al[1], who sub classified bAVM grade 3 of the S-M. In this study, we divided bAVM grade 3 into two groups: modified S-M 3A and S-M 3B. The bAVMs that received a total of three points for medium size (2 points), eloquent location (1 point) and only superficial venous drainage (0 points) were classified as 3A, whereas those that were small (1 point), located in eloquent areas (1 point), and a deep venous drainage (1 point) were classified as 3B. In Figure 1, we present an example of AVM grades 3A and B.

Intralesional flow

BAVMs were classified as high- or low-flow. High-flow referred to cases where opacification after contrast injection occurred only in the malformation without filling other normal branches of this territory. In low-flow lesions, other arteries of the same vascular territory were also opacified.

Intranidal aneurysms

These are aneurysmal formations located inside the nidus. All intranidal aneurysms were confirmed in more than one angiographic projection (Figure 2-A).

Arterial aneurysms (not intranidal)

Aneurysms not directly related to the nidus of the AVM were divided into two: flow-related aneurysms, which refer to the location at the arterial pathway supplying the AVM, and aneurysms not related to the main supply for the AVM[7].

Venous aneurysms

These are localized aneurysmatic dilatations in a vein draining the lesion, which were confirmed by different angiographic projections (Figure 2-B).

Venous ectasia

This refers to a marked increase in the diameter of the vessel that drains the AVM associated with tortuosities (Figure 2-B)[8].

Table 1. Description of demographic and angioarchitectural characteristics analyzed in this study.

Characteristics studied	Description
Clinical presentation	Five groups were created: 1) intracranial hemorrhage, 2) epileptic seizures, 3) persistent headache, 4) progressive neurological deficits, 5) incidental finding on image exam.
Topography	Lesions related to cerebral cortex were classified as superficial AVMs; in the basal ganglia (exclusive nutrition by perforating branches) as deep lesions. Those located in the cerebellum or in the brainstem were classified as posterior fossa AVMs[5].
Grade 3 Spetzeler-Martin scale modified	Grade 3 Spetzeler-Martin Scale was divided into two groups: grade 3A and 3B. AVMs that received two points for medium size, one point for eloquent location, and zero for superficial venous drainage were classified as 3A. Those that were small (1 point), located in eloquent areas (1 point), and a deep venous drainage (1 point) were classified as 3B (Figure 1).
Intralesional flow	Classified as high or low flow. High flow referred to cases where contrast opacification occurred only in the malformation without filling other normal branches of this territory. In low-flow lesions, other arteries of the same vascular territory were also opacified.
Intranidal aneurysms	Aneurysmal formation located inside the nidus and confirmed in more than one angiographic projection (Figure 2-A).
Venous aneurysms	Aneurysmatic dilatations in a vein draining the lesion, confirmed by different angiographic projections (Figure 2-B).
Venous ectasia	Marked increase in the diameter and tortuosities of the vessel that drains the AVM (Figure 2-B)[8].
Venous congestion	Redirecting draining flow to other veins hindering normal brain-tissue drainage (Figure 2-C).
Arterial steal	Insufficient filling of the normal branches at the same territory where the AVM are located.
Dural vascularization	Participation of dural vessels supplying the AVM (Figure 2-D).
Deep venous drainage	Direct drainage to the deep venous system (Figure 3)[9].

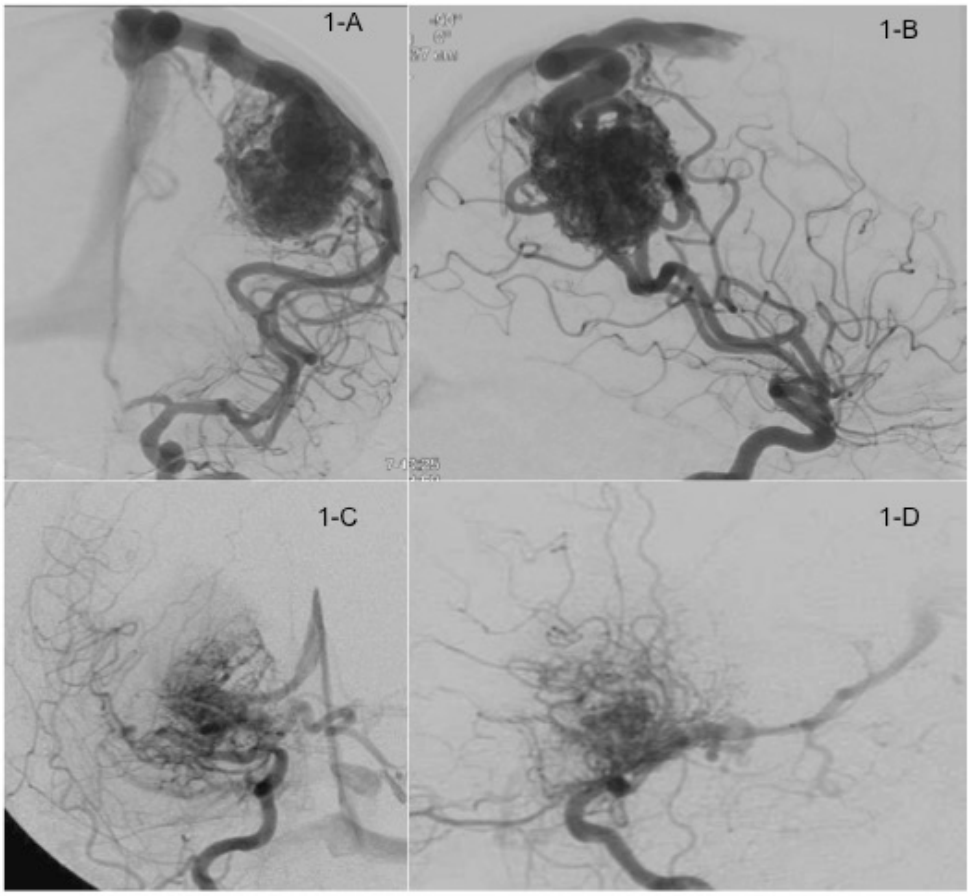

Figure 1. A: Left internal carotid artery angiogram, late arterial phase (frontal view), showing a medium (3 – 6 cm) AVM in a superficial location with exclusive superficial venous drainage. B: Left internal carotid artery angiogram, late arterial phase (lateral view), of the same AVM in 1A, which was classified as 3A. C: Right internal carotid artery angiogram, late arterial phase (frontal view), showing a small (less than 3 cm) AVM in the basal ganglia (deep location) with deep venous drainage; D: Right internal carotid artery angiogram, late arterial phase (lateral view) of the same AVM in 1C, which was classified as 3B.

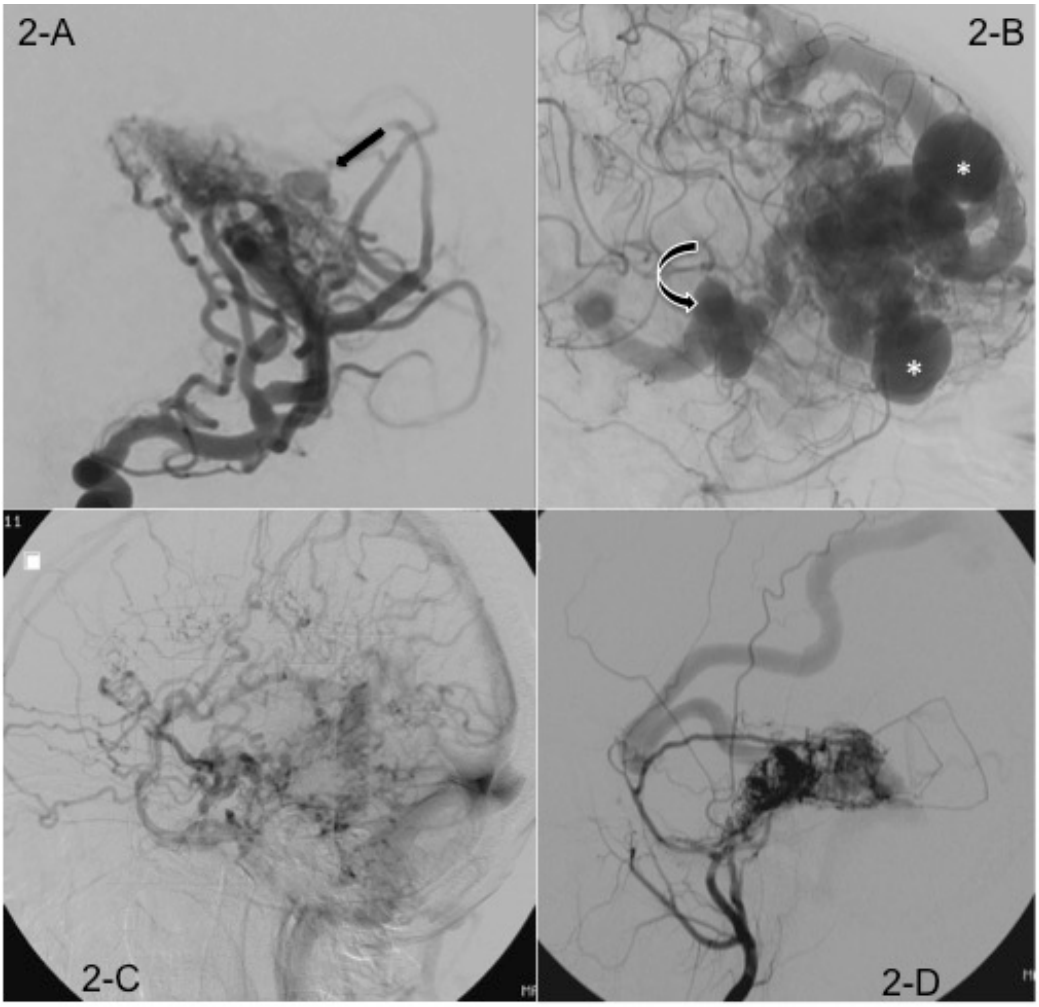

Figure 2. A: Left internal carotid artery angiogram, arterial phase in oblique view, highlighting an intranidal aneurysm (arrow); B: Left internal carotid artery, venous phase in lateral view, demonstrating two venous aneurysms (asterisk) and venous ectasia (curved arrow); C: Left internal carotid artery, late venous phase in lateral view, showing a venous congestion; D: Right external carotid angiogram, arterial phase in lateral view, demonstrating the dural vascularization of the AVM.

Venous congestion

This is the case when, in addition to the anatomically expected venous drainage, the flow is redirected to other veins, obstructing the normal drainage of brain tissue (Figure 2-C).

Arterial steal

This is related to a lack of filling of the normal branches of the same area where the AVM is located. These branches present retrograde filling by pial anastomoses, which could also supply the nidus.

Dural vascularization

This describes a situation in which the AVM is also supplied by dural vessels (Figure 2-D).

Deep venous drainage

All bAVMs presenting direct drainage to the deep venous system were included in this group (Figure 3)[9].

Image acquisition

All patients underwent a complete angiographic study, which consisted in the analysis of the internal and external carotid arteries and vertebral arteries, in at least anteroposterior and lateral views. Other views were analyzed to disclose arterial or venous stenosis or aneurysms. The angiographic equipments used were: Philips Integris biplane (between 2006 and 2014) and Philips Allura Xper FD biplane (between 2014 and 2016). Images were stored in the Aurora PACS system version 1.6.7. UCB and RLP researchers analyzed all images together.

Statistical analysis

Data were analyzed using the following softwares: SPSS V17, Minitab 16, and Excel Office 2010. Statistical resources used were equality of proportions test, Chi-Square test, odds ratio, and multivariate analysis by logistic regression. The logistic regression models were confirmed by the Pearson, deviance, and Hosmer-Lemeshow tests. The level of significance was set at $p < 0.05$.

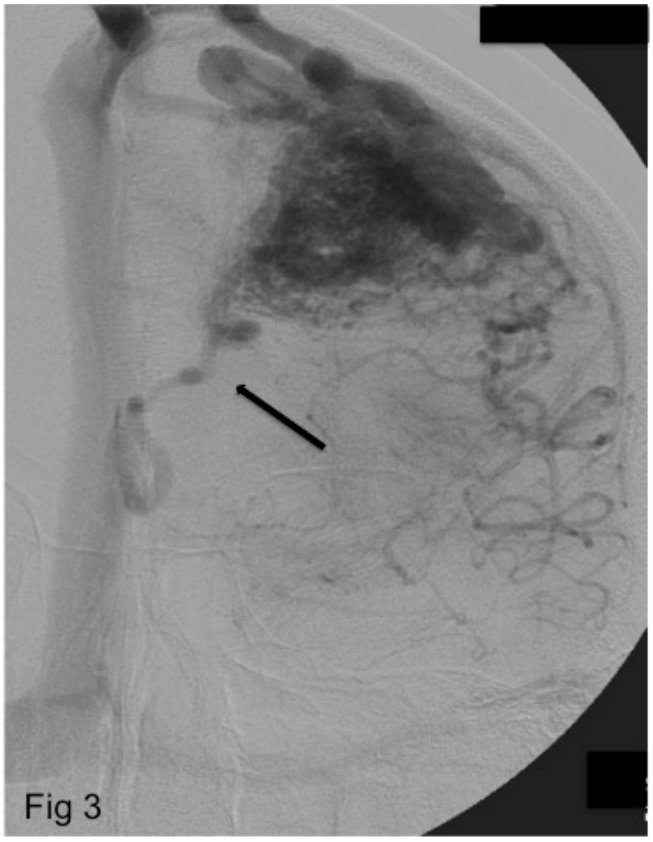

Figure 3. Left internal carotid angiogram, capillary phase (frontal view), showing a superficial AVM with deep venous drainage promoted by only one vessel (arrow). Although the major AVM drainage is done by superficial vessels, according to Spetzler-Martin Classification, the presence of this deep channel of drainage classifies this malformation as having deep venous drainage.

RESULTS

Epidemiological analysis

A total of 183 patients were included with 93 (50.8%) males. The mean age of onset was 37 years (ranging from 18 to 84 years; SD: ±14.0).

Cases were divided into five groups according the clinical presentation at diagnostic: group 1 (hemorrhage): 56 cases (30.6%); group 2 (seizure): 49 cases (26.7%); group 3 (headache): 41 cases (22.4%); group 4 (Progressive neurological deficits): 28 cases (15.3%), and group 5 (Incidental): 9 cases (4.9%).

Regarding the location of the lesions, superficial AVMs were the most common, with 124 cases (67.7%), followed by the deep AVMs, with 36 cases (18.6%) and by lesions located in the posterior fossa, with 23 cases (12.5%). Table 2 summarizes these findings and the results for each group.

When comparing groups, a difference was found in the mean age of symptom onset between groups 2 and 4 ($P < 0.01$) and 3 and 4 ($P < 0.01$). The other groups did not differ in the mean age of onset.

Considering sex, a higher prevalence of bleeding was found in women while a higher prevalence of seizures was found in men ($P < 0.014$). There was no statistical difference between sexes in the other groups.

The topography of the AVMs was also studied within each group, comparing the three possible locations, as shown in Table 1. There was a correlation between hemorrhage and deep lesions or lesions in the posterior fossa compared to superficial lesions ($P < 0.0003$ and $P < 0.002$, respectively). An important difference was also observed in group 2, in which patients with superficial AVMs had a higher incidence of epilepsy compared to patients with deep lesions ($P < 0.002$). Differences were also observed between superficial and deep or posterior fossa AVMs in group 4, showing that superficial lesions presented more PND than lesions with other topographies ($P < 0.007$ and $P < 0.01$, respectively). No statistical differences were observed among patients who presented headaches. Table 3 summarizes all these findings.

The results of the epidemiological analysis of each group studied are presented:

- Group 1 (hemorrhage) – 56 patients: The mean age of this group was 37.5 years (ranging from 18 to 75 years; SD: ± 11.97), with 22 (39.2%) males. In 24 (42.8%) cases, the lesion had a superficial location, in 19 cases (33.9%)

Table 2. Distribution of 183 patients according to demographic characteristics.

Demographic characteristics	General	%	Hemorrhage	%	Seizure	%	Headache	%	PND	%	Incidental	%
Mean age	37		37,5		32		34,5		45,2		45,4	
Maximum age	84		75		55		69		71		84	
Minimum age	18		18		18		18		22		19	
Standat deviation	14		12		10,3		13,5		16,2		22,5	
Male	93	50.8	22	39.2	31	63.2	18	43.9	17	60.7	5	55.5
Female	90	49.2	34	60.7	18	36.8	23	56.1	11	39.3	4	44.5
Superficial lesion	124	67.7	25	44.6	46	93.9	32	75.6	17	60.7	4	44.4
Deep lesion	36	18.6	19	33.9	3	6.1	6	14.6	6	21.4	2	22.2
Posterior fossa lesion	23	12.5	12	21.4	0	0	3	7.3	5	17.8	3	33.3
Total	183		56		49		41		28		9	

AVMs were deep and in the remaining 12 cases (21.4%) AVMs were located in the posterior fossa. Deep and posterior fossa AVMs presented a higher incidence of hemorrhage than superficial AVMs (P < 0.01).

- Group 2 (seizure) – 49 patients: The mean age of this group was 32 years (ranging from 18 to 55 years, SD: ± 10.37) and 31 (63.2%) were male. In 46 (93.8%) cases, lesions were located superficially, in three patients (6.2%) AVMs were deeply located, and no patient who presented with epilepsy had lesions in the posterior fossa. Superficial AVMs had a higher incidence of epilepsy compared to deep AVMs (P < 0.01).
- Group 3 (headache) – 41 patients: Patients in this group had a mean age of 34.5 years (ranging from 18 to 69 years, SD: ± 13.5), 18 (44%) of whom were male. The main location was superficial in 32 cases (78%), followed by deep lesions with 10 (14.6%) patients, and those located in the posterior fossa with seven (7.3%) cases. There was no statistical difference between lesions locations in this group.
- Group 4 (progressive neurological deficits) – 28 patients: The mean age in this group was 45.2 years (range 22-71, SD: ± 16), and 17 (60.7%) were male. Superficial lesions were the most frequent, with 17 (60.7%) patients, followed by the deep AVMs and AVMs in the posterior fossa, with six (21.4%) and five (17.8%) cases, respectively. The superficial location correlated with neurological deficits compared to the other locations in this group (P < 0.01).
- Group 5 (incidentals): 9 patients: Patients had a mean age of 45.4 years (ranging from 19-84 years; SD: ± 22.5), with the male sex accounting for five (55.5%) patients. The AVM were superficial in four (44.4%) cases, deep in two (22.2%) and located in the posterior fossa in three (33.3%) cases.

Angioarchitectural analysis

The angioarchitectural characteristics of 183 bAVM were analyzed. The results for bAVMs as a total group and by subgroup are summarized in Table 3.

Modified Spetzler-Martin classification

AVM classified as SM 3B had a higher risk of bleeding than the other classifications (P < 0.0015, OR: 3.82, 95% CI, 1.70-8.57). In addition, patients in the epilepsy group were less likely to have a deep AVM (P < 0.01; OR: 3.8; CI: 1.70 - 8.57).

Study of AVM flow velocity

Lesions with low flow were more susceptible to hemorrhage (P < 0.032; OR: 2.29; CI: 1.12 - 4.68) compared to the other groups.

Presence of intranidal aneurysms

The presence of intranidal aneurysms in AVM did not correlate with any clinical presentation (P = 0.22).

Arterial aneurysms

High-flow aneurysms and aneurysms not related to high-flow had an incidence of 22.4% and 7.1%, respectively. The

Table 3. General and group distribution of the 183 MAVs in relation to the angioarchitectural characteristics studied.

Angioarchitectural characteristics	General	%	Hemorrhage	%	Seizure	%	Headache	%	PND	%	Incidental	%
SM 1	47	25.6	16	28.5	11	22.4	10	24.4	7	25	3	33.3
SM 2	61	33.3	13	23.2	17	34.6	21	42.8	10	35.7	2	22.2
mSM 3A	30	16.3	7	12.5	11	22.4	8	19.5	4	14.3	1	11.1
mSM 3B	30	16.3	17	30.3	2	4	3	7.3	6	21.4	2	22.2
SM 4	13	7.1	3	5.3	8	16.3	0	0	1	3.6	1	11.1
SM 5	2	1	0	0	1	2	0	0	1	3.6	0	0
High flow	65	35.5	13	23.2	20	40.8	19	46.3	11	39.2	2	22.2
Intranidal aneurysms	41	22.4	16	28.5	10	40.8	6	14.6	5	17.8	4	44.4
Venous aneurysms	30	16.3	5	8.9	8	16.3	10	24.4	5	17.8	2	22.2
Venous ectasias	26	14.2	5	8.9	12	24.5	2	4.9	7	25	0	0
Venous congestions	39	21.3	9	16	9	18.3	10	24.4	9	32.1	2	22.2
Arterial steal phenomenon	6	3.2	0	0	4	8.1	1	2.4	0	0	1	11.1
Dural vascularization	13	7.1	4	7.1	5	10.2	3	7.3	0	0	1	11.1
Deep venous drainage	64	34.9	25	44.6	13	26.5	9	22	13	46.4	4	44.4
Total	183		56		49		41		28		9	

combination of cerebral aneurysm and AVM had an incidence of 29.5%.

Venous aneurysms

There was no statistical correlation between the presence of venous aneurysms and the clinical presentation of patients (P = 0.11).

Venous ectasia

The presence of venous ectasia did not show statistical correlation with hemorrhage (P = 0.31; OR: 0.52; 95% CI: 1.18-1.47). However, it was statistically significant in the epilepsy group (P = 0.03; OR: 2.77; 95% CI: 1.18 - 6.53)

Venous congestion

The presence of venous congestion was not significantly correlated with clinical presentation (P = 0.34).

Arterial "steal"

Arterial "steal" was significantly correlated with epilepsy (P = 0.02).

Dural vascularization

There was no statistical significance between dural vascularization and the clinical presentation (P = 0.76).

Deep venous drainage (DVD)

There was a correlation trend for DVD in the hemorrhage group (P < 0.08).

Table 3 summarizes the results of the univariate analysis of angioarchitectural characteristics per group of patients.

Correlation between high-flow AVM and other angioarchitectural characteristics

Lesions with a high flow had a higher prevalence of intranidal aneurysms, venous ectasia, venous congestion and arterial "steal", as summarized in Table 4.

After univariate analysis, a multivariate logistic regression study was performed to evaluate the possibility of creating models that could predict the studied clinical presentations. We found a positive correlation between hemorrhage and female sex (P < 0.02), AVM S-M 3B (P < 0.001), and low flow (P < 0.04).

In patients with epilepsy, we observed an association with age less than 36 years (P < 0.001), male sex (P < 0.018), superficial lesions not classified as SM 3B (P < 0.002), presence of venous ectasia (P <0.03), and arterial "steal" phenomenon (P < 0.03). Predictive models could not be generated for the other groups. Table 5 summarizes these findings.

DISCUSSION

BAVMs are rare lesions, but they may have serious clinical consequences, such as intracranial hemorrhage[1,8] that result in severe morbidity and even death[2]. In addition to hemorrhage, epileptic seizures, persistent headaches, and progressive neurological deficits are also associated with these lesions, which increase morbidity in these patients. Considering these points, evaluation of the AVM angioarchitecture is fundamental for the

Table 4. Univariate analysis of the AVM distribution according to the angioarchitectural characteristics and topography.

Angioarchitectural characteristics	Hemorrhage			Seizure			Headache			PND		
	P	OR	CI	P	OR	CI	P	OR	CI	P	OR	CI
Superficial x deep location	**0.0003**	0.22	0.10 - 0.49	**0.002**	6.48	1.88 - 22.34	0.361	1.73	0.66 - 4.56	**0.0007**	7.72	2.42 - 24.62
Superficial x PF location	**0.0028**	0.23	0.09 - 0.585	0	0	0	0.29	2.31	0.64 - 8.32	**0.012**	5.56	1.59 - 19.37
Deep x PF location	0.82	1.02	0.35 - 2.92	0	0	0	0.995	1.33	0.29 - 5.95	0.8845	0.72	0.19 - 2.70
Grade 3B mSM scale	**0.0015**	3.82	1.70 - 8.57	–	–	–	–	–	–	–	–	–
Low flow	**0.032**	2.29	1.12 - 4.68	0.46	1.36	0.69 - 2.67	0.144	1.8	0.88 - 3.65	0.811	1.21	0.52 - 2.76
Intranidal aneurysms	0.25	1.63	0.78 - 3.37	0.848	0.85	0.381 - 1.90	0.25	0.52	0.20 - 1.35	0.7	0.71	0.25 - 2.02
Venous aneurysms	0.11	0.4	0.14 - 1.10	0.83	0.99	0.41 - 2.40	0.18	1.96	0.83 - 4.62	0.96	1.13	0.39 - 3.25
Venous ectasias	0.31	0.52	0.18 - 1.47	**0.03**	2.77	1.18 - 6.53	0.1	0.26	0.05 - 1.17	0.109	2.53	0.94 - 6.80
Venous congestions	0.34	0.61	0.27 - 1.40	0.7	0.78	0.34 - 1.78	0.74	1.25	0.55 - 2.85	0.204	1.97	0.81 - 4.79
Arterial "steal"	0	0	0	**0.02**	5.86	1.03 - 33.11	0.87	0.68	0.07 - 6.03	0	0	0
Dural vascularization	0.76	1.00	0.29 - 3.42	0.21	2.38	0.77 - 7.29	0.77	1.04	0.27 - 3.97	0	0	0
Deep venous drainage	0.087	1.79	0.94 - 3.44	0.191	0.58	0.28 - 1.19	0.08	0.45	0.20 - 1.03	0.25	1.75	0.77 - 3.95

Table 5. Multivariate analysis for the creation of predictive models for the clinical presentations studied (hemorrhage and epilepsy).

Multivariate analysis	Hemorrhage		Seizure	
	P	OR (CI 95%)	P	OR (CI 95%)
Mean age			0.001	0.95 (0.92 - 0.98)
Male	0.021	0.45 (0.23 a 0.89)	0.018	2.46 (1.17 a 5.19)
S-M 3B	0.001	3.95 (1.69 a 9.2)	0.002	0.08 (0.01 a 0.4)
High flow studied	0.047	0.47 (0.22 a 0.99)		
Intranidal aneurysm				
Venous aneurysm				
Venous ectasia			0.037	2.84 (1.07 a 7.56)
Venous congestion				
Arterial steal phenomenon			0.039	2.3 (1.04 a 5.1)
Dural vascularization				
Deep venous drainage				

management of these patients. Tong et al found that female sex correlated with hemorrhagic presentations, whereas men had a higher risk of epileptic seizures, which was similar to our findings[10].

The mean age of symptom onset of our patients was similar to those found in the literature[11-14]. However, pediatric patients are commonly included, which may affect the age of onset of patients with AVM. Hetts et al only studied adult patients, reporting a mean age of clinical symptoms of 42.6 years for patients with AVM[15], slightly higher than our sample. We did not find studies that grouped the age of clinical presentation of AVM according to clinical presentation. In our study, we observed that PND patients were more advanced in age at the onset of symptoms than those patients with epilepsy or headaches *(P* < .01). However, with regard to age, patients with hemorrhagic AVMs did not show any differences relative those from the other groups.

According to the literature[16-18], deep AVMs have a higher rate of hemorrhage. Lesions classified as S-M 3B were also more related to hemorrhagic events than other lesions (P < 0.01). The topography of the lesions was also studied within each group, showing that patients who had hemorrhagic events had deep or posterior fossa lesions (P < 0.003 and P < 0.00028, respectively), with no differences between these two presentation sites (P > 0.82). In patients with epilepsy, lesions were predominantly superficial (P < 0.002), as well as in patients with DNP, where superficial lesions predominated compared to deep-seated lesions or lesions located in the posterior fossa (P < 0.0007 and P < 0.01, respectively). This is probably a causative phenomenon, that is, the superficial location may increase the chances of cortical irritation with gliosis, leading to epileptic seizures[6].

Kim et al[19] and Duong et al[20] studied predictive factors for hemorrhage in patients with AVMs, finding a correlation between exclusive deep-vein drainage and hemorrhagic presentation. However, according to Spetzler et al[6], deep-vein drainage is characterized by at least one deep vessel. By considering lesions with exclusive deep-vein drainage, we found similar results (P < 0.0015). However, if we maintained the original S-M classification of DVD, we found only a tendency for hemorrhage in patients with this type of drainage (P < 0.087). We believe that deeply located AVMs are more prone to hemorrhage and that the majority of deep-seated lesions cause deep-vein drainage.

Kubalek et al also reported that low-flow AVMs had a higher risk of hemorrhage, similar to our findings (P > 0.03, OR 2.29, 95% CI 1.12-4.68)[12]. Of note, the majority of AVMs that present bleeding are deep-seated, and high flow is not commonly found in that location.

Stapf et al reported a positive correlation between the presence of intranidal aneurysms and hemorrhagic events.[21] However, Pollock et al[22], in a study of 313 patients, did not report any relationship between the presence of intranidal aneurysm and hemorrhage, which was similar to our findings. Intranidal aneurysms were more frequently observed in lesions with high flow, suggesting that they are a secondary event, as observed in our series. Mast et al studied the correlation between arterial steal and DNP, and found no statistical significance between these characteristics[23]. However, we found this correlation in patients who presented epilepsy (P = 0.02). It should be noted that, similar to intranidal aneurysms, this phenomenon is more prevalent in lesions with a high flow, which are also more commonly found in patients with epilepsy (P < 0.03, OR 10, 95% CI 1.14-87.5).

Redekop et al and Kubalek et al reported that the incidence of hyperflow aneurysms in patients with bAVMs were 15.3% and 12.3%, respectively[7,12]. In these two studies, it was found that the association of aneurysm and AVMs had an incidence of hemorrhage of about 7%/year[7]. In our sample, we found a high incidence of these aneurysms (22.4% of hyperflow aneurysms and 7.1% of non-hyperflow aneurysms).

Shankar et al studied the effects of venous ectasia on cerebral AVMs, and, similar to our findings, observed that the ectasied drainage vessels showed a positive correlation with epilepsy (P < 0.03, OR 2.77, 95% CI, 1.18-6.53)[13].

Pan et al reported that vascularization by perforating arteries and exclusive deep-vein drainage presented a higher rate of hemorrhage[17]. It is interesting to note that in the study, the deep location of AVMs did not present positive results, even though the vascularization of perforating arteries and exclusive deep-vein drainage are strongly related to this location. Kandai et al and Stefani et al also reported that the deep location of lesions is the main predictive characteristic for bleeding events[16,18]. In our study, the predictive model for hemorrhage showed that female gender (P < 0.02), lesions classified as modified S-M 3B (small, deep, and with exclusively deep-vein drainage) (P < 0.001) and low-flow AVMs (P < 0.047) were associated with high risk of hemorrhage. These results are interesting, because they differ from those of epilepsy-related lesions, which have stronger association with younger age (P < 0.004), male sex (P < 0.03), superficial location (P < 0.002), presence of venous ectasia (P < 0.03) and arterial steal phenomenon (P < 0.03).

We concluded that angioarchitectural characteristics of bAVMs may be correlated with some clinical presentations as well as with some clinical data. Hemorrhagic events were associated with female sex, deep location, and low-flow AVMs. Epilepsy presentation was associated with younger age, male sex, superficial location, presence of ectasied veins, and arterial steal phenomenon. Posterior fossa lesions were not correlated with epilepsy in our series, and there was more frequent observation of PND in older patients.

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ARTICLE

Functional outcomes in children related to self-care, mobility, and social function after stroke in early childhood: a cohort study

Evolução funcional de crianças em autocuidado, mobilidade e função social após acidente vascular cerebral na primeira infância: um estudo coorte

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ABSTRACT

Background: Stroke has been increasingly recognized as an important morbidity and mortality factor in neonates and children. Children have different and more diverse risk factors than adults, commonly related to an underlying disease. Stroke may compromise functional capacity in children. Few studies have focused on functional outcomes related to activities and participation. **Objectives:** To investigate post-stroke functionality of children related to self-care, mobility, and social function. **Methods:** We assessed the functional outcome of 14 children younger than 7.5 years who suffered a stroke in early childhood through the use of the Pediatric Evaluation of Disability Inventory (PEDI). **Results:** The average age of the sample at assessment was 3.6 ± 1.4 years (2 - 6 years). The average scores in the PEDI functional domains of self-care, mobility, and social function were, respectively, 37.6 ± 15.4, 36.2 ± 15.4, and 48.7 ± 11.1. Children showed age-appropriate functional outcomes in the PEDI functional domains: 71.4% of them in self-care and mobility and 92.9% in social function. Children with bilateral injuries (p = 0.05) and longer hospital stays (r = -0.79, p = 0.001) showed the worst scores in PEDI's social function domains. **Conclusions:** Overall, our sample of preschool children showed age-appropriate functional outcomes on self-care, mobility, and social function domains after stroke. However, children with bilateral injuries and longer hospital stays showed the worst scores in social function domains. We recommend focusing on functional rehabilitation to promote activities and participation and to monitor the development of children's social skills after stroke.

Keywords: Stroke; Child; Self-Care; Locomotion; Social Skills.

RESUMO

Antecedentes: O acidente vascular cerebral (AVC) tem sido reconhecido como um importante fator de morbimortalidade em neonatos e crianças. As crianças têm fatores de risco diferentes e mais variados que os adultos, comumente relacionados a uma doença subjacente. A funcionalidade das crianças pode estar comprometida após um AVC. Poucos estudos focaram em desfechos funcionais relacionados à atividade e participação. **Objetivos:** Investigar a funcionalidade de crianças com AVC, relacionada à autocuidado, mobilidade e função social. **Métodos:** Avaliamos a evolução funcional de 14 crianças com idade menor que 7,5 anos com AVC na primeira infância pela aplicação do PEDI. **Resultados:** A idade média de nossa amostra na avaliação foi de 3,6 ± 1,4 anos (2 - 6 anos). O escore médio nos domínios de autocuidado, mobilidade e função social do PEDI foram, respectivamente, 37,6 ± 15,4, 36,2 ± 15,4 e 48,7 ± 11,1. As crianças apresentaram evolução adequada para a idade nos domínios do PEDI: 71,4% delas em autocuidado e mobilidade e 92,9% em função social. Piores escores no domínio função social se relacionaram com lesões bilaterais (p = 0,05) e maior tempo de internação (r = -0,79; p = 0,001). **Conclusões:** Nossa amostra de crianças em idade pré-escolar mostrou, em geral, evolução funcional adequada para a faixa etária nos domínios de autocuidado, mobilidade e função social. Porém, lesões bilaterais e internações hospitalares mais longas se relacionaram com piores performances no domínio função social. Sugerimos focar na reabilitação funcional e acompanhar o desenvolvimento das habilidades sociais de crianças pós-AVC.

Palavras-chave: Acidente Vascular Cerebral; Criança; Autocuidado; Locomoção; Habilidades Sociais.

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Authors' contributions: LIP: study design and manuscript drafting; DRBS: study design, training in the assessment instrument and manuscript drafting; LATM: data collection/interpretation and manuscript drafting.

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INTRODUCTION

Stroke, once considered a health problem in adults, is increasingly recognized as an important morbidity and mortality factor in neonates and children[1]. The annual incidence of pediatric strokes (ischemic and hemorrhagic), considering the neonatal period and childhood, varies from 3 to 25 per 100,000 children in developed countries[1]. The incidence is higher in neonates: 1 in 4,000 live births[1]. While the predominant risk factors in adults include hypertension, diet, diabetes mellitus, obesity, and smoking, among others[2], children have different and more varied risk factors. Risk factors for childhood stroke (CS) include vasculopathies (such as sickle cell anemia, Moyamoya syndrome and autoimmune disorders), prothrombotic conditions (such as polycythemia, antiphospholipid antibody), heart disorders, genetic and metabolic disorders (such as homocystinuria, Fabry disease), infections, vascular abnormalities, coagulation disorders and tumors[3].

Stroke may compromise children's functioning. According to the International Classification of Functioning, Disability and Health (ICF), the concept of functioning includes all body functions and those related to activity and participation[4]. After stroke, the following body functions may be compromised: mental function (attention, information processing)[5], working memory, visuomotor processing speed[6], intellectual function[7], and neuromusculoskeletal/movement-related functions (such as muscle tone)[8]. Activities and participation functions that may be altered include personal care[9,10], learning and knowledge application (school problems)[10-12], interpersonal relationships (behavioral)[11], and mobility[13]. After stroke, the child's functionality may be influenced by contextual factors (personal and environmental) such as the child's age and age at stroke, parental education, socioeconomic conditions, family support network, and rehabilitation[8].

Most previous studies have focused on limitations in body functions and structures after a childhood stroke. Few studies have focused on activities and participation functional outcomes and on the influence of the contextual factors on the child's functioning[8]. The few available data (mentioned above) are from international studies[9-13], which may not reflect the reality of functional outcome after childhood stroke in developing countries due to socioeconomic and cultural differences. To the best of our knowledge, there are only four studies on functional outcomes after childhood stroke in Brazil. They reported impairments in motor skills, writing, reading, memory[14,15], and language[16]; one study on quality of life reported decreased functional capacity[17]. We found no Brazilian studies on functional outcomes in activities of daily living (ADLs) and participation after childhood stroke. There is a need to know the functional outcome of children after stroke to provide the most appropriate intervention focusing on activity and participation skills rather than just improving impairments in body structure/function levels. Thus, the objective of this study was to investigate the functionality of children after a stroke in terms of social function, mobility, and self-care skills.

METHODS

This was a retrospective longitudinal observational cohort study. We used the STROBE checklist (https://www.strobe-statement.org).

Participants

The inclusion criteria were: stroke diagnosis (ischemic and hemorrhagic) and age between 6 months and 7.5 years* (*age covered by the evaluation instrument used in the study (PEDI) for the normative score). The exclusion criteria were: no signed informed consent, presence of traumatic brain injury or diffuse brain injury, peri-intraventricular hemorrhage, other causes of cerebral ischemia, associated pathologies with a significant neuropsychomotor development delay such as Down syndrome, West syndrome, and others.

Instruments

Pediatric evaluation of disability inventory (PEDI)[18,19]

The PEDI is administered as a structured interview with one of the child's parents/guardian and informs about the children's profile in three functional domains: self-care, mobility, and social function. The PEDI's functional profile consists of three parts; in this study, we applied part I, referring to the child's functional skills. We used the raw score to calculate the continuous score and normative score according to each child's age. The normative score reflects a child's performance concerning a reference sample; it must be between 30 and 70 to be considered age-appropriate. The item maps show the functions of which the child is capable or incapable. The items are arranged on the map in ascending level of difficulty, being the most complex closest to 100. According to the child's raw score and age, the continuous score and standard deviation are plotted on the map. The items to the left of this range are less complex, so we expected the child to be able to perform them.

Brazil economic classification criterion[20]

The Brazil Economic Classification Criterion (BECC) is an economic segmentation instrument. This Criterion differentiates the population in economic classification strata (A1, A2, B1, B2, C1, C2, D, and E). The A1 stratum refers to the best financial condition and the E stratum, the worst economic situation. The classification is based on the family provider's educational level and household characteristics (presence and quantity of some household comfort items).

Data collection procedures

The Research Ethics Committee of the Ribeirao Preto Medical School of the University of São Paulo approved this

study. All participants' parents/guardians were informed about the study and provided a signed informed consent form.

We performed a review of medical data of all childhood stroke cases admitted to the Clinical Hospital of Ribeirao Preto Medical School of the University of São Paulo between 2005 and 2012. This is a tertiary-level university hospital. Then, we reviewed the medical records of selected children to identify childhood strokes. We scheduled the children's assessment for the exact date they would return for a clinical follow-up appointment. Based on the family's preference, children that were not scheduled to return by April 2013 were assessed at home.

We applied the PEDI's part 1 questionnaire in an in-person structured interview with the children's parents/guardians.

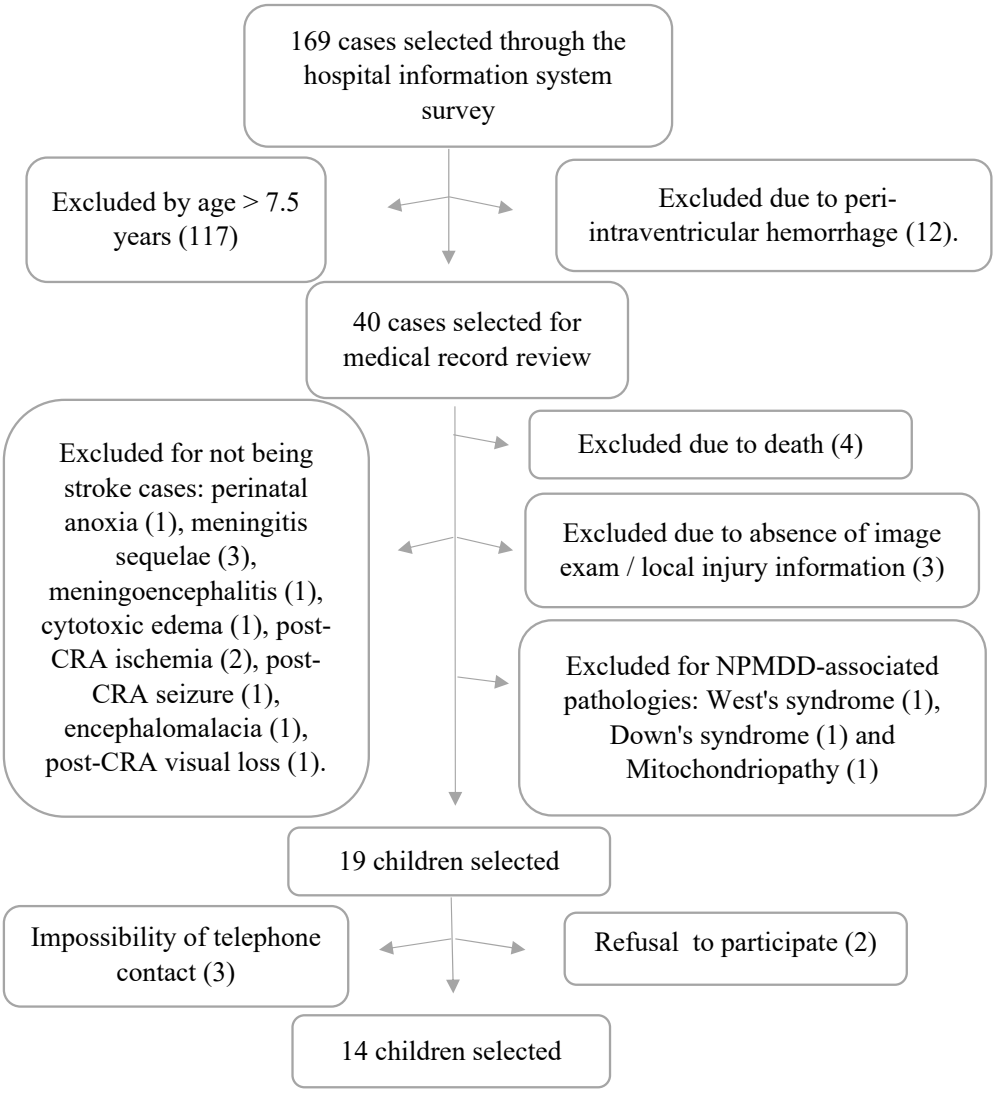
Data analysis

We analyzed the correlation between the PEDI's normative scores in self-care, mobility and social function domains with the following categorical variables: age at stroke (≤1 /> 1 year), injury site (lobar/infratentorial/deep), presence of hydrocephalus (yes/no), presence of intraventricular hemorrhage (yes/no), sex (female/male), stroke type (ischemic/hemorrhagic), affected hemispheres (unilateral/bilateral), and socioeconomic status (Brazil Economic Classification Criterion) using the Mann-Whitney non-parametric test. We also correlated such categorical variables with the child's current age and hospital stay (numerical variables) using the Spearman correlation coefficient.

RESULTS

Figure 1 describes the participants' screening and selection process.

The mean age at stroke was 1.5 ± 1.4 years (range: 2 days to 4.4 years). The average age at assessment was 3.6 ± 1.4 years (range: 2.2 to 6.3 years). Table 1 describes the participants' characteristics**.**



CRA: cardiorespiratory arrest; NPMDD: neuropsychomotor development delay.
Figure 1. Flowchart for the selection of childhood stroke participants.

Table 1. Participants' characteristics (n=14).

Patients characteristics		Number of patients (n)
Age at stroke	< 1 year	6
	> 1 year	8
Sex	Female	8
	Male	6
Lesion location	Deep	5
	Lobar/Infratentorial	9
Stroke Type	Ischemic	8
	Hemorrhagic	6
Side	Unilateral	10
	Bilateral	4
Intraventricular Hemorrhage	No	12
	Yes	2
Hydrocephalus	No	12
	Yes	2
Socioeconomic status	B1	1
	B2	1
	C	12
School	Yes	9
	No	5
Brothers/sisters	0	4
	1	8
	2	2

We applied the PEDI after an average interval of 2.5 ± 1.3 years post-stroke (range: 1 to 5.5 years). Of 14 children, 7 had another comorbidity in addition to the underlying disease: 6 (42.9%) had epilepsy and 1 (7.1%) had strabismus. Only 4 (28.6%) children underwent physical therapy rehabilitation (one of them had only 10 sessions before discharge). Of these, 2 (14.3%) also received occupational therapy and 1 (7.1%) received speech therapy. At the time of assessment, no child was receiving any type of rehabilitation intervention.

The average normative score for PEDI's functional skills in the self-care domain was 37.6 ± 15.4; in the mobility domain, it was 36.2 ± 15.4, and in the social function domain, it was 48.7 ± 11.1. Most children scored between 30 and 70 on the normative score profile. Only 4 (28.6%) children did not perform adequately in the self-care domain, 4 (28.6%) in mobility, and only 1 (7.1%) in social function. Among children with age-appropriate functional outcome, the average of normative scores for PEDI's functional skills in self-care, mobility and social function were, respectively, 46 ± 6.8, 43.7± 9.5, and 50.7 ± 8.7. Table 2 presents the children's normative score in self-care, mobility and social function skills.

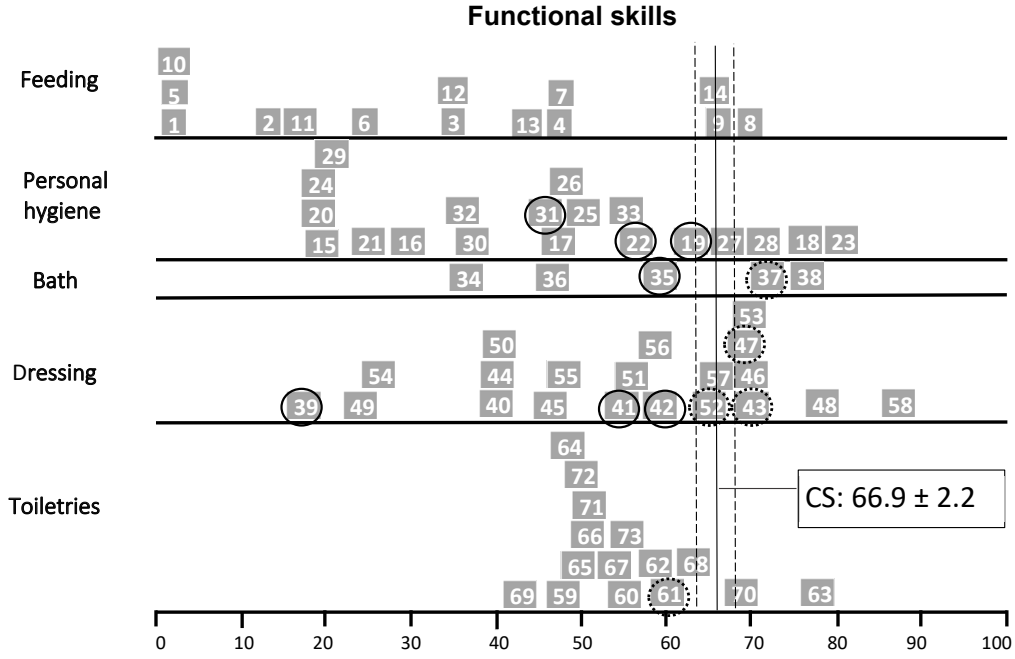
The self-care functional skills item maps of child P4 (Figure 2) showed that she performed below average compared to the normative sample on tasks related to personal hygiene (3 of 20 items), bathing (1 of 5 items) and dressing (3 of 21 items), especially on bimanual tasks or tasks that required movements of the upper limbs up to shoulder level. Similarly, the item

Table 2. Participants' characteristics and normative scores in the three PEDI functional domains.

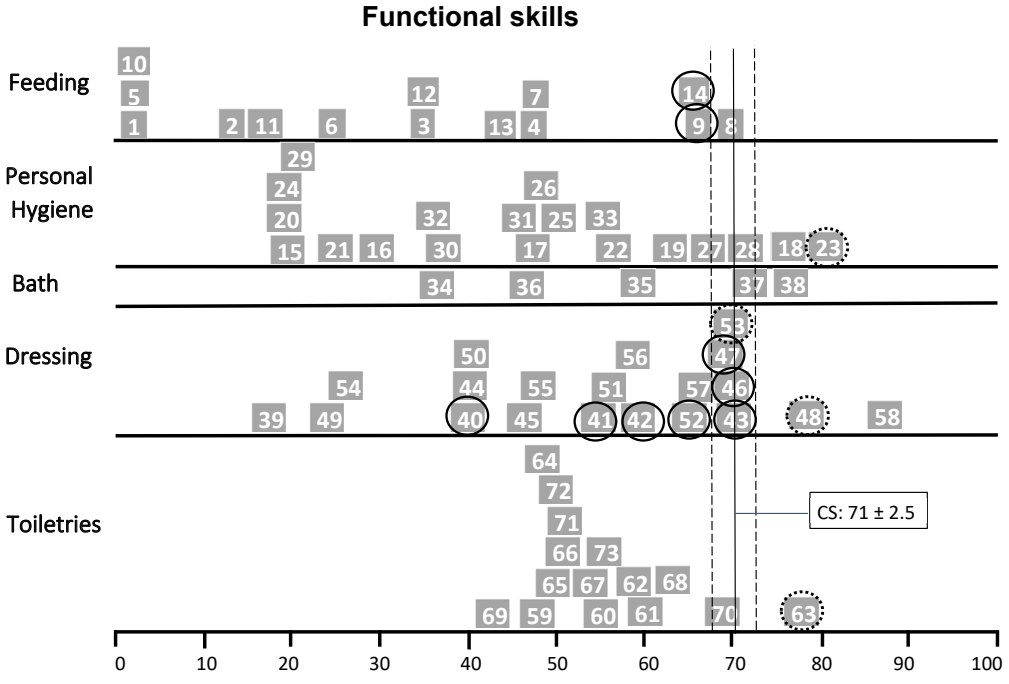
P (n=14)	Age at stroke	Age at assessment (years)	Stroke type	Lesion location	SCFS score	MOFS score	SFFS score
P1	2 d	5	H	Lobar	42.2	29.3*	54.3
P2	1.4 m	2	H	Deep	42.4	39.5	55.6
P3	2.0 m	2	I	Lobar	34.6	41	63.3
P4	4.9 m	4	I	Deep/ Infratentorial	21.2*	31	46.6
P5	6.8 m	2	I	Lobar	41.6	36.4	53.1
P6	11.2 m	3	I	Lobar	44.9	43.8	45.2
P7	12.9 m	2	H	Lobar	59.1	57.1	43.1
P8	13.2 m	5	I	Deep	23.3*	<10*	67.3
P9	18.6 m	3	I	Deep	47.3	39.4	45.2
P10	21.1 m	3	I	Lobar/Deep/ Infratent.	12.1*	<10*	23.3*
P11	24.3 m	3	I	Infratentorial	46.8	36.2	42.5
P12	38.8 m	6	H	Infratentorial	54.2	56.3	58.3
P13	46.9 m	6	H	Lobar	47.2	56.2	45.3
P14	52.8 m	5	H	Lobar	<10*	22.6*	38.9

P: participant; SCFS: Self-Care Functional Skills; MOFS: Mobility Functional Skills; SFFS: Social Function Functional Skills; I: Ischemic; H: Hemorrhagic; d: days; m: months; *score below that expected for the age (between 30-70).

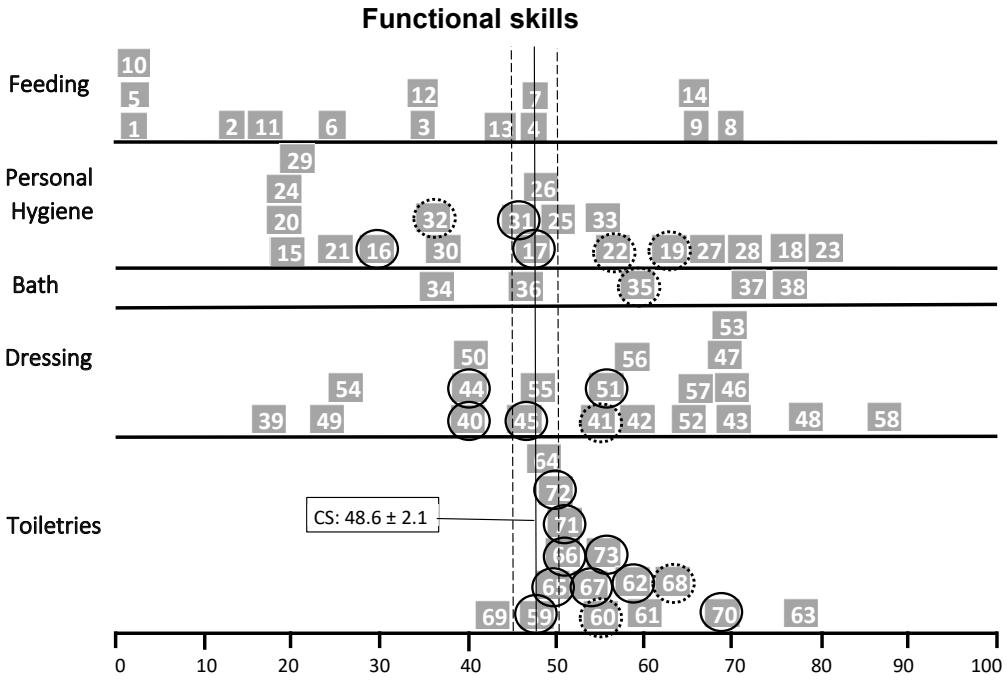
map of child P8 showed inadequate performance in feeding (2 of 15 items) and dressing (7 of 21), especially bimanual task items (Figure 3). Child P10's item map (Figure 4) showed an age-inappropriate performance on personal hygiene (3 items out of 20), dressing (4 of 21 items), and toiletries (9 of 15 items). This child's tasks limitations were related to the neuromotor and cognitive demands of the task's items. Child P14 showed inadequate performance on some feeding (2 items out of 15), personal hygiene (2 of 20 items), and toiletries items (3 of 15 items) and on most bathing (4 of 5 items) and dressing tasks (9 of 21 items), mainly related to routine care with the hemodialysis catheter (Figure 5).



◯ >90% of the children in the age group can do the task;
◌ >75% of the children in the s age group already can do the task;
CS: Continue Score; PEDI: Pediatric Evaluation of Disability Inventory.
Figure 2. PEDI Item Maps in Self-Care Functional Skills of child P4.

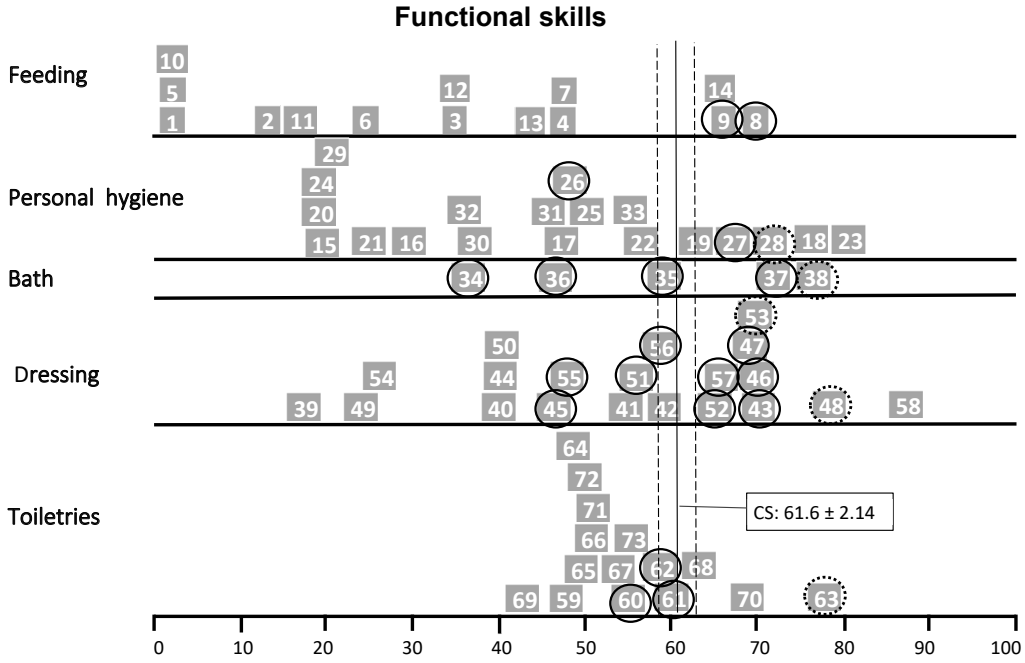


◯ >90% of the children in the age group can do the task;
◌ >75% of the children in the age group can do the task;
CS: Continue Score; PEDI: Pediatric Evaluation of Disability Inventory.
Figure 3. PEDI Items Map in Self-Care Functional Skills of the child P8.



◯ >90% of the children in the age group can do the task;
◌ >75% of the children in the age group can do the task;
CS: Continue Score; PEDI: Pediatric Evaluation of Disability Inventory.

Figure 4. PEDI Items Map in Self-Care Functional Skills of the child P10.



◯ >90% of the children in the age group can do the task;
◌ >75% of the children in the age group can do the task;
CS: Continue Score; PEDI: Pediatric Evaluation of Disability Inventory.

Figure 5. PEDI Items Map in Self-Care Functional Skills of the child P14.

In the mobility domain, child P8 only performed inadequately in bus transfers (2 of 5 items), shower transfers (1 of 5 items), indoor locomotion (1 of 13 items), outdoor locomotion (1 of 12 items) and stair climbing (2 of 10 items). Child P10 showed inadequate performance in all mobility sets: transfers in bathroom/ chair (5 of 10 items), in car (1 of 5 item), in shower (4 of 5 items), in bed (1 of 5 item), indoor locomotion (4 of 13 items), outdoor locomotion (3 of 12 items) and stair climbing (6 of 10 items). In the social function domain, this child had limitations in the following items: functional communication

use (1 of 5 items), expressive communication complexity (2 of 5 items), interactive social games playing with adults (2 of 5 items), playing with objects (4 of 5 items), self-information (2 of 10 items), housework (1 of 5 items), self-protection (2 of 5 items), and community function (1 of 5 items).

There was no correlation between scores in self-care and mobility domains with any of the analyzed independent variables (Table 3). The social function domain score was the only one that showed a significant correlation: the score was higher (better) for children who had a unilateral injury (p = 0.05).

When analyzing the PEDI's domain scores concerning hospital stay and current age, the social function domain score showed a strong negative correlation with hospital stay (r = -0.79; p = 0.001), as shown in Table 4.

Table 3. PEDI functional domains scores related to patients' characteristics (categorical)*.

Patients characteristics (n=14)		SCFS score	P-value	MOFS score	P-value	SFFS score	P-value
Age at stroke	< 1 year	37.8 ± 8.9	0.37	36.8 ± 5.7	0.90	53 ± 3.6	0.14
	> 1 year	37.4 ± 19.5		35.9 ± 20.2		45.5 ± 13	
Sex	Feminine	43.1 ± 11.7	0.37	41.4 ± 10.6	0.20	50.8 ± 7.6	0.56
	Male	30.3 ± 17.5		29.5 ± 18.7		45.9 ± 14.9	
Injury site	Deep	29.3 ± 14.9	0.26	25.8 ± 15.3	0.10	47.6 ± 16.2	0.79
	Lobar/Infratentorial	42.2 ± 14.2		42.1 ± 12.4		49.3 ± 8.2	
Stroke type	Ischemic	34 ± 13.5	0.24	30.9 ± 13.7	0.20	48.3 ± 13.6	0.79
	Hemorrhagic	42.4 ± 17.5		43.5 ± 15.3		49.3 ± 7.9	
Affected side	Unilateral	36.4 ± 13.3	0.37	33.6 ± 14.7	0.48	51.2 ± 12.3	0.05**
	Bilateral	40.6 ± 21.5		43 ± 16.7		42.4 ± 2.7	
Intraventricular hemorrhage	No	39.5 ± 14.1	0.27	37.1 ± 16	0.58	49 ± 11.5	0.72
	Yes	26 ± 23.3		31.1 ± 12		47.2 ± 11.8	
Hydrocephalus	No	39.5 ± 14.1	0.27	37.1 ± 16	0.58	49 ± 11.5	0.72
	Yes	26 ± 23.3		31.1 ± 12		47.2 ± 11.8	
Socioeconomic status	B	22 ± 17.8	0.10	31.8 ± 13	0.72	51.1 ± 17.2	1.00
	C	40.2 ± 14		37 ± 16		48.3 ± 10.8	

SCFS: Self-Care Functional Skills; MOFS: Mobility Functional Skills; SFFS: Social Function Functional Skills; I: Ischemic; H: Hemorrhagic; *Mann-Whitney non-parametric test; **Statistically significant.

Table 4. PEDI functional domain scores related to patients' characteristics*.

Patients characteristics	SCFS	p-value	MOFS	p-value	SFFS	p-value
Age at assessment (years)	-0.34	0.91	-0.18	0.54	0.08	0.8
Hospital stay (days)	-0.12	0.7	-0.84	0.78	-0.79**	0.001**

SCFS: Self-Care Functional Skills; MOFS: Mobility Functional Skills; SFFS: Social Function Functional Skills; I: Ischemic; H: Hemorrhagic; *:Spearman's correlation coefficient; **: Statistically significant.

DISCUSSION

We analyzed the functional outcome of 14 children diagnosed with stroke in early childhood. Overall, the children showed age-appropriate functional outcomes measured by the PEDI's functional domains: over 70% of them in self-care and mobility and 90% in social function. Children with bilateral injuries and longer hospital stays showed the worst scores in PEDI's social function domains.

Of the 4 children with age-inappropriate self-care performance (P4, P8, P10, P14), two (P4, P8) had typical hemiparetic sequelae limitations. Child P10 showed limitations related to neuromotor and cognitive demands on self-care tasks; this is the only child with age-inappropriate social function. The child had multiple lacunar infarctions and microangiopathy due to hemolytic-uremic syndrome (HUS) during hospital stay. Previous case reports of post-HUS children aged 15 and 21 months (the same age as the child in our study) also described neuromotor and language impairments[21]. On the other hand, child P14 had no evident motor deficit; most of its limitations in self-care were related to routine care of the hemodialysis catheter due to chronic kidney disease.

Among the children with age-inappropriate mobility (P1, P8, P10, P14), children P8 and P10 had neuromotor limitations to a lesser or greater degree. However, the low scores of children P1 and P14 may be due to a limitation on the normative scale. At the time of data collection, both children were between 5 years and 5 years and 5 months old. Within this age range, raw

scores of P1 and P14 reflect an age-inappropriate performance when compared to normative scores (below 30). However, similar scores in the following age range (5 years and 6 months to 5 years and 11 months) reflected an age-appropriate performance, with normative scores greater than 30. Considering that certain scores are considered age-inappropriate in a certain age range, but identical scores are considered age-appropriate in an older age range, it is possible that the normative scores are a limitation and may require further investigation.

To the best of our knowledge, only Galvin et al.[9] used the PEDI to assess functional outcomes after childhood stroke. However, the authors only presented each domain's average score (not the children's frequency of appropriate outcomes), precluding the comparison with our results. The children in our study presented age-appropriate average scores in self-care, mobility, and social function domains, although scores were close to the lower limit of normality. This is in accordance with previous childhood stroke studies showing good mobility, even with hemiparesis and requiring orthoses[13,22]. Cooper et al.[23] found good motor recovery (fine and gross motor function) in children (0-19 years) over the first year after stroke, with more pronounced improvement in preschool-age children[23].

Conversely, Galvin et al.[9] observed that children with ischemic stroke showed lower levels of functional skills in all domains: self-care (70.36 ± 30.82), mobility (77.97 ± 27.58) and social function (74.88 ± 30.57). Previous studies have demonstrated that children with stroke showed unsatisfactory performance for ADLs, communication, and social function activities[12,22], especially in early-age stroke children[22], which does not corroborate with our results. However, the age range of our sample may explain such discrepancy. Specifically, the studies mentioned above involved children up to 16 [9] and 18 years of age[12,22], while our study included children up to 7.5 years of age. In this age range, deficits in complex communication, ADLs, and social skills may not be as obvious. Also, the development of each of these skills influences that of the other; Cooper et al.[23] described that communication skills may influence ADL throughout children's development[23].

Similarly, studies suggest that children present reduced communication skills, as well as the cognition-related and social functions after stroke. Friefeld et al.[24] observed that the quality of life (QoL) related to physical aspects and the domestic environment was less impaired and the QoL related to school and playing were more affected, mainly due to cognitive and behavioral elements[24]. Based on the literature, about half of the children with childhood stroke present limitations on school activities and participation and require specialized education[12,22,25,26]. Additionally, children present significant impairment on cognition-related functions, intelligence, memory, language, and social function[6,26,27]. Studies have also shown that cognitive social and task performances were worse in children who had stroke at a younger age[6,26,28].

The significant negative correlation between length hospital stay and social function may be reflecting the impact of the chronic underlying condition on socialization. Of the four children with longer hospital stays, only one had evident neuromotor sequelae (P10). However, all of them had a systemic condition (chronic liver or renal disease/ vasculopathy with toes amputation) with potential clinical complications, which could affect the dynamics of family functioning related to child care. Supporting this speculation, Christerson and Strömberg[12] reported that post-stroke children's outcomes were more dependent on etiology and recurrences (rebleeding, metabolic diseases, Moya-Moya syndrome) than the age at stroke or injury site. A weak social competence may not be due solely to brain injuries but to the child's experience with the particularities of the illness in their social world[29].

The relationship between worse scores in social function and bilateral injury may be related to the children's interhemispheric neuroplasticity process. Mosch et al.[30] observed that, differently from adults, children with right cerebral hemisphere (RCH) injury did not present reduced social function, suggesting a positive plasticity process in children. However, children with left cerebral hemisphere (LCH) injury presented worse social function (and better language function) than adults with an LCH injury. Authors speculate that after LCH injury in children, the plasticity process may involve recruiting RCH contralateral areas previously intended for social function to preserve LCH functions, such as language[30]. In our study, social function skills did not correlate with LCH injury. This may be due to the younger age of our sample. The complexity of preschool social demands is low and usually related to lower-order skills, which can be attributed to less complex neural networks and often have good functional recovery[31-33]. The more complex skills that are usually impaired after childhood stroke (executive, cognitive, social skills) are needed as children grow up and move into more socially complex environments like school, college, and work[6,22,24,26,34].

The age-appropriate functional outcomes in childhood after stroke found in our study should be interpreted with caution and considered especially from a functional perspective. The finding shows that preschool children can functionally keep up with their peers despite stroke. The PEDI score is influenced by the ICF model, in which the functionality in a specific domain results from the interaction between health condition and the contextual factors (environmental and personal)[4]. Functional performance in a given task is influenced not only by the child's characteristics but also by the task's specific demands and the environmental aspects with which the child interacts[35]. According to the ICF, effective rehabilitation requires going beyond pathological conditions/sequels and promoting the individual's activity and participation[36].

One limitation of our study is the small number of participants. On the other hand, this allowed rich inferences from the occasional analysis of isolated cases. As an implication for research, our study reinforces the importance of the interhemispheric neuroplasticity process in children and the impact of the chronic nature of the underlying condition/stroke on social

functions. Moreover, it has implications for clinical practice by supporting recovery based on activity/participation levels and increase surveillance of children with stroke, mainly related to social function, even when there are no obvious deficits at discharge.

In summary, preschool children showed age-appropriate functional outcomes on self-care, mobility, and social function domains after stroke. However, children with bilateral injuries and longer hospital stays had the worst scores in social function domains. We recommend focusing on functional rehabilitation to promote activities and participation and to monitor the development of the children's social skills after stroke.

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ARTICLE

Accuracy of the Brief Cognitive Screening Battery for diagnosing Alzheimer's disease defined by cerebrospinal fluid biomarkers and AT(N) classification: a case-control study

Acurácia da Bateria Breve de Rastreio Cognitivo no diagnóstico da doença de Alzheimer definida por biomarcadores no líquido cefalorraquidiano e classificação pelo sistema AT(N): estudo caso-controle

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ABSTRACT

Background: Validation of cognitive instruments for detection of Alzheimer's disease (AD) based on correlation with diagnostic biomarkers allows more reliable identification of the disease. **Objectives:** To investigate the accuracy of the Brief Cognitive Screening Battery (BCSB) in the differential diagnosis between AD, non-AD cognitive impairment (both defined by cerebrospinal fluid [CSF] biomarkers) and healthy cognition, and to correlate CSF biomarker results with cognitive performance. **Methods:** Overall, 117 individuals were evaluated: 45 patients with mild cognitive impairment (MCI) or mild dementia within the AD *continuum* defined by the AT(N) classification [A+T+/-(N)+/]; 27 non-AD patients with MCI or mild dementia [A-T+/-(N)+/-]; and 45 cognitively healthy individuals without CSF biomarker results. All participants underwent evaluation using the BCSB. **Results:** The total BCSB and delayed recall (DR) scores of the BCSB memory test showed high diagnostic accuracy, as indicated by areas under the ROC curve (AUC): 0.89 and 0.87, respectively, for discrimination between AD and non-AD *versus* cognitively healthy controls. Similarly, total BCSB and DR displayed high accuracy (AUC-ROC curves of 0.89 and 0.91, respectively) for differentiation between AD and controls. BCSB tests displayed low accuracy for differentiation between AD and non-AD. The CSF levels of biomarkers correlated significantly, though weakly, with DR. **Conclusions:** Total BCSB and DR scores presented good accuracy for differentiation between patients with a biological AD diagnosis and cognitively healthy individuals, but low accuracy for differentiating AD from non-AD patients.

Keywords: Alzheimer Disease; Cognitive Dysfunction; Diagnosis; Biomarkers; Cognition.

RESUMO

Antecedentes: A validação de testes cognitivos para identificação da doença de Alzheimer (DA) definida por biomarcadores aumenta a confiabilidade diagnóstica. **Objetivos:** Investigar a acurácia da Bateria Breve de Rastreio Cognitivo (BBRC) no diagnóstico diferencial entre DA, comprometimento cognitivo não-DA (ambos diagnósticos definidos por biomarcadores no líquido cefalorraquidiano-LCR) e indivíduos cognitivamente saudáveis, e investigar correlações entre desempenho nos testes e concentrações dos biomarcadores no LCR. **Métodos:** No total, 117 indivíduos foram avaliados. Quarenta e cinco pacientes com comprometimento cognitivo leve (CCL) ou demência leve com diagnóstico do *continuum* de DA definido pela classificação AT(N) [A+T+/-(N)+/-], 27 pacientes com CCL ou demência leve não-DA [A-T+/-(N)+/-], e 45 controles cognitivamente saudáveis sem estudo de biomarcadores no LCR. Os participantes foram submetidos à BBRC. **Resultados:** O escore total da BBRC e a evocação tardia (ET) no teste de memória da BBRC apresentaram elevada acurácia diagnóstica na diferenciação entre DA e não-DA *versus* controles, indicada pelas áreas sob a curva ROC (AUC) de 0,89 e 0,87, respectivamente. De modo semelhante, o escore total da BBRC e a ET mostraram elevadas acurácias (AUC-ROC de 0,89 e 0,91, respectivamente) para o diagnóstico diferencial entre

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DA e controles. A acurácia da BBRC foi baixa na diferenciação entre DA e não-DA. Os níveis dos biomarcadores no LCR se correlacionaram de forma significativa, embora fraca, com ET. **Conclusões:** Os escores totais da BCSB e a ET apresentaram boa acurácia na diferenciação entre pacientes com diagnóstico biológico de DA e controles cognitivamente saudáveis, mas baixa acurácia para diferenciar DA de não-DA.

Palavras-chave: Doença de Alzheimer; Disfunção Cognitiva; Diagnóstico; Biomarcadores; Cognição.

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia worldwide[1,2,3], although often underreported[4,5,6]. Until recently, AD was diagnosed based solely on identification of a characteristic cognitive profile and through ruling out other diseases using ancillary tests. Lately, important advances have been achieved through development of specific biomarkers[7].

The cerebrospinal fluid (CSF) biomarker profiles associated with AD consist of reduced concentration of beta-amyloid (Aβ42) and increased concentrations of total tau (T-Tau) and phosphorylated tau (P-Tau). Detection of these biomarkers, by means of CSF analysis or neuroimaging methods, allows a biological diagnosis of AD and differentiation from non-AD dementias through the AT(N) classification. In the AT(N) system, A+ individuals, regardless of whether T and (N) are + or -, are qualified as presenting the *continuum* of the AD pathological process. However, determining these diagnostic biomarkers is costly or invasive, besides being commonly unavailable. Thus, the most-used diagnostic methods are clinical assessment, laboratory tests and structural neuroimaging[8].

The Brief Cognitive Screening Battery (BCSB) is a useful tool for detect dementia, particularly AD[9]. Several studies have investigated the psychometric characteristics of the BCSB[10,11,12]. However, the BCSB has not been investigated or validated among patients with a biological AD diagnosis, which could enhance the evidence for its clinical use.

The present study aimed to investigate the BCSB for diagnosing the AD *continuum* and the association between BCSB scores and CSF biomarker concentrations.

METHODS

Our institution's research ethics committee approved the study.

Participants

The sample was divided into AD (i.e., AD *continuum*), non-AD and control groups. Individuals with schooling levels of less than four years or with scores below 20 points in the Mini-Mental State Examination (MMSE)[13,14] were excluded.

AD and non-AD patients presented a clinical diagnosis of mild cognitive impairment (MCI) or mild dementia. All patients underwent CSF biomarker analysis, with concentration measurements on Aβ42, T-tau and P-tau. The diagnostic categorization of AD and non-AD was purely biological, independent of the cognitive results. Thus, two diagnostic classifications were established: 1) clinical, in accordance with consensual criteria for AD[15,16] behavioral variant frontotemporal dementia[17], vascular dementia[18,19], primary progressive aphasia[20] and dementia with Lewy bodies[21,22]; and 2) biological, based on CSF biomarkers and on the AT(N) classification. The clinical and biological classifications were performed by independent researchers.

The cognitively healthy controls used in this study did not have any history of neurological or psychiatric disorders, or depression according to clinical assessment, were not taking medications with cognitive effects and presented normal MMSE[13,14] scores for their age and education[23]. CSF biomarkers were not available for controls.

Instruments

The participants underwent MMSE and BCSB assessments. The BCSB comprises three tests: 1. Figure memory test (FMT)[24], including naming, incidental memory, immediate memory, learning, delayed recall (DR) and recognition; 2. Verbal fluency (VF) test, in animals/minute[25] 3. Clock drawing test (CDT)[26].

In the FMT, a board with 10 drawings is presented to participants, who are asked to name them; then, without the board, these subjects are asked to evoke the drawings (incidental memory). Subsequently, the board is shown twice for 30 seconds, for two recalls (immediate memory and learning). VF and CDT are administered as interference tests, followed by DR of the drawings and recognition. BCSB administration usually takes eight to 10 minutes.

Total scores were calculated for each task separately and were transformed into z scores based on BCSB[11] normative data, stratified according to age and education.

Biological analysis

CSF analyses were conducted in two laboratories, following the same procedures. CSF samples were centrifuged at 3,000 revolutions per minute for 10 minutes, at 4ºC, no more than four hours after collection. CSF aliquots were frozen in polypropylene tubes at -80ºC until analysis. Biomarkers were measured by means of the enzyme-linked immunosorbent assay (ELISA) technique using INNOTEST hTAU Ag, PHOSPHO-TAU (181P) and β-Amyloid (1-42) kits (Fujirebio Europe NV, Gent, Belgium), following the manufacturer's instructions. The reference values for AD diagnosis were Aβ42 < 700 pg/mL, T-tau

> 375 pg/mL and P-tau > 60 pg/mL. The reference values for non-AD diagnoses were Aβ42 ≥ 700 pg/mL, T-tau ≤ 375 pg/mL, P-tau ≤ 60 pg/mL[27].

Statistical analysis

First, we conducted descriptive analysis on the sociodemographic data and on the raw scores from the cognitive tests. Then, we used the Kruskal-Wallis test with z-scores controlled according to age and education, to investigate differences in BCSB subtests between AD *vs.* non-AD *vs.* controls. Effect sizes were calculated. The Kendall method, with Bonferroni corrections, was used to explore correlations between biomarkers and cognitive performance. The sensitivity and specificity of BCSB subtests for diagnosing clinical groups were determined through receiver operating characteristic (ROC) curves. Lastly, logistic regression analysis was used to investigate the likelihood of identifying clinical cases using BCSB subtests.

RESULTS

The AD group included 45 participants (57.7% women), with a mean age of 65.3 years (SD = 6.5) and mean schooling of 13.1 years (SD = 5.1) [34 A+T+(N)+; 2 A+T+(N)-; 9 A+T-(N)-]. The AD patients had a mean symptom duration of 2.7 years (SD = 1.8). The non-AD group included 27 participants (37.0% women), with a mean age of 64.5 years (SD = 6.4) and mean schooling of 11.9 years (SD = 4.6) [21 A-T-(N)-; 1 A-T-(N)+; 1 A-T+(N)-; 4 A-T+(N)+]. The non-AD group included 13 participants with behavioral variant temporal dementia, eight patients with MCI, three with semantic variant-primary progressive aphasia, one with vascular dementia, one with dementia with Lewy bodies and one with dementia of undefined etiology. The non-AD patients had a mean symptom duration of 2.1 years (SD = 1.1). The control group included 45 participants (44.4% women), with a mean age of 68.9 years (SD = 5.6) and mean schooling of 10.0 years (SD = 5.1). Table 1 presents sociodemographic and cognitive performance data for each group.

The AD patients performed significantly worse than both the non-AD patients and the controls only in the DR subtest. In the incidental memory subtest, the AD patients displayed significantly lower performance than the controls, but performed similarly to the non-AD patients. In the VF subtest, the AD patients performed better than the non-AD participants, but worse than the controls. In immediate memory, learning and recognition, the AD and non-AD groups performed significantly worse than the controls, although AD and non-AD performances were similar.

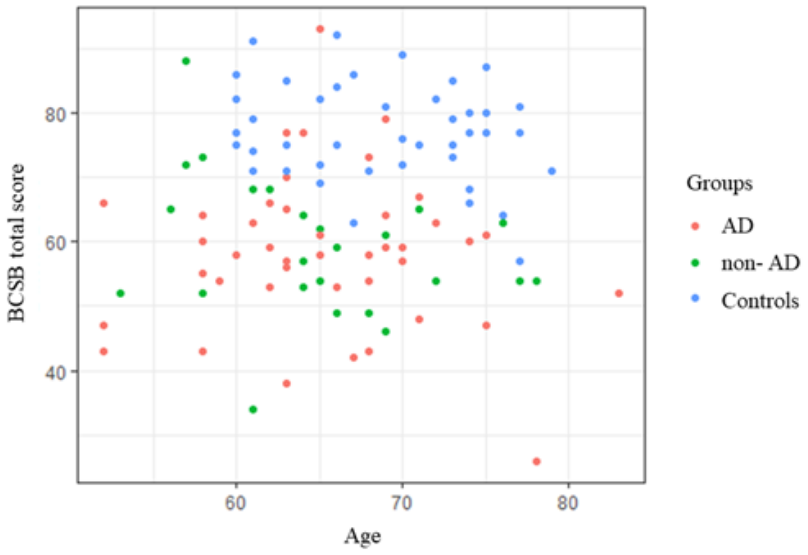
Regarding BCSB total scores, the AD and non-AD groups displayed significantly lower performance than the controls. Figure 1 shows the dispersion of cases according to age, total BCSB score and group.

The area under the ROC curve (AUC), confidence interval, sensitivity, specificity and best cutoff scores were calculated for each BCSB variable for differential diagnoses between AD, non-AD and controls (Table 2).

Table 1. Sociodemographic and cognitive data of the AD, non-AD and control groups.

Subtests	AD (n = 45)	Non-AD (n = 27)	Controls (n = 45)	K	P	Post-hoc (Dunn test)	Effect size
Age	65.3 (6.5)	64.5 (6.4)	68.9 (5.6)	5.35	< 0.005	0 = 1 < 2	d = 0.31
Schooling	13.1 (5.1)	11.9 (4.6)	10.0 (5.1)	4.48	< 0.01	0 = 1 > 2	d = 0.28
Sex					p < 0.007	x^2 = 5.28	
Men	19	17	16				
Woman	26	10	29				
MMSE	24.1 (2.8)	24.2 (2.1)	28.0 (1.2)	14.31	< 0.001	0 = 1 < 2	η^2 = 0.10
Naming	9.8 (0.5)	9.7 (0.8)	9.9 (0.2)	0.59	0.74	–	–
Inc. Mem	4.5 (1.9)	5.1 (1.8)	5.8 (1.3)	9.34	< 0.001	0 < 2; 1 = 2	η^2 = 0.06
Im. Mem	6.2 (1.64)	6.7 (1.6)	8.1 (1.19)	31.77	< 0.001	0 = 1 < 2	η^2 = 0.25
Learning	7.0 (1.7)	7.4 (2.2)	8.9 (1.0)	26.26	< 0,001	0 = 1 < 2	η^2 = 0.21
DR	4.5 (2.2)	6.1 (2.4)	8.3 (1.2)	48.46	< 0.001	0 < 1 < 2	η^2 = 0.40
Recognition	8.7 (2.0)	8.0 (2.2)	9.8 (0.4)	16.26	< 0.001	0 = 1 < 2	η^2 = 0.12
VF	13.3 (5.1)	11.4 (4.6)	17.7 (4.7)	25.61	< 0.001	1 < 0 < 2	η^2 = 0.21
CDT	6.9 (2.3)	6.6 (2.3)	8.3 (1.7)	6.48	< 0.03	–	–
BCSB total	59.4 (12.4)	59.7 (10.7)	77.1 (7.4)	31.98	< 0.001	0 = 1 < 2	η^2 = 0.26

0: AD; 1: non-AD; 2: Control; MMSE: Mini-Mental State Examination; Inc. Mem: incidental memory; Im. Mem: immediate memory; DR: delayed recall; VF: verbal fluency; CDT: clock drawing test; BCSB: Brief Cognitive Screening Battery.



BCSB: Brief Cognitive Screening Battery.

Figure 1. Dispersion according to age and total BCSB score.

Table 2. Data from ROC curves for comparisons between clinical groups (AD and non-AD) and controls, and between AD and non-AD patients.

	Variable	Naming	Inc Mem	Im Mem	Learning	DR	Recognition	VF	CDT	BCSB total
Clinical groups vs. Controls	AUC	0.53	0.68	0.79	0.78	0.87	0.69	0.78	0.69	0.89
	95% CI	0.43 to 0.62	0.58 to 0.76	0.71 to 0.86	0.69 to 0.851	0.79 to 0.92	0.59 to 0.77	0.69 to 0.85	0.59 to 0.78	0.83 to 0.95
	Sensitivity	5.56	65.28	51.39	76.39	80.56	48.61	68.18	63.33	88.89
	Specificity	100	64.44	93.33	71.11	77.78	86.67	80.00	75.56	81.94
	Cutoff	≤ 8	≤ 5	≤ 6	< 8	< 7	≤ 9	≤ 13	≤ 8	≤ 68
AD vs. Controls	AUC	0.53	0.71	0.82	0.82	0.91	0.70	0.75	0.67	0.89
	95% CI	0.43 to 0.62	0.60 to 0.81	0.73 to 0.89	0.72 to 0.89	0.84 to 0.96	0.60 to 0.80	0.64 to 0.83	0.56 to 0.77	0.81 to 0.94
	Sensitivity	5.57	71.11	57.78	82.22	68.89	51.11	67.44	62.16	80
	Specificity	100.00	64.44	93.33	71.11	100	86.67	73.33	75.56	91.11
	Cutoff	≤ 8	≤ 5	≤ 6	≤ 8	≤ 5	≤ 9	≤ 14	≤ 8	≤ 67
AD vs. non-AD	AUC	0.51	0.58	0.58	0.60	0.69	0.55	0.63	0.54	0.50
	95% CI	0.39 to 0.63	0.46 to 0.70	0.46 to 0.70	0.48 to 0.71	0.57 to 0.79	0.43 to 0.67	0.50 to 0.75	0.41 to 0.67	0.38 to 0.62
	Sensitivity	100	71.11	57.78	53.33	53.33	26.67	72.09	64.86	80.00
	Specificity	3.7	44.44	59.26	62.96	81.48	85.19	52.17	43.48	7.41
	Cutoff	> 5	≤ 5	≤ 6	≤ 7	≤ 4	≤ 8	> 10	> 5	> 48

AUC: area under the curve; 95% CI: Confidence interval; Criterion: cutoff point; Inc. Mem.: incidental memory; Im. Mem.: immediate memory; DR: delayed recall; VF: verbal fluency; CDT: clock drawing test; BCSB: Brief Cognitive Screening Battery.

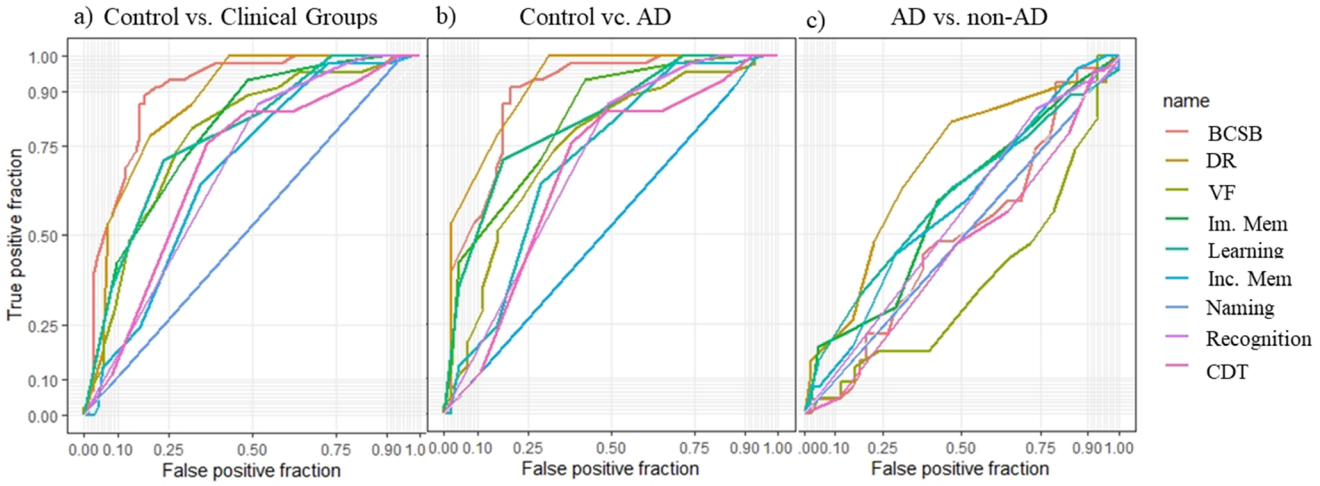
As can be seen in Figure 2 (A, B), naming did not present satisfactory AUC in any of the comparisons. The DR subtest and total BCSB score presented the best AUC values for comparisons between clinical groups and controls, and between AD and controls. None of the BCSB subtests displayed good AUC for differentiation between AD and non-AD (Figure 2C).

In the logistic regression analysis, DR and total BCSB scores displayed the best results regarding diagnostic prediction of clinical groups. The learning subtest of the FMT was the only test that significantly differentiated AD from non-AD cases (Table 3).

Correlations between CSF biomarkers and performance in the BCSB among AD and non-AD patients were weak, but significant between biomarkers and DR. A positive correlation between DR and Aβ42 (K = 0.17; $p < 0.03$), and negative correlations between DR and T-tau (K = - 0.24; $p < 0.003$) and P-tau (k = - 0.24; $p < 0.004$) were observed.

DISCUSSION

The BCSB proved to be a good screening instrument for identifying AD *continuum* and non-AD patients, as defined through the CSF biomarkers and AT(N) classification system, in MCI or mild dementia stages, with good sensitivity and specificity.



Inc. Mem: incidental memory; Im. Mem: immediate memory; DR: delayed recall; VF: verbal fluency; CDT: clock drawing test; BCSB: Brief Cognitive Screening Battery (total).

Figure 2. ROC curves for comparisons between groups.

Table 3. Results from logistic regression comparisons between groups.

	Variable	Naming	Inc Mem	Im Mem	Learning	DR	Recognition	VF	CDT	BCSB total
Clinical groups *vs.* Controls	Odds ratio	1.00	0.80	1.23	0.99	2.40	1.04	1.17	1.10	1.22
	95% CI	0.82 to 1.21	0.46 to 1.36	0.69 to 2.24	0.58 to 1.68	1.40 to 4.69	0.83 to 1.38	0.94 to 1.46	0.83 to 1.46	1.04 to 1.52
	p value	0.72	< 0.001	< 0.001	0.08	< 0.001	0.18	0.09	0.3	< 0.05
AD *vs.* Controls	Odds ratio	0.9	0.8	1.22	1.23	2.95	0.94	1.06	1.14	1.26
	95% CI	0.63 to 1.23	0.39 to 1.56	0.61 to 2.47	0.59 to 2.14	1.55 to 6.88	0.66 to 1.33	0.75 to 1.37	0.80 to 1.63	1.02 to 1.80
	p value	0.77	< 0.001	< 0.001	< 0.01	< 0.001	0.74	0.58	0.44	0.02
AD *vs.* Non-AD	Odds ratio	0.78	0.71	0.69	1.88	1.38	0.85	0.68	1.01	1.3
	95% CI	0.56 to 1.01	0.31 to 1.50	0.34 to 1.29	1.15 to 3.50	0.90 to 2.38	0.66 to 1.07	0.38 to 1.03	0.67 to 1.57	0.89 to 2.09
	p value	0.2	0.99	0.51	< 0.01	0.09	0.09	0.06	0.92	0.19

Inc. Mem: incidental memory; Im. Mem: immediate memory; DR: delayed recall; VF: verbal fluency; CDT: clock drawing test; BCSB: Brief Cognitive Screening Battery.

In most subtests, AD patients performed worse than controls. Moreover, the DR subtest displayed good specificity for differentiating AD from non-AD, although with low sensitivity.

The sensitivity and specificity in our study were lower than those found in previous investigations using the BCSB[12,13,16]. It is possible that inclusion of non-amnestic AD patients, together with FTD patients with possible memory changes in the non-AD group, may have decreased BCSB accuracy. Furthermore, the increased diagnostic precision determined by biomarkers may also have influenced the results. It should also be considered that the AT(N) classification does not encompass the full spectrum of possible pathophysiological changes associated with aging. Accordingly, new CSF biomarkers (e.g. neurofilament light chain and neurogranin) have been used to optimize dementia diagnoses[28]. In addition, cognitive deficits are not specific for each clinical condition and usually overlap across

different diseases[29]. In sum, our results confirm that cognitive tests are sensitive tools for MCI/dementia screening, but the correspondence between clinical and underlying pathological features is not linear.

The BCSB displayed good diagnostic accuracy, thus corroborating previous results[11,12,13,30]. DR was the best BCSB subtest, in comparing AD and controls. Previous studies[31,32] identified that the BCSB DR test was superior to CERAD DR among illiterate individuals[33,34] DR, while these tests had similar accuracy among literate people.

Interestingly, the learning subtest of FMT was the only significant variable in the logistic regression to discriminate between AD and non-AD. However, DR was only marginally significant, and the results suggest that this test was also able to discriminate between AD and non-AD patients. The ROC curve analysis showed that DR was slightly superior to learning, with similar sensitivity, but with greater specificity. Thus, caution is needed in interpreting these results, because our non-AD group included patients with different etiologies and also with episodic memory deficits.

Negative correlations were found between DR and CSF T-tau and P-tau concentrations, and a positive correlation between DR and Aβ42. However, all these correlations were weak. It is important to highlight that elevated T-tau levels in the CSF, indicative of neurodegeneration or (N+), were observed in 3/4 of AD patients, but in less than 10% of non-AD cases.

Investigation of CSF biomarkers in association with cognitive testing contributes to understanding deficits that may be attributable to the biological substrates of AD. In two studies that investigated CSF biomarkers in relation to cognition, Rolstad et al. observed that Aβ42 levels correlated with episodic memory deficits, starting from the onset of the disease[35], while T-tau levels had a small to moderate influence on all cognitive domains, except for visuospatial abilities, in patients with MCI[36]. Some studies[37,38] correlated biomarkers and cognition in a temporal pattern, such that cognitive performance correlated first with Aβ42, then with T-tau and P-tau. This suggested that combination of neuropsychological assessment with CSF biomarkers is useful for making AD differential diagnoses. Additionally, the concentrations of P-tau have greater specificity for AD diagnosis, showing good discrimination between AD and frontotemporal dementia, since the levels of this biomarker are more associated with cognition in AD and correlate with disease stage[39].

The BCSB cutoff scores presented in our study indicate high precision in identifying AD and non-AD, since the diagnoses were based on CSF biomarkers. However, the present study was limited by the lack of biomarker data among the controls and by small sample sizes. In addition, although biomarker analyses were carried out using the same diagnostic kit, the tests were conducted in two laboratories, which might have skewed the biomarker measurements.

Combination of less invasive and more accessible tests makes it possible to overcome the financial and structural challenges of the healthcare system, without neglecting diagnostic reliability. In view of the growing demand for differential diagnoses of dementia, it is necessary to use validated instruments to assist in diagnostic investigation. We conclude that the BCSB displays good accuracy for differentiation between patients with a biological diagnosis of AD, non-AD patients and controls, thus confirming its value as a cognitive screening tool for clinical practice.

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ARTICLE

Verbal Learning as a predictor of risks of accidents in elderly drivers

Aprendizado verbal como preditor de risco de acidentes em idosos

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ABSTRACT

Background: Age-related cognitive decline impacts cognitive abilities essential for driving. **Objective:** We aimed to measure main cognitive functions associated with a high number of traffic violations in different driving settings. **Methods:** Thirty-four elderly individuals, aged between 65 and 90 years, were evaluated with a driving simulator in four different settings (Intersection, Overtaking, Rain, and Malfunction tasks) and underwent a battery of cognitive tests, including memory, attention, visuospatial, and cognitive screening tests. Individuals were divided into two groups: High-risk driving (HR, top 20% of penalty points) and normal-risk driving (NR). Non-parametric group comparison and regression analysis were performed. **Results:** The HR group showed higher total driving penalty score compared to the NR group (median=29, range= 9–44 vs. median=61, range= 47–97, p<0.001). The HR group showed higher penalty scores in the Intersection task (p<0.001) and the Overtaking and Rain tasks (p<0.05 both). The verbal learning score was significantly lower in the HR group (median=33, range=12–57) compared with the NR group (median=38, range=23–57, p<0.05), and it was observed that this score had the best predictive value for worse driving performance in the regression model. General cognitive screening tests (Mini-Mental State Examination and Addenbrooke's Cognitive Evaluation) were similar between the groups (p>0.05), with a small effect size (Cohen's d=0.3 both). **Conclusion:** The verbal learning score may be a better predictor of driving risk than cognitive screening tests. High-risk drivers also showed significantly higher traffic driving penalty scores in the Intersection, Overtaking, and Rain tests.

Keywords: Automobile Driving; Memory; Risk Management; Aged.

RESUMO

Antecedentes: O declínio cognitivo relacionado à idade impacta as habilidades cognitivas essenciais para direção. **Objetivos:** Nosso objetivo foi medir as funções cognitivas associadas ao alto número de violações de trânsito em diferentes contextos de direção. **Métodos:** Trinta e quatro idosos entre 65 e 90 anos foram avaliados em simulador de direção em quatro diferentes contextos (Travessia, Ultrapassagem, Chuva e Mal-funcionamento) e realizaram uma série de testes cognitivos, incluindo memória, atenção, visuoespacial e rastreamento. Indivíduos foram então divididos em dois grupos: Alto Risco de condução (HR, top 20% de pontos de penalidades de condução), e Risco Normal (NR). Comparações não-paramétricas e análise de regressão foram realizadas. **Resultados:** O grupo HR mostrou aumento no escore total de penalidades de condução quando comparado com o grupo NR (mediana=29, limites=9-44 vs. mediana=61, limites=47-97, p<0.001). O grupo HR mostrou maiores escores de penalidade na tarefa de Travessia (p<0.001), Ultrapassagem e Chuva (p<0.05 ambos). O escore de aprendizado verbal foi significativamente menor no grupo HR (mediana=33, limite=12-57) comparado com o grupo NR (mediana=38, limite=23-57, p<0.05), e foi observado que este escore foi o melhor preditor de pior performance de condução no modelo de regressão. Testes de rastreio cognitivo (Mini-exame do estado mental e Avaliação Cognitiva de Addenbroke) foram similar entre os grupos (p>0.05), com pequena magnitude de efeito (Cohen's d=0.3). **Conclusões:** O escore de aprendizado verbal pode ser o melhor preditor de risco de condução do que os testes de rastreio cognitivos. Motoristas de alto risco também mostraram maior escores de penalidade de trânsito nos testes de Travessia, Ultrapassagem e Chuva.

Palavras-chave: Condução de Veículo; Memória; Gestão de Riscos; Idoso.

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Authors' contributions: AMV: collected the data, wrote the manuscript and designed this study; WVB: analyzed the results, wrote the manuscript and reviewed its final version; MSP: designed the study, coordinated it and reviewed the final version; MWP: coordinated the study and reviewed its final version.

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INTRODUCTION

Traffic accidents are a major cause of death in all age groups[1]. There is a growing number of individuals driving cars in urban areas, especially older adults[2], and with the constant increase in the geriatric population, the number of older adults obtaining a driver's license has increased[3]. However, age-related cognitive decline affects driving abilities and may increase the number of traffic violations and accidents[4].

Driving plays an important role in social integration and promotes psychological and physical well-being. There is a clear association between driving cessation and impact on autonomy and quality of life. Driving cessation in elderly leads to an important shift in productive engagement and to higher rates of depressive symptoms[5,6]. The transition to a stage of inability to drive may be inevitable with cognitive decline, but it is not crlearly defined in older adults without dementia[7].

As driving a vehicle is a highly complex task, several cognitive skills must be integrated simultaneously. Assessing driving capacity requires a broad evaluation of both qualitative and quantitative measures, including cognitive, psychological, and emotional factors. Some earlier studies did not find any clear association between a cognitive measure and driving capacity[8]. Safe driving requires adequate functioning of attentional and visuospatial skills, which are domains that typically decline with aging. Furthermore, older adults have longer reaction times[9] and tend to make more safety errors while driving[10]. Visual-spatial abilities and their integration with motor tasks are more vulnerable to the aging process, and therefore, severely affect the driving skills of older adults.

Driving simulators have been widely used for multiple neurological conditions[11]. There are some strengths and weaknesses in assessing driving abilities with a simulator[12]. A driving simulator, most commonly used for improving driving performance in older adults, is also useful for attention skills[13]. Older drivers in particular may benefit from a simulator setting because it is an efficient and valid training instrument for multiple cognitive abilities[12] and provides a safe environment. Besides, it is also useful in generating highly accurate research data in studies involving neurocognitive abilities and their relationship to drivers. On the other hand, a simulator may not correspond to the reality of driving, apart from the motion sickness associated with virtual reality[14,15].

Impaired driving due to an underlying neurological condition may pose a risk to society. There are many studies showing a higher incidence of traffic violations in individuals with dementia[16]. Patients diagnosed with Parkinson's or Alzheimer's disease show significantly high executive difficulties and reduced operational level in driving performances[11,15]. Brain amyloid burden is also associated with a significantly higher crash risk, even in asymptomatic individuals[17,18]. Furthermore, even healthy older adults are vulnerable to severe injuries caused by traffic accidents, with slower recovery rate than younger individuals[19].

In this context, the evaluation of asymptomatic healthy older adults is fundamental. A higher risk of collision exists for many individuals without known neurological condition. We investigated the relationships between some commonly used neuropsychological tests in older adults at high risk for driving violations and in different driving situations.

METHODS

Participants

Thirty-three individuals aged between 65 and 90 years (median age = 71) with a valid national driver's license and still driving were included. Nine individuals from the initial sample were excluded because of "simulator sickness", which is a type of motion sickness related with virtual reality [14]. All participants gave written informed consent and had have no clinical evidence of neurological or psychiatric disease (Beck Anxiety Inventory < 16 and Geriatric Depression Scale < 6)[20,21] and preserved activities of daily living. They were recruited from the general population that volunteered or entered the Driving Center for any reason. All had normal or corrected-to-normal vision and none reported having a hearing problem.

Road driving simulator

Participants were asked to drive on a road driving simulator (Auto SmartSim, Esteio, Brazil, 2013) in four different situations. Following a previous study[22] and based on an experienced driving instructor, four driving situations were selected for this study. These scenarios were chosen based on frequent traffic violations by older adults[23,24]. Initially, they performed a training session of five minutes without traffic. At first, in the *Intersection* scenario, the driver had to cover a guided route with pedestrian lanes, traffic lights, and signaled intersections where people and cyclists cross the road. In the second scenario, *Overtaking*, the driver must perform a safety overtaking maneuver with a car. In the third scenario, *Rain*, the driver must control the vehicle during rain and fog. Fourth, *Malfunction*, the driver must detect an electrical or mechanical malfunction of the engine and give and appropriate signal to stop. The duration of each test varied (range=12–30 min).

Penalty scores

Traffic violations were classified according to the standards of the Brazilian Law, which is based on the Vienna Convention on Road Traffic[25]. Participants received penalty points according to the level of the penalty (Table 1). Scores were automatically attributed according to traffic violations during the trips and manually checked in the meantime.

There were four types of errors, with scores from 1–4 according to the severity of traffic violation. Traffic violation score was the total number of errors performed during the four tasks.

Table 1. Description of International Driving Law and correspondence to driving scores.

Driving penalty (points)	Description of traffic violations
Mild (1)	Touching the clutch pedal while driving
Moderate (2)	Turning off the car while driving; sudden stopping; driving with the handbrake pulled; incorrect upshifting; driving in neutral
Severe (3)	Turning with signaling errors
Most severe (4)	Colliding; Driving above the speed limit; Passing a red traffic light

According to a previously described procedure[26], individuals were then separated in two subgroups, High-risk (HR) and Normal-risk Driving (NR) by the mean values of the total driving penalty score. The HR group presented significantly higher driving penalties in the total driving penalty score when compared to the NR group ($p<0.001$). This method successfully classified individuals that performed the top 20% driving penalty scores (>0.5 SD of total mean) of the sample into the high-risk group.

Neuropsychological evaluation

Soon after the driving simulator, all participants underwent cognitive measurement on relevant domains for driving[8], according to the availability of cultural validation of the tests. The battery included the Mini-Mental State Examination (MMSE), the Digit Symbol, from the WAIS III[27], Trail Making Test A (TMTA) and B (TMTB)[28], Addenbrooke's Cognitive Evaluation–Revised (ACE)[29], the Rey Auditory-Verbal Learning Test (RAVLT)[30], both learning and delayed-recall scores, and the Category Fluency Test with animals (CFT)[31]. We also performed the Test of Divided Attention (TDA)[32], commonly used for periodic driving evaluation in Brazil. This test evaluates an individual's ability to search and find one different stimulus, randomly distributed among 400 symbols. The total number of symbols correctly pointed in four minutes is recorded.

Statistical analysis

The sample normality was assessed with the Kolmogorov-Smirnov test. Spearman's correlation was used to examine the relationship between age, education, and driving penalty score. Wilcoxon's sum-rank test was used for the comparison of the cognitive tests and groups. We also evaluated the effect size of cognitive tests using Cohen's d value.

A stepwise regression model was run to evaluate which cognitive measure score was most strongly associated with the driving penalty score of each test. We determined the adjusted R-squared and considered it to be statistically significant when p-values were less than 0.05.

All statistical analyses were performed using R Studio v1.0.136.

RESULTS

The characteristics of the sample are described in Table 2. There was no gender discrepancy among the driving risk groups ($p>0.05$). Age was moderately correlated with the Intersection score ($r=0.48$, $p=0.004$) and total driving penalty score ($r=0.37$, $p=0.03$). The years of education were inversely correlated to the total driving penalty score ($r=-0.39$, $p=0.02$).

The HR group showed higher driving penalty scores in the Intersection, rain, and overtaking tests compared to the NR group. Malfunction test scores were similar between both groups and presented a moderate effect size (Cohen's $d=-0.59$). The HR group showed a significantly lower learning score in the RAVLT than the NR group, but not in the delayed-recall test ($p=0.45$). The Digit Symbol test (Cohen's $d=0.97$) and the learning score of the RAVLT (Cohen's $d=1.006$) had the largest effect sizes of performed tests. MMSE and ACE showed small effect sizes (Cohen's $d=0.3$ both).

In the regression model, we included the TDA ($p=0.02$), Digit Symbol test ($p=0.002$), TMTB ($p=0.1$), learning score of the RAVLT ($p=0.009$), delayed-recall of the RAVLT ($p=0.09$), and visuospatial subtest of the ACE ($p=0.02$). The results of the regression analysis are shown in Table 3 and the correlation between tests are shown in Table 4.

The best predictors of each test were: delayed-recall score of the RAVLT for total driving penalty score ($R2 = 0.445$); learning and delayed-recall scores of the RAVLT for the Intersection test ($R2 = 0.502$); the visuospatial subtest of the ACE, the TDA, and the learning score of the RAVLT for the Overtaking test ($R2 = 0.617$); the TDA, the TMT-A, and the delayed-recall scores for the Rain test ($R2 = 0.605$); and the TMT-A, the Memory subtest, and the Attention/Orientation subtest of the ACE for the Malfunction test ($R2 = 0.506$). The Intersection test showed the highest correlation coefficient with the total driving penalty score ($r=0.77$) when compared with other tests ($r=0.68$, $r=0.59$, $r=0.23$ for Overtaking, Rain, and Malfunction tests, respectively). Furthermore, the RAVLT had an inverse moderate correlation with total driving penalty scores ($r= -0.47$).

DISCUSSION

This is the first study from Brazil to evaluate cognitive functions of older adults using a driving simulator. Considering different settings in a driving ability test for older adults is only possible with a reproducible tool such as a simulator. Although Brazil is a country with the a relatively low level of education, our sample had an intermediate level of education, probably because the ability to read and perform basic attention tests

Table 2. Demographic characteristics of the sample.

	Driving risk		
	Normal (n= 27)	High (n= 7)	Total sample
Age, median (range)	70 (65–85)	73 (65–90)	71 (65–90)
Years of education, median (range)	12 (7–18)	11 (8–15)	11 (7–18)
Years of driving, median (range)	44 (20–65)	49 (34–56)	44 (20–65)
Females	9	3	12
MMSE, median (range)	28 (23–30)	28 (21–30)	28 (21–30)
Driving score, median (range)	29 (9–44)	61 (47–97)[a]	30.5 (9–97)
Intersection test	10 (2–33)	38 (6–49)[a]	14 (2–49)
Overtaking test	4 (0–12)	6 (0–36)*	4 (0–36)
Rain test	4 (0–21)	12 (6–26)*	6 (0–26)
Malfunction test	4 (1–27)	5 (0–18)	4 (0–27)
Cognitive tests, median (range)			
ACE	90.5 (72–98)	91 (68–94)	91 (68–98)
Digit Symbol	49 (28–89)	33 (12–57)	49 (12–89)
TDA	75.5 (6–172)	55 (0–124)	69.5 (0–172)
TMT-A	72 (36–115)	81 (45–101)	74.5 (36–115)
TMT-B	135 (62–279)	199 (95–300)	135 (62–300)
RAVLT–Sum	38 (23–57)	33 (20–38)*	37.5 (20–57)
RAVLT–Delayed recall	7 (2–14)	6 (0–8)	6.5 (0–14)
CFT	16.5 (3–28)	14 (8–19)	15.5 (3–28)

MMSE: Mini-Mental State Examination; ACE: Addenbrooke's Cognitive Evaluation; DS: Digit Symbol; TDA: Test of Divided Attention; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; RAVLT-Sum: Rey auditory-verbal learning test, the sum from A1 to A5 lists; RAVLT-A7: Rey auditory-verbal learning test, delayed-recall list; CFT: Category Fluency Test, Animals; *p<0.05; [a]p<0.001.

are required to obtain a driver's license. Furthermore, this study will be very useful in the field as the number of older drivers in society is increasing. Life expectancy also increases proportionally, leading to a significant increase in cognitively healthy older adults who still drive and are independent. A driving simulator is essential in identifying older people with a high risk for unsafe driving, thus avoiding any risk associated with an evaluation on the road and accident. In addition, individuals who continue to drive at high risk can be asked to stop driving, avoiding harm on the road.

In this sample, older age was moderately associated with worsening in some cognitive abilities, as well as with the Intersection and total driving penalty scores. The fatal crash rate per mile is increased in drivers over 70 years of age, which confirms our findings[33]. The Mini-Mental State Examination (MMSE) is still the most widely used cognitive screening tool. However, the MMSE score showed a poor correlation with driving performance for both high and low cognitions[34]. In this study, general cognitive evaluation, assessed with the MMSE and the ACE, was not an adequate criterion to discriminate normal from high-risk older drivers. It is possible that these tests are not sensitive in detecting mild to moderate cognitive decline[35]. Besides, our regression analysis confirmed previous studies in which an association between driving and cognition was reported[10]. Total driving score was significantly associated with learning score (Table 3). A single test may not accurately predict driving performance, as this requires a highly complex and synchronous ability between several cognitive domains.

Some specific cognitive tests were associated with HR driving. The learning ability of older drivers, measured by the sum of the five first lists of the RAVLT, was significantly different between the high-risk and normal-risk driving older adults as indicated by a large effect size. Previous studies have shown that learning ability is associated with driving penalty scores but may not be associated with driving skills, but is a potential target for improving driving skills[36]. In this study, the learning score of the RAVLT was moderate and inversely associated with total driving penalty scores. The RAVLT has been found to be a sensitive test for detecting of early signs of cognitive impairment[37]. Among the different tests used in this study, the RAVLT was the only one that could distinguish high-risk older drivers from those at normal risk. Driving assessment may benefit from the RAVLT in the identification of older adults with a high risk for accidents during periodic driver's license renewal.

Scores for all settings were significantly impaired in the HR group, except the Malfunction test. Perhaps a malfunction forces the driver to stop the car and either ask for help or fixing the problem. The Intersection test was highly correlated with the total driving penalty scores, and learning and delayed-recall abilities (Table 4). This is probably the most commonly performed task for drivers and requires attention to effectively avoid traffic violations and collisions. However, we found that

Table 3. Stepwise regression model adjusted for education.

Tests	R^2	Regression coefficient		Standardized coefficient	p-values
		B	Standard error b	Beta	
Total driving score	0.568				
(Constant)		139.022	37.711		**0.001**
RAVLT-Sum		−0.912	0.333	−0.4277	**0.007**
Visuospatial		−4.646	2.610	−0.28	0.085
Intersection	0.501				
(Constant)		40	8.32		**<0.001**
RAVLT-Sum		−0.983	0.306	−0.71	**0.002**
RAVLT-A7		1.798	0.920	0.432	0.059
Overtaking	0.616				
(Constant)		59.911	14.013		**<0.001**
Visuospatial		−4.871	1.333	−0.814	**0.002**
TDA		−0.042	0.026	−0.244	0.108
Rain	0.603				
(Constant)		26.726	5.751		**<0.001**
TDA		−0.076	0.028	−0.482	**0.010**
TMT-A		−0.103	0.050	−0.360	0.050
RAVLT-A7		−0.766	0.344	−0.375	**0.033**
Malfunction	0.496				
(Constant)		−47.860	18.881		**0.017**
TMT-A		0.132	0.049	0.490	**0.010**
Attention/Orientation		1.969	0.949	0.362	**0.047**
Memory (ACE)		0.506	0.281	0.298	0.076

RAVLT-Sum: Rey auditory-verbal learning test, the sum from A1 to A5 lists; RAVLT-A7: Rey auditory-verbal learning test, delayed-recall list; TDA: Test of Divided Attention; TMT-A: Trail Making Test A; ACE: Addenbrooke's Cognitive Evaluation. ($P < 0.05$ in bold)

Table 4. Intercorrelations among cognitive measures and driving tasks.

Measures	1	2	3	4	5	6	I	O	R	M
DS (1)	1									
TDA (2)	0.64	1								
RAVLT-Sum (3)	0.50	0.39	1							
RAVLT-A7 (4)	0.45	0.45	0.71	1						
ACE (5)	0.36	0.57	0.48	0.46	1					
CFT (6)	0.34	0.41	0.50	0.26	0.57	1				
Driving tasks										
Intersection (I)	−0.25	−0.14	−0.40	−0.07	−0.20	−0.27	1			
Overtaking (O)	−0.46	−0.40	−0.30	−0.26	−0.26	−0.10	0.23	1		
Rain (R)	−0.34	−0.46	−0.45	−0.44	−0.44	−0.19	0.19	0.54	1	
Malfunction (M)	−0.20	−0.08	0.10	−0.11	0.24	0.13	−0.06	0.03	−0.12	1
Total Score	−0.49	−0.40	−0.48	−0.31	−0.29	−0.23	0.77	0.68	0.59	0.23

DS: Digit Symbol; TDA: Test of Divided Attention; RAVLT-Sum: Rey auditory-verbal learning test, the sum from A1 to A5 lists; RAVLT-A7: Rey auditory-verbal learning test, delayed-recall list; ACE: Addenbrooke's Cognitive Evaluation; CFT: Category Fluency Test, Animals.

the learning and delayed-recall memory scores, both measured with the RAVLT, were associated with this task. The RAVLT is an important predictor of white matter changes[38] and other structural brain changes in individuals presenting further cognitive decline[37,39]. The use of a simulator, however, is also associated with learning skills, which could influence the lower scores on traffic penalty. Besides, the HR group showed an almost three-fold higher score in the Rain test, which corroborates

with previous studies on adverse weather conditions[40]. This may be due to the decreased ability to identify traffic signs by older adults with a higher risk during adverse weather conditions with decreased visibility. Other contributing factors, such as the reflex speed and motor responses, are also responsible for an increased crash rate of older drivers[33]. Further studies may corroborate these findings with evaluations on the road.

Despite our efforts, this study had some limitations that must be discussed. A major limitation is the sensibility of the simulator, which may cause an overrepresentation of scores. Furthermore, our sample consisted only of individuals who accepted the invitation to participate, which may lead to a selection bias toward older adults with better cognitive performance. The sample size was also a factor of limitation, and some results should be replicated to improve external validity.

In conclusion, high-risk older drivers had lower verbal learning test scores compared with normal-risk older drivers, but the same was not true for general cognition tests. High-risk older drivers also showed significantly higher traffic penalties in Intersection, Overtaking and Rain tests, but not in the Malfunction simulator test compared with the normal-risk older drivers. In addition, the Rey auditory-verbal learning test was the best predictor of safe driving in our regression model.

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Spanish version of the Frontotemporal Dementia Knowledge Scale: adaptation and validation

Versión en español de la escala de conocimiento sobre demencia frontotemporal: adaptación y validación

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ABSTRACT

Background: Frontotemporal dementia (FTD) is a neurodegenerative disease and is one of the most common causes of dementia in people under 65. There is often a significant diagnostic delay, as FTD can be confused with other psychiatric conditions. A lack of knowledge regarding FTD by health professionals is one possible cause for this diagnostic confusion. **Objectives:** The aim of this study was to adapt and validate the Frontotemporal Dementia Knowledge Scale (FTDKS) in Spanish. **Methods:** A translation was done, following cross-cultural adaptation guidelines, which consisted of forward translation, blind back translation, and an analysis by a committee of experts. For the present study, 134 professionals from different health areas responded the Spanish version of the FTDKS. The statistical analysis was performed using R version 4.0.0 "Arbor day" and the Psych, sjPlot packages. **Results:** The Spanish version of the FTDKS had good reliability and internal consistency (Cronbach alpha 0.74.). The sample's mean score was 19.78 (range = 4-32, SD 6.3) out of a maximum of 36 points. **Conclusions:** The results obtained show that the Spanish version has good psychometric properties. The FTDKS is applicable in our environment and can be a useful tool to evaluate the knowledge of health professionals regarding frontotemporal dementia.

Keywords: Frontotemporal Dementia; Frontotemporal Lobar Degeneration; Aphasia; Dementia; Diagnostic Errors; Neuropsychiatry.

RESUMEN

Antecedentes: La demencia frontotemporal (DFT) es una enfermedad neurodegenerativa y es una de las causas más comunes de demencia en personas menores de 65 años. A menudo existe un retraso significativo en el diagnóstico, ya que la FTD puede confundirse con otras afecciones psiquiátricas. La falta de conocimientos sobre la DFT por parte de los profesionales de salud es una posible causa de esta confusión diagnóstica. **Objetivos:** El presente estudio describe nuestros esfuerzos para adaptar y validar la Escala de Conocimiento de la Demencia Frontotemporal (FTDKS) en español. **Métodos:** Se realizó una traducción, siguiendo las pautas de adaptación transcultural, que consistió en una traducción directa, una traducción inversa ciega y un análisis por parte de un comité de expertos. Para el presente estudio, 134 profesionales de diferentes áreas de la salud respondieron la versión en español del FTDKS. El análisis estadístico se realizó utilizando la versión 4.0.0 de R "Arbor day" y los paquetes Psych, sjPlot. **Resultados:** La versión en español del FTDKS tiene una buena fiabilidad y consistencia interna (alfa de Cronbach 0,74.). La puntuación media de la muestra fue de 19,78 (rango = 4-32, SD 6,3) sobre un máximo de 36 puntos. **Conclusiones:** Los resultados obtenidos muestran que la versión española tiene buenas propiedades psicométricas. El FTDKS es aplicable en nuestro medio y puede ser una herramienta útil para evaluar los conocimientos de los profesionales sanitarios sobre la demencia frontotemporal.

Palabras claves: Demencia Frontotemporal; Degeneración Lobar Frontotemporal; Afasia; Demencia; Errores Diagnósticos; Neuropsiquiatría.

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INTRODUCTION

Frontotemporal dementia (FTD) is one of the most common causes of dementia in people under 65 years of age, and the third most prevalent cause of dementia altogether[1].

Clinically, the FTD syndromes include the behavioral variant of FTD (bvFTD) and two language syndromes, the semantic (svPPA) and the nonfluent/agrammatic (nfvPPA) variants of primary progressive aphasia. Between these FTD syndromes, bvFTD is the most common clinical presentation. It is characterized by personality changes with behavioral disinhibition, apathy, loss of empathy, compulsive or ritualistic behavior, hyperorality, and dysexecutive symptoms[2]. In the language variants, the key component is progressive aphasia.

Unlike other dementias, such as Alzheimer's disease, FTD mainly affects behavior, language, or the motor system. Due to these characteristics, it is often misdiagnosed as a primary psychiatric illness[3]. Importantly, misdiagnosis has a negative impact on patients and their families who seek an answer to symptoms that continue to progress, compromising the patient's personality, isolating them from social ties, undermining the family economy, and further disorienting the professionals who do not know how to deal with this disease. To support proper diagnosis, many workgroups have evaluated potential reasons for the diagnostic delay of FTD[4,5,6]. One study evaluated the mean duration from the onset of symptoms to the diagnosis of a neurodegenerative disorder in each of the FTD syndromes (3.7 years for bvFTD, 3.5 years for nfvPPA, and 1.4 for svPPA)[7]. The authors concluded the reasons behind this delay to be related to a misdiagnosis, with the symptoms of FTD being misattributed to a primary psychiatric disorder[3,4].

Furthermore, we suspect that diagnosis errors could be even more important in Argentina and the surrounding region. For example, the estimated prevalence of FTD in the US for the population between 45 to 64 years is 15-22 per 100.000[8]. Based on these rates, Argentina (a country with approximately 10,040,258 inhabitants in that age range[9]), should have a prevalence of 1,500 to 2,200 FTD cases. However, Argentina does not maintain an active countrywide registry of these cases, so no reliable epidemiological information regarding FTD exists. Fleni, situated in Buenos Aires, is one of the largest neurology tertiary referral centers in Argentina in which more than 1000 patients with dementia are evaluated annually and clinical care is integrated with extensive research programs. Despite this, Fleni has identified only 50 patients with FTD from its records from 2010 to the present day, likely representing an underestimation. In the literature, it is well recorded that the given prevalence varies from country to country and even in the same country from one study to another[7,8,10,11,12,13]. The main reason for this is that this disease is still missed and misdiagnosed and most numbers probably underestimate its true prevalence[4]. However, even if we ignore this fact and accept the estimated cases for this prevalence numbers, the recorded cases in Argentina seem to be below what we would estimate.

Based on these arguments and considering the prevalence and the frequent misdiagnosis, one possible explanation is that health professionals lack important knowledge regarding FTD and thus may fail to diagnose it in its early stages. Given this, it is essential to assess FTD knowledge among health professionals. To accomplish this, Wynn et al. developed the Frontotemporal Dementia Rating Scale (FTDKS). In this 18-item scale, the respondents answer objective questions about FTD using a 4-point Likert scale format (False, Probably False, Probably True, True), with an auxiliary "I don't know" option.

To understand the low frequency of FTD diagnosis in Argentina, our intention was to assess disease knowledge among health professionals. As a first step, we adapted the FTDKS scale into Spanish and report on its psychometric properties.

METHODS

Cross-cultural adaptation process

In order to initiate the adaptation to Spanish and validation of the FTDKS, we first asked for and obtained consent from the original author of the scale (Wynn et al.).

Following established guidelines[14], adapting the FTDKS to Spanish involved four-steps: the forward translation, the blind back translation, a review by an expert committee, and administration to a validation sample.

Forward translation

The first stage in the adaptation process was translating the FTDKS into Spanish. A bilingual experimental psychologist from Argentina, familiar with both cultures, translated the survey into Spanish.

Blind back translation

A second independent translator, a clinician with the source language (English) as their mother tongue and who was blind to the original version, translated the scale back into English. This process revealed that the Spanish (translated) and English (original) versions reflected the same content.

Expert committee

A committee composed of a cognitive neurologist, neuropsychiatrist, neuropsychologist, and the two translators who performed the initial translation and backward translation assessed semantic, idiomatic, and conceptual equivalence of the Spanish FTDKS.

Final version

The final FTDKS Spanish version (Table 1), like the original version, consists of 18 items where respondents answer factual questions about FTD using a 4-point Likert-type scale format (*False*, *Probably False*, *Probably True*, *True*), with an auxiliary *Don't Know* option. Respondents receive 2 points for a correct *True* or *False* response, 1 point for a correct *Probably True* or *Probably False* response, and 0 points for an incorrect or *Don't Know* response.

Table 1. Psychometric properties of the scale's items. The statement column represents the final form of the translated item. In parenthesis, the original version following the correct answer.

Item	Statement	Mean	Standard deviation	Skew	Item difficulty	Item discrimination	A if deleted
1	La Demencia Frontotemporal (DFT) es una variante de la Enfermedad de Alzheimer (Frontotemporal dementiais a type of Alzheimer disease) (F)	1.66	0.68	-1.77	0.83	0.39	0.72
2	Para la mayoría de las personas con DFT los síntomas aparecen antes de los 65 años de edad (For the majority of people with frontotemporal dementia, symptoms appear before they are 65 years old) (T)	1.25	0.85	-0.5	0.62	0.32	0.72
3	Entre todas las personas con demencia, un 5 a 10% de ellos tiene demencia frontotemporal (Among all people with dementia, 5-10% of them have frontotemporal dementia) (F)	0.31	0.65	1.87	0.16	0.02	0.74
4	Las personas que rondan los treinta años de edad pueden tener demencia frontotemporal (People in theirthirties can developsymptomsof frontotemporal dementia) (T)	0.9	0.84	0.2	0.45	0.21	0.73
5	La pérdida de memoria es un problema mayor en la demencia frontotemporal (Memory loss is a major symptom of frontotemporal dementia) (F)	1.37	0.86	-0.81	0.69	0.32	0.72
6	La demencia frontotemporal puede ser transmitida genéticamente de los padres a los hijos (Frontotemporal dementia can be passed down from parent to child) (T)	0.87	0.84	0.24	0.44	0.30	0.73
7	Dentro de las personas menores de 60 años de edad, la demencia frontotemporal es tan común como la enfermedad de Alzheimer (Among people under 60 y old, frontotemporal dementia is about as common as Alzheimer disease) (T)	0.63	0.82	0.77	0.32	0.28	0.73
8	Los estudios de neuroimagenes (tomografía y/o resonancia magnética) pueden por sí solos decir si una persona tiene demencia frontotemporal (The results of a brain scan by itself can tell you whether a person has frontotemporal dementia) (F)	1.39	0.87	-0.85	0.69	0.3	0.73
9	La personas con demencia frontotemporal tienen mejor desempeño cuando deben elegir entre varias opciones predefinidas (People with frontotemporal dementia do best when given choices among many options) (F)	0.84	0.92	0.33	0.42	0.23	0.73
10	Existen tratamientos para disminuir la velocidad de progresión de la demencia frontotemporal (There are treatments to slow down frontotemporal dementia) (F)	0.76	0.87	0.49	0.38	0.38	0.72
11	Luego de que aparecen los primeros síntomas de demencia frontotemporal, la expectativa de vida media es de 7 a 13 años (After symptoms of frontotemporal dementi aappear, the average life expectancy is 7 to 13 years) (T)	1.09	0.85	-0.17	0.54	0.27	0.73
12	Basándose en la edad, es más probable que desarrollen demencia frontotemporal las personas que rondan los 70 años de edad en comparación con las personas que rondan los 50 años (On the basis of their age, people who are 70 years old are more likely to develop frontotemporal dementia than people who are 50 years old) (F)	1.05	0.91	-0.1	0.53	0.52	0.70
13	En línea general los cuidadores de personas con demencia frontotemporal reportan mayores niveles de estrés que los cuidadores con otras formas de demencia (On average, caregivers of people with frontotemporal dementia report more stress than caregivers of people with other dementias) (T)	1.43	0.75	-0.88	0.71	0.20	0.73

Table 1. Cont.

Item	Statement	Mean	Standard deviation	Skew	Item difficulty	Item discrimination	A if deleted
14	Las medicaciones diseñadas para mejorar la cognición y memoria en personas con Alzheimer son también apropiadas para personas con demencia frontotemporal (Medications designed to improve memory and thinking in people with Alzheimer disease are also appropriate for people with frontotemporal dementia) (F)	1.02	0.9	-0.04	0.51	0.40	0.72
15	Las variantes del lenguaje de la demencia frontotemporal son más comunes que la variante conductual (The language variant of frontotemporal dementia is more common than the behavioral variant) (F)	1.22	0.85	-0.43	0.61	0.43	0.71
16	Los pacientes con la variante conductual de la demencia frontotemporal suelen tener dificultad en evocar eventos del pasado (People with the behavioral variant of frontotemporal dementia have difficulty remembering events from the past (F)	1.19	0.89	-0.38	0.59	0.43	0.71
17	Las personas con la varianteconductual de la demencia frontotemporal en general carecen de interés en las cosas que antes disfrutaban (People with the behavioral variant of frontotemporal dementia lack interest in things they used to find enjoyable) (T)	1.58	0.66	-1.32	0.79	0.20	0.73
18	Las personas con las variantes del lenguaje de la demencia frontotemporal son capaces de leer y escribir sin dificultad (People with the language variant of frontotemporal dementia are able to read and write without difficulty) (F)	1.22	0.88	-0.46	0.61	0.32	0.72

F: false statement; T: true statement.

Validation Sample

The final version of the Spanish FTDKS, along with a demographic questionnaire, was distributed in a Google Forms format among health professionals using snowball sampling techniques. The survey was distributed among colleagues using social networks and email, both directly and using professional groups from the leading Argentine societies of health professionals. In this way, 134 responses were obtained exclusively from health professionals (neurologists, psychiatrists, clinical psychologists, and neuropsychologists).

In addition to responses to the Spanish version of the FTDKS, demographic data was collected including: age, sex, education, professional discipline/specialty, years of experience, academical or research activities, health system where they work (public or private), practice settings, number of patients seen per month, self-reported knowledge of FTD (prior to answering the FTDKS), and clinical experience with dementia.

Results were analyzed to obtain a global Cronbach's α value. An isolated item analysis was performed to determine skewness, item difficulty, item discrimination, and global α if the item is deleted.

The *item difficulty* evaluates the proportion of respondents who answer an item correctly.

The *item discrimination* indicates how well an item discriminates respondents' knowledge. A high discrimination index indicates that the item works differently between respondents with higher and lower scores, suggesting that the item identifies respondents with more or less knowledge

The statistical analysis was performed using R version 4.0.0 "Arbor day" and the Psych[15], sjPlot[16], and Table 2 packages[17].

RESULTS

Sample characteristics

One hundred thirty-four health professionals completed the Spanish version of the FTDKS. There were no reported difficulties in understanding the instructions or in completion of the scale.

The sample characteristics are shown in Table 2. The mean age was 42.9 years (range = 25-77 years). Most of the professionals were highly educated and trained, with 80 (59.7%) having finished at least the residency and 82 (61.2%) having 8 or more years of clinical experience. The main area of work was with outpatients (n = 113), and most of the sample worked in the private sector (n = 77). Regarding experience, many of the professionals (n=66) saw more than 100 patients per month. Of the sample, the majority were neurologists (n=51), followed by psychiatrists (n=50) and clinical psychologists (n=15). From the total sample, 73 (54.5%) reported having academic or research-related activities. In terms of self-reported knowledge of FTD, the majority of professionals reported knowing "something" about the disease (n = 81), whereas a smaller percentage reported knowing "a lot" (n = 22) and only 1 respondent considered themselves an "expert" (n = 1).

Table 2. Demographics of the sample.

Characteristics	Total (n=100)	
Age (years)	Mean (SD)	42.9 (12.5)
Sex	Female	78%
Education level	Ph.D., Master or Fellowship	41 (30.59%)
	Residency (complete)	39 (29.10%)
	Residency (undergoing)	10 (7.46%)
	University degree	44 (32.83%)
Professional discipline/specialty	Clinical psychologist	15 (11.19%)
	Neurologist	51 (38.05%)
	Neuropsychologist	10 (7.46%)
	Psychiatry	50 (37.31%)
	Other	8 (5.97%)
Years of experience in healthcare	0-4 years	31 (23.13%)
	5-10 years	40 (29.85%)
	>10 years	63 (47.01%)
Academical/research activity	Yes	73 (54.47%)
Health system	Private	77 (57.46%)
Practice setting	Outpatient clinic	113 (84.32%)
	Inpatient clinic	5 (3.73%)
	Emergency service	7 (5.22%)
	Chronic inpatient institution	9 (6.71%)
Patients seen per month	1-99	68 (50.74%)
	100-199	47 (35.07%)
	More than 200	19 (14.17%)
Perceived knowledge of FTD	None	3 (2.23%)
	A little	27 (20.14%)
	Moderate	81 (60.44%)
	A lot	22 (16.41%)
	Expert	1 (0.74%)
Experience in dementia	No experience	16 (11.94%)
	Some experience	44 (32.83%)
	Moderate experience	58 (43.28%)
	A lot of experience	12 (8.95%)
	Extensive experience	4 (2.98%)
Experience in FTD	No experience	39 (29.10%)
	Some experience	61 (45.52%)
	Moderate experience	30 (22.38%)
	A lot of experience	2 (1.49%)
	Extensive experience	2 (1.49%)

SD: Standard deviation; FTD: Frontotemporal dementia.

Psychometric properties of the Spanish FTDKS

The mean score for the Spanish FTDKS was 19.78 (range = 4-32, SD 6.38). Table 1 shows the mean score per question for each item in the scale, the standard deviation (SD), the item difficulty, the item discrimination, and internal consistency (Cronbach α). The mean score per response ranged from 0.31 for statement 3 ("Among all people with dementia, 5-10% of them have frontotemporal dementia", False) to 1.66 for statement 1 ("Frontotemporal dementia is a type of Alzheimer disease", False). The internal consistency reliability (Cronbach α) for this sample was 0.74, 95% CI [0.67 ,0.8]), indicating acceptable reliability.

DISCUSSION

The aim of the current study was to translate and adapt the original English version of the FTDKS published by Wynn et al. into Spanish. The results obtained show that the Spanish version has a good reliability and internal consistency and that it can be a useful tool to evaluate the knowledge of health professionals in the field of FTD.

A surprising result is the low mean accuracy score obtained for the third item (related to the prevalence of FTD). Considering the lack of a registry of FTD cases in Argentina, there are at least two interpretations for this. First, it is possible that the prevalence of the disease in our country is, in fact, lower than that reported in the international literature (from which the validity of the scale question is based). If this were the case, the answers given by the respondents would not be incorrect. However, according to the hypothesis that led us to start this work, it is possible that the information on prevalence is ignored or unknown by respondents and the low mean score on that item reflects a general lack of awareness of the disease by Argentine health professionals.

Another interesting factor is the low overall result obtained in the FTDKS by our sample. With a mean of 19.78 (SD 6.3) and a range of 4 to 32, out of a maximum of 36 possible points, these results are significantly lower than those described in the original article by Wynn et al. In that study, health professionals mean score on the FTDKS was 25 (SD = 5.47, range = 10 – 36). These results reinforce the notion that FTD is a poorly known illness among health professionals. With this instrument validated in Spanish, we propose to study the level of knowledge of professionals in Argentina and eventually throughout Latin America, focusing on the specialties that are likely to deal first with these patients due to the characteristics of the disease: neurologists, psychiatrists, clinical psychologists, and neuropsychologists.

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ARTICLE

EEG education in Brazil: a national survey of adult neurology residents

Educação em EEG no Brasil: uma pesquisa nacional com residentes de neurologia de adultos

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ABSTRACT

Background: In light of the established challenges of resident EEG education worldwide, we sought to better understand the current state of neurology resident EEG education in Brazil. **Objective**: To define Brazilian EEG practices including in-residency requirements for EEG training and competency. **Methods**: We assessed the perspectives of adult residents (PGY1-3) on EEG education and their level of confidence interpreting EEG with a 24-question online survey. **Results**: We analyzed 102 responses from 52 Brazilian neurology residency programs distributed in 14 states. There were 18 PGY1s, 45 PGY2s, and 39 PGY3s. Ninety-six percent of participants reported that learning how to read EEG during residency was very or extremely important. The most commonly reported barriers to EEG education were insufficient EEG exposure (70%) and ineffective didactics (46%). Residents believed that standard EEG lectures were the most efficient EEG teaching method followed by interpreting EEG with attendings' supervision. Roughly half of residents (45%) reported not being able to read EEG even with supervision, and approximately 70% of all participants did not feel confident writing an EEG report independently. **Conclusion**: Despite the well-established residency EEG education requirements recommended by the Brazilian Academy of Neurology (ABN), there seems to be a significant lack of comfort interpreting EEG among Brazilian adult neurology residents. We encourage Brazilian neurology residency leadership to re-evaluate the current EEG education system in order to ensure that residency programs are following EEG education requirements and to assess whether EEG benchmarks require modifications.

Keywords: Electroencephalography; Neurology; Epilepsy; Internship and Residency; Education.

RESUMO

Antecedentes: Diante dos desafios da educação em EEG estabelecidos em todo o mundo, buscamos compreender melhor o estado atual da educação em EEG durante a residência de neurologia no Brasil. **Objetivo**: Investigar práticas de EEG no Brasil, incluindo requisitos para treinamento e competência durante a residência de neurologia. **Métodos**: Avaliamos as perspectivas dos residentes (R1-3) de neurologia (adulto) sobre educação em EEG e nível de confiança ao interpretá-lo através de questionário online de 24 perguntas. **Resultados**: Foram analisadas 102 respostas de 52 programas de residência distribuídos em 14 estados. Dezoito R1s, 45 R2s e 39 R3s responderam à pesquisa. Noventa e seis por cento dos participantes relataram que aprender a ler EEG durante a residência é muito ou extremamente importante. As barreiras mais relatadas para educação em EEG foram exposição insuficiente ao EEG (70%) e didática ineficaz (46%). Os participantes apontaram aulas como método de ensino mais eficaz, seguido pela interpretação do EEG supervisionada pelos chefes. Aproximadamente metade dos residentes (45%) relatou não ser capaz de ler EEG mesmo com supervisão e cerca de 70% não se sente confiante para escrever um laudo de EEG de forma independente. **Conclusões**: Apesar dos requisitos estabelecidos pela Academia Brasileira de Neurologia (ABN) sobre ensino de EEG durante a residência, há significativa falta de confiança na sua interpretação pelos residentes de neurologia (adulto). Incentivamos as lideranças a reavaliar o sistema de educação para garantir que os programas de residência sigam requisitos de educação em EEG e se os benchmarks de EEG requerem modificações.

Palavras-chave: Eletroencefalografia; Neurologia; Epilepsia; Internato e Residência; Educação.

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INTRODUCTION

Brazilian adult neurology residency training consists of three years, the first of which focuses on internal medicine rotations. Recommendations posted by the National Medical Residency Commission in conjunction with the Brazilian Academy of Neurology (ABN) mandate that graduating adult neurology residents should be able to "know the indications of EEG and interpret it in the various neurological diseases"[1]. These expectations are similar in the U.S. as American graduating adult residents are recommended to be able to "interpret common EEG abnormalities, recognize normal variants, and create a report"[2] .

American data, however, suggests that a large portion of graduating neurology residents do not feel confident interpreting EEGs independently[3-5]. This issue is at least partially explained by a lack of consistency in teaching and evaluating residents during in-residency EEG training[6]. Nuances of EEG teaching and learning in Brazil have not yet been explored. Herein, we sought to define current neurology and EEG practices in Brazil including in-residency requirements for EEG training and competency.

METHODS

We assessed adult neurology residents' perspectives on EEG education and their level of confidence interpreting EEG with a 24-question online survey (Supplementary File 1) hosted on Survey Monkey. The survey was adapted from a recently published North-American study[5] and consisted of five questions focused on participants' demographics, nine questions focused on perspectives on EEG education, and ten questions focused on level of confidence interpreting EEG, writing an EEG report, and identifying select EEG findings. All questions were close-ended except for one, which asked for suggestions to improve EEG teaching.

The survey was disseminated among adult neurology residents (PGY1-3) through email and social media. There are currently 89 adult neurology residency programs in Brazil located in 20 of the 26 Brazilian states and one Federal District[7]. Trainees undergoing specialization in neurology, rather than neurology residency, were excluded. Invitations to participate in this study were sent by email to (i) residency program directors, whose contact information was obtained from the Medical Residency Commission, and (ii) directly to residents through partnership with the ABN. Data collection was performed from November 2020 to January 2021. This study was approved by the Neurological Institute of Curitiba (INC) institutional regulatory board (IRB).

RESULTS

We obtained responses from 123 subjects, 21 of whom were excluded for not being residents. We analyzed the remaining 102 responses. Participating residents were from 52 different Brazilian adult neurology residency programs distributed in 14 states (Figure 1A). Among all participants, there were 18 PGY1s, 45 PGY2s, and 39 PGY3s. Main results are summarized in Figure 1. We classified hospitals affiliated to residency programs according to [8,9] a) level of care: secondary (specialized care) or tertiary (highly specialized care); b) ownership status: public, private, or charity; and c) size: special (over 500 beds), large (151 to 500 beds), medium (51 to 150 beds), and small (less than 51 beds). This data is summarized in Supplementary File 2.

Residents' perspectives on EEG education

The vast majority of residents (96%) reported that learning how to read EEGs during residency was very important or extremely important. Similarly, virtually all residents (98%) disagreed that learning to read EEG during residency is important only if one is pursuing further training in neurophysiology and/or epilepsy.

Residents considered insufficient EEG exposure (70%), ineffective didactics (46%), suboptimal supervision from residents/fellows (34%), insufficient responsibility to read EEG during rotations (34%), and inability to link EEG learning to direct patient care (29%) as the most prominent barriers to learning EEG. Through qualitative assessment, participants also mentioned "not having access to EEG tracings". Intuitively, the most commonly reported solutions to improvement in EEG education comprised increased EEG exposure (78%) and more efficient didactics (58%). Residents highlighted the importance of "increased supervision from the ABN in order to ensure that EEG is being taught" and one participant emphasized the challenge arising from "EEG learning not being required". Many residents asked for "more EEG learning material" with "video, books, and online courses". Participants were asked to rate different EEG teaching methods by level of efficiency. In a descending order, these were the methods reported: standard EEG lectures, interpreting EEG with attendings' supervision, interpreting EEG with fellows' supervision, interpreting independently followed by attendings' review, and interpreting independently followed by fellows' supervision.

In terms of ensuring competency in reading EEG, participants considered the number of EEGs read (85%) and number of hours reading EEG (56%) as the best objective measures. Alternative methods reported comprised written (37%) and oral (24%) EEG tests. Further, most residents (75%) reported that reading more than 50 EEGs is required to ensure competency in EEG.

Residents' level of confidence in EEG

Participants were asked whether they felt confident identifying particular EEG findings and/or states. Residents stated not being able to independently recognize a normal awake and sleep EEG in adults (35%) and children (72%), status epilepticus (26%), common artifacts (31%), common abnormalities

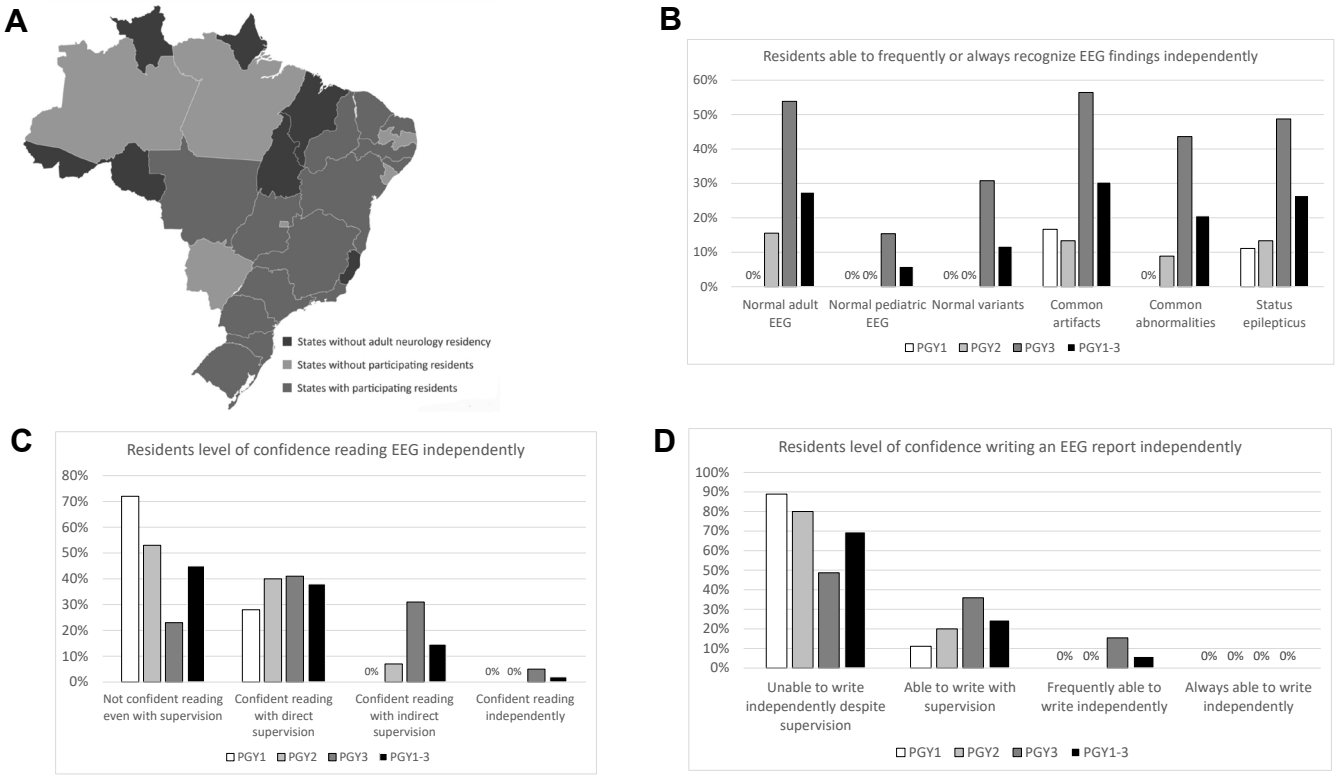

Figure 1. Summary of survey findings.

(34%), and common normal variants (46%). Additional data regarding residents' level of confidence in EEG interpretation is summarized in Figure 1B.

Overall, almost half of residents (45%) reported not being able to read EEG even with supervision. Roughly 70% of residents did not feel confident writing an EEG independently. This data is summarized in Figure 1C-D. Lastly, 91% of residents felt null to little confidence explaining an EEG and its findings to patients and/or students. This percentage also varied between PGY classes: 94% (PGY1), 96% (PGY2), 85% (PGY3).

DISCUSSION

This is the first nationwide study assessing adult neurology resident EEG education in Brazil. Responses were received from approximately 10% of all Brazilian adult neurology residents based on latest available demographic data[10]. Virtually all participants (96%) felt as though learning to read EEG in residency was important. This seems to be in line with resident perception data highlighted in other studies[3,5].

Despite the overwhelming evidence suggesting that EEG education is perceived as highly important by residents, trainees continue to report not being able to read or write EEG reports even with supervision. In our study, roughly half of residents (45%) reported not being able to read EEG even with supervision. This figure progressively decreased from PGY1 to PGY3; nonetheless, it remained high even among PGY3s (23%). In terms of writing EEG reports, almost 70% of all participants felt unable to do so independently. Although this percentage progressively declined from PGY1 to PGY3, it was still high in the PGY3 subgroup (49%). Overall, a significant portion of residents did not feel confident recognizing multiple EEG findings even with supervision.

A smaller, single-center cohort of American adult neurology residents showed similarly alarming results: 43% reported not being able to read EEG even with supervision, and 21% not being able to write an EEG report independently[5]. These residents were not categorized by postgraduate year level. An additional American survey-based study including 15 adult neurology PGY4s assessed these residents' level of confidence in "interpreting common EEG abnormalities and creating a report" – the median was 67%[4]. Lastly, according to the last triannual American Academy of Neurology (AAN) survey, only 37.3% of graduating adult neurology residents felt confident performing or interpreting EEG independently[3].

We also asked for participants' opinions on multiple aspects of EEG education. The most commonly reported barriers to EEG learning were insufficient EEG exposure (70%) and ineffective didactics (46%). The former seems to be an issue in the American residency EEG education system as well[5]. Our study results also showed that participants believed that the two most efficient ways to teach EEG are standard EEG lectures

and interpreting EEG with attendings' supervision. Participants considered the number of EEGs read (85%) and number of hours reading EEG (56%) as the best objective measures to ensure EEG reading competency. Three-quarters of residents agreed that reading more than 50 EEGs would be required to ensure competency. A combination of didactic lectures and reading EEG with supervision were also considered the most efficient ways to teach EEG by an American cohort of adult neurology residents[5]. The latter cohort also felt as though the number of EEGs reviewed and number of hours spent reviewing EEG were the most effective competency measures[5].

Our study has limitations. We surveyed approximately 10% of all adult neurology residents in Brazil, a small number relative to the entire adult neurology trainee cohort in the country. Additionally, we only sampled residents from 14 out of the 20 Brazilian states where there are adult neurology residency program(s). Further, our survey might have suffered selection bias where residents who felt as though they had received inadequate EEG training were more likely to participate in our study. As a result, one needs to be cautious when extrapolating our study data to all residents on a national level.

In Brazil, graduating adult neurology residents are expected to "know the indications of EEG and interpret it in the various neurological diseases"[1]. Moreover, residents must read 250 EEGs throughout their training (50 as PGY2 and 200 as PGY3) and earn a minimum of 320 credit hours in clinical neurophysiology (EEG and EMG) to be eligible to graduate[1]. The importance of ensuring that graduating residents are able to read EEG independently arises from the fact that, in Brazil, EEGs may be read by physicians with or without training in clinical neurophysiology or epilepsy[11] – presumably most frequently by general neurologists. Scenarios where EEGs are read by physicians who are not entirely comfortable with interpreting EEGs share intrinsic concerns especially in the realm of patient care[12].

In spite of the established requirements for residency EEG education[1], there seems to be a significant lack of comfort interpreting EEG among Brazilian adult neurology residents. Based on our survey data, the two most commonly reported barriers to learning EEG were insufficient exposure and ineffective didactics. We hypothesize that these issues may arise from clinically demanding residency training programs as well as a lack of consistency in teaching and evaluating residents among the programs. Future studies including a larger sample of residents would be warranted to potentially confirm our findings and further analyze underlying issues precluding optimal resident EEG education.

We encourage Brazilian residency leadership to re-evaluate the current EEG education system in order to (i) ensure that residency programs are following ABN requirements[1] and (ii) assess whether EEG benchmarks require modifications. Possible improvements may include increasing resident EEG exposure, optimizing didactics, and maximizing faculty time reviewing studies with trainees. It would also be reasonable - especially if our findings are confirmed by more comprehensive studies - to consider enhancing specific resident EEG milestones and creating objective and standardized methods of competency evaluation. We believe that improving resident EEG education results in optimization of nationwide EEG practices thereby ultimately improving patient care.

SUPPLEMENTARY FILES

Supplementary File 1. Survey utilized in this study.

Supplementary File 2. Classification of hospitals affiliated with participating residency programs based on location, level of care, ownership status, and size.

ACKNOWLEDGMENTS

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ARTICLE

Endogenous and exogenous serotonin, but not sumatriptan, ameliorate seizures and neuroinflammation in the pentylenetetrazole-induced seizure model in rats

A serotonina endógena e exógena, mas não o sumatriptano, melhora as convulsões e a neuroinflamação no modelo de convulsão induzida por pentilenotetrazol em ratos

Ibrahim Ethem TORUN[1], Yasemin BARANOGLU KILINC[2], Erkan KILINC[1]

ABSTRACT

Background: Epilepsy has neuropsychiatric comorbidities such as depression, bipolar disorder, and anxiety. Drugs that target epilepsy may also be useful for its neuropsychiatric comorbidities. **Objective:** To investigate the effects of serotonergic modulation on pro-inflammatory cytokines and the seizures in pentylenetetrazole (PTZ)-induced seizure model in rats. **Methods:** Male Wistar rats were injected intraperitoneally with serotonin, selective serotonin reuptake inhibitor fluoxetine, 5-HT1B/D receptor agonist sumatriptan, or saline 30 min prior to PTZ treatment. Behavioral seizures were assessed by the Racine's scale. Concentrations of IL-1β, IL-6, and TNF-α in serum and brain tissue were determined by ELISA. **Results:** Serotonin and fluoxetine, but not sumatriptan, alleviated PTZ-induced seizures by prolonging onset times of myoclonic-jerk and generalized tonic-clonic seizures. The anti-seizure effect of fluoxetine was greater than that of serotonin. Likewise, serotonin and fluoxetine, but not sumatriptan, reduced PTZ-induced increases in the levels of IL-1β and IL-6 in both serum and brain tissue. None of the administered drugs including PTZ affected TNF-α concentrations. **Conclusions:** Our findings suggest that endogenous and exogenous serotonin exhibits anticonvulsant effects by suppressing the neuroinflammation. It seems that 5-HT1B/D receptors do not mediate anticonvulsant and anti-neuroinflammatory effects of serotonin.

Keywords: Serotonin 5-HT1 Receptor Agonists; Fluoxetine; Seizures; Epilepsy; Inflammation.

RESUMO

Antecedentes: A epilepsia apresenta comorbidades neuropsiquiátricas como depressão, transtorno bipolar e ansiedade. Os medicamentos que visam o tratamento da epilepsia podem ser úteis para a epilepsia e suas comorbidades neuropsiquiátricas. Objetivo: Investigar os efeitos da modulação serotonérgica em citocinas pró-inflamatórias e as convulsões no modelo de convulsão induzida por pentilenotetrazol (PTZ) em ratos. Métodos: Ratos Wistar machos foram injetados intraperitonealmente com serotonina, inibidor seletivo da recaptação da serotonina fluoxetina, sumatriptano agonista do receptor 5-HT1B / D ou solução salina 30 min antes do tratamento com PTZ. As crises comportamentais foram avaliadas pela escala de Racine. As concentrações de IL-1β, IL-6 e TNF-α no soro e tecido cerebral foram determinadas por ELISA. Resultados: A serotonina e a fluoxetina, mas não o sumatriptano, aliviaram as convulsões induzidas por PTZ ao prolongar os tempos de início das convulsões mioclônicas e tônico-clônicas generalizadas. O efeito anticonvulsivo da fluoxetina foi maior do que o da serotonina. Da mesma forma, a serotonina e a fluoxetina, mas não o sumatriptano, reduziram os aumentos induzidos por PTZ nos níveis de IL-1β e IL-6 no soro e no tecido cerebral. Nenhum dos medicamentos administrados, incluindo PTZ, alterou as concentrações de TNF-α. Conclusões: Nossos achados sugerem que a serotonina endógena e exógena exibe efeitos anticonvulsivantes por suprimir a neuroinflamação. Aparentemente, os receptores 5-HT1B / D não medeiam os efeitos anticonvulsivantes e anti-neuroinflamatórios da serotonina.

Palavras-chave: Agonistas do Receptor 5-HT1 de Serotonina; Fluoxetina; Convulsões; Epilepsia; Inflamação.

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INTRODUCTION

Epilepsy is one of the most common neurological disorders and it is characterized by recurrent seizures. It affects over 70 million people worldwide[1]. Although it is widely accepted that an impairment between excitatory and inhibitory neurotransmission leads to epileptic seizures, the exact mechanisms underlying this imbalance are still unclear. However, increasing evidence suggests that neuroinflammation, as a trigger for the seizures, is implicated in the pathophysiology of epilepsy[2-4]. Aberrational inflammatory processes such as long-lasting inflammation cause abnormal neural connectivity and hyperexcitability that result in the induction of epileptic seizures[5,6]. Additionally, about one third of the patients are resistant to anti-epileptic drugs that act by different mechanisms. There is an urgent need for new drugs that ensure the complete recovery.

Serotonergic transmission of the brain plays a key role in the regulation of cortical excitatory and inhibitory balance[7]. Data from preclinical and clinical studies indicate that while decreased serotonergic neurotransmission in the brain is implicated in the generation and aggravation of epileptic seizures, the elevated concentrations of synaptic serotonin might exhibit anticonvulsant actions[7-10]. It was demonstrated that serotonin depletion enhanced spontaneous recurrent seizures and destroyed hippocampal neurons in kainic acid-induced epilepsy rat model[11]. Reduced concentrations of hippocampal serotonin were found in patients with refractory unilateral temporal lobe epilepsy with hippocampal sclerosis who underwent epilepsy surgery[12]. Moreover, epilepsy occurs considerably more frequent among depressed patients compared to the general population[9]. Such serotonergic involvements in the pathophysiology of epilepsy suggest that prominent neuropsychiatric comorbidities of epilepsy such as depression, bipolar disorders, and anxiety can enhance the risk of seizures or vice versa[13].

The anticonvulsant effects of enhanced serotonergic tone in the brain are well known. However, mechanisms mediating the action of serotonin and its potential relationship with neuroinflammatory processes remain unclear. We explored the effects and potential mechanisms of action of the modulation of the serotonergic system by serotonin, selective serotonin reuptake inhibitor (SSRI) fluoxetine, and 5-HT1B/D receptor agonist sumatriptan on the neuroinflammatory markers and epileptic seizures in the pentylenetetrazole-induced seizure model in rats.

METHODS

Animals

Ethical approval for animal experiments was obtained from Bolu Abant Izzet Baysal University Animal Experiments Local-Ethics Committee. Male Wistar rats 9-11 weeks old and weighing 190 to 220 g were used in the experiments. Rats were supplied from the Animal House of Bolu Abant Izzet Baysal University, Turkey. Rats were handled in compliance with the Guide for the Care and Use of Laboratory Animals. All rats had free access to a standard rodent feed and water, and were exposed a 12-h light/dark cycle at 22 ± 2°C.

Drugs and reagents

Pentylenetetrazole (PTZ), serotonin hydrochloride (5-HT), sumatriptan succinate, fluoxetine hydrochloride, cOmplete™ protease inhibitor cocktail, and phosphate-buffered saline were purchased from Sigma-Aldrich (Schnelldorf, Germany); IL-1β, IL-6, and TNF-α ELISA kits were purchased from ELABscience (Wuhan, P.R. China). Pentylenetetrazole, serotonin, sumatriptan, and fluoxetine were dissolved in physiological saline (0.9% NaCl).

Experimental groups, drug administrations and induction of epileptic seizures

Rats were randomly divided into 5 groups, as follows: Control (n=6), NS (normal saline)+PTZ (n=9), 5-HT+PTZ (n=8), Fluoxt+PTZ (n=8), and Sumt+PTZ (n=8). We adjusted the number of rats in the groups to obtain at least 6 surviving animals in each group for biochemical analyses, since early death can occur in the PTZ-induced seizure model we used. All drug administrations were performed via the intraperitoneal route. The control group was administered 0.2 mL of physiological saline both at the start time and after 30 min. The other groups were administered 0.2 mL of physiological saline, 10 mg/kg serotonin[14], 10 mg/kg selective serotonin reuptake inhibitor fluoxetine[14], and 600 μg/kg 5-HT1B/D receptor agonist sumatriptan[15], and also after 30 min, all of them were administered 45 mg/kg of pentylenetetrazole[2,8,16,17] to induce epileptic seizures. Experimental groups and applications are shown in Figure 1. Following PTZ administration, rats were placed in plexiglass cages (40 cm X 40 cm X 30 cm) and videotaped for 30 min to assess behavioral seizures using the Racine's scale. The stages of seizures were assessed by Racine's scoring (0-5) as previously described[2,8]: stage 0, absence of response; stage 1, facial movements with saccade of ears and whiskers; stage 2, myoclonic jerks without rearing; stage 3, clonus of one forelimb; stage 4, rearing with bilateral forelimb clonus; stage 5, generalized tonic-clonic seizures. Based on our previous dose adjustment studies and papers of other groups, we determined the dose of PTZ as 45 mg/kg that induced seizure stages specified in the Racine's scale[2,8,16,17].

Collection of blood and brain samples

Since 6 rats survived 24 hours after PTZ administration in PTZ-treated groups, blood and tissue were collected from 6 rats in each group. Briefly, under ketamine anesthesia (90 mg/kg, i.p.), about 5 mL of blood was collected by a syringe from the right ventricle of rats that survived 24 hours after PTZ injection (number of deaths induced by PTZ in the groups is given in Table 1). Shortly after, the head regions of all animals were perfused transcardially with 150 mL heparinized phosphate-buffered

saline (PBS, pH 7.4) to remove blood from the brain tissue. Blood samples were immediately centrifuged at 1000 *g* for 15 min at 4°C. The separated serum samples were stored at -80°C for a week until assayed for cytokines. After transcardial perfusion, the cranium of rats was opened and the whole brain without cerebellum was gently harvested. The brain tissue samples were homogenized at 4°C in fixed volumes (100 mg wet tissue/1 mL) of PBS (pH 7.4) containing the protease inhibitor cocktail using a light-duty Ultra-Turrax homogenizer (ISOLAB, Wertheim, Germany). The homogenates were centrifuged at 10,000 g for 15 min at 4°C, and the separated supernatant samples were stored at -80°C until assayed for cytokines.

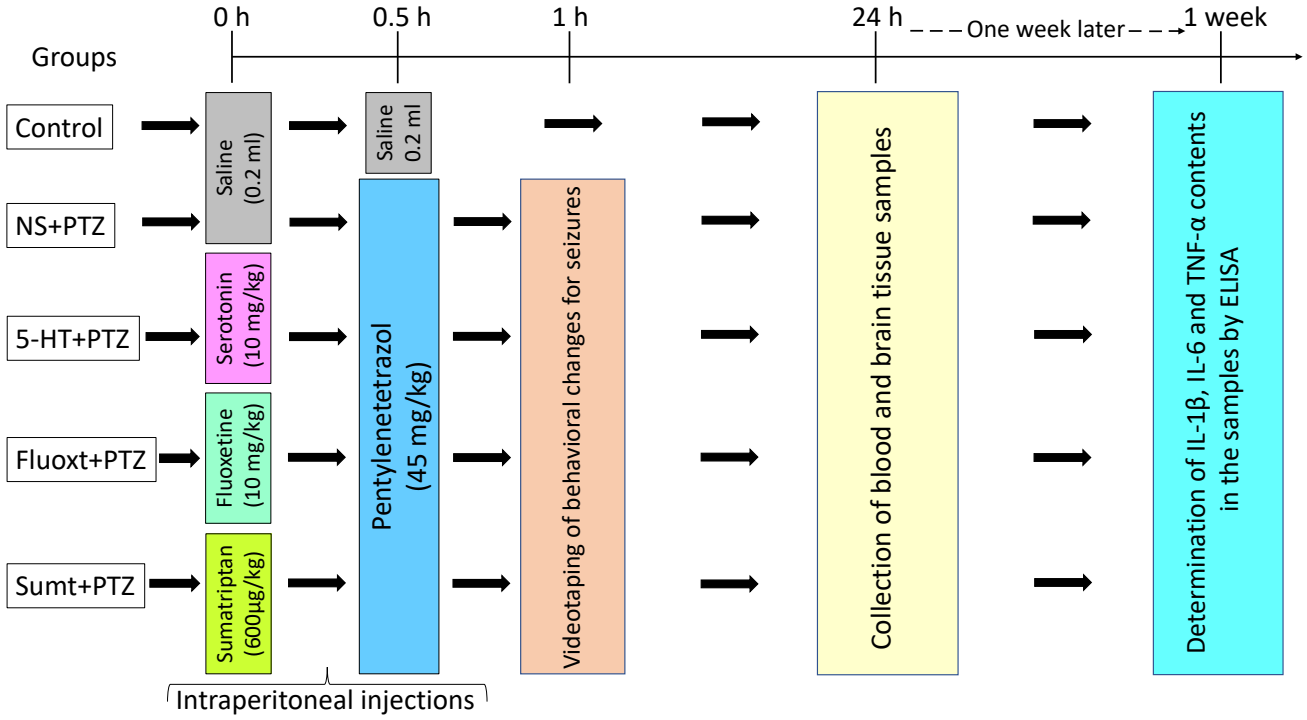


Figure 1. Experimental design and applications.

Table 1. The number and percentage of animals with generalized tonic-clonic seizures and deaths induced by PTZ in the groups.

Groups	GTCS		Deaths		Total number of subject
	number	%	number	%	
NS+PTZ	9	100	3*	33.3	9
5-HT+PTZ	8	100	2*	25	8
Fluoxt+PTZ	8	100	2*	25	8
Sumt+PTZ	8	100	2*	25	8

*P=0.973 (Pearson Chi-Square). NS: normal saline; 5-HT: serotonin; fluoxt: fluoxetine; sumt: sumatriptan; PTZ: pentylenetetrazole.

Determination of IL-1β, IL-6, and TNF-α in brain homogenates by ELISA

The concentrations of IL-1β, IL-6 and TNF-α in brain tissue were determined by enzyme-linked immunosorbent assay kits. The detection limit was ~19 pg/mL for IL-1β, ~38 pg/mL for IL-6 and ~47 pg/mL for TNF-α. The assay was performed in compliance with the instructions of manufacturer and in duplicates. After, 100 µL of sample or IL-1β, IL-6, and TNF-α standard was added to wells of a 96-well plate. The plate was incubated for 1.5 h at 37°C. Next, the liquids in the plate were removed, and instantly 100 µL biotinylated detection Ab solution was added to the wells, and the plate was incubated for 1 h at 37°C. Next, the plate was washed 3 times with the wash buffer, 100 µL HRP conjugate was added to the wells, and the plate was incubated for 0.5 h at 37°C. Next, the plate was washed 5 times with the wash buffer, 90 µL substrate solution was added to the wells, and the plate was incubated for 15 min at 37°C. Then, 50 µL of stop solution was added to the wells. The optical density was determined at 450 nm in the microplate reader (Epoch BioTek Instruments, Inc. Highland Park).

Statistical analysis

Data are given as mean±SEM. SPSS statistical package program was used for the statistical analysis of the data (IBM SPSS Statistics for Windows, Version 22.0, IBM Corp, Armonk, NY, USA). Analysis of data distribution was carried out using the Shapiro-Wilk test. The groups were compared by ANOVA followed by Bonferroni post hoc tes, or by Kruskal-Wallis followed by Dunn's multiple comparison test. A $p<0.05$ was considered significant.

RESULTS

The effects of serotonergic drugs on the PTZ-evoked seizures

All rats developed seizures following PTZ injection (Table 2). Pre-administration of both serotonin and fluoxetine significantly extended the onset time of the first myoclonic jerk compared with the NS+PTZ group (P=0.001 and P= 0.0001, Figure 2A). However, sumatriptan pre-treatment had no effect on the onset time of the first myoclonic jerk compared with the NS+PTZ group (P=1.0, Figure 2A).

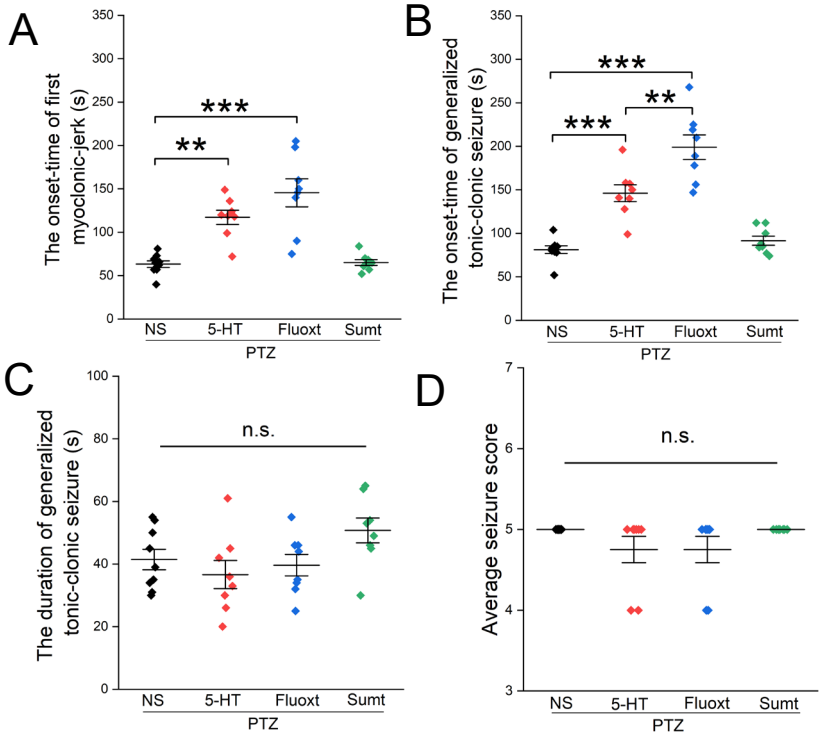
In addition, pre-administration of both serotonin and fluoxetine significantly extended the onset time of generalized tonic-clonic seizures compared with the NS+PTZ group (P=0.0001, Figure 2B). Moreover, the effect of fluoxetine was greater than that of serotonin (Fluoxt+PTZ group versus 5-HT+PTZ group, P=0.002, Figure 2B). Sumatriptan pre-treatment did not affect the onset time of generalized tonic-clonic seizures compared with the NS+PTZ group (P=1, Figure 2B).

The pre-administration of serotonin, fluoxetine and sumatriptan had no effect on the duration of generalized tonic-clonic seizures compared with the NS+PTZ group (P=0.08, Figure

Table 2. Number of rats displaying seizures after PTZ injection.

Seizure stage	Groups			
	NS+PTZ (n=9)	5-HT+PTZ (n=8)	Fluoxt+PTZ (n=8)	Sumt+PTZ (n=8)
Stage 0	0	0	0	0
Stage 1	0	0	0	0
Stage 2	0	0	0	0
Stage 3	0	0	0	0
Stage 4	0	2	2	0
Stage 5	9	6	6	8

NS: normal saline; 5-HT: serotonin; fluoxt: fluoxetine; sumt: sumatriptan; PTZ: pentylenetetrazole; GTCS: generalized tonic-clonic seizures.



**P < 0.01 and ***P < 0.001. ANOVA followed by Bonferroni post-hoc test. NS: normal saline; 5-HT: serotonin; fluoxt: fluoxetine; sumt: sumatriptan; PTZ: pentylenetetrazole; n.s.: non-significance.

Figure 2. The effects of serotonin, fluoxetine and sumatriptan on behavioral seizures and seizure score in PTZ-induced epileptic rats. A: Effects of serotonin, fluoxetine, and sumatriptan on the onset time of first myoclonic jerk; B: Onset time of generalized tonic-clonic seizure; C: Duration of generalized tonic-clonic seizure; D: Average seizure score.

2C). Similarly, these drugs did not affect the average seizure score (P=0.196, Figure 2D). Additionally, pre-administrations of serotonin, fluoxetine, and sumatriptan did not affect survival in PTZ-induced epileptic rats compared with the NS+PTZ group (P=0.973, Pearson Chi-Square test, Table 1). Analysis of behavioral parameters of seizures, except for survival rates, was performed by ANOVA followed by Bonferroni post-hoc test. Mean values of drug effects on the behavioral seizures' parameters are given in Table 3.

Effects of serotonergic drugs on the concentrations of pro-inflammatory cytokines in the serum and brain tissue in PTZ-induced epileptic rats

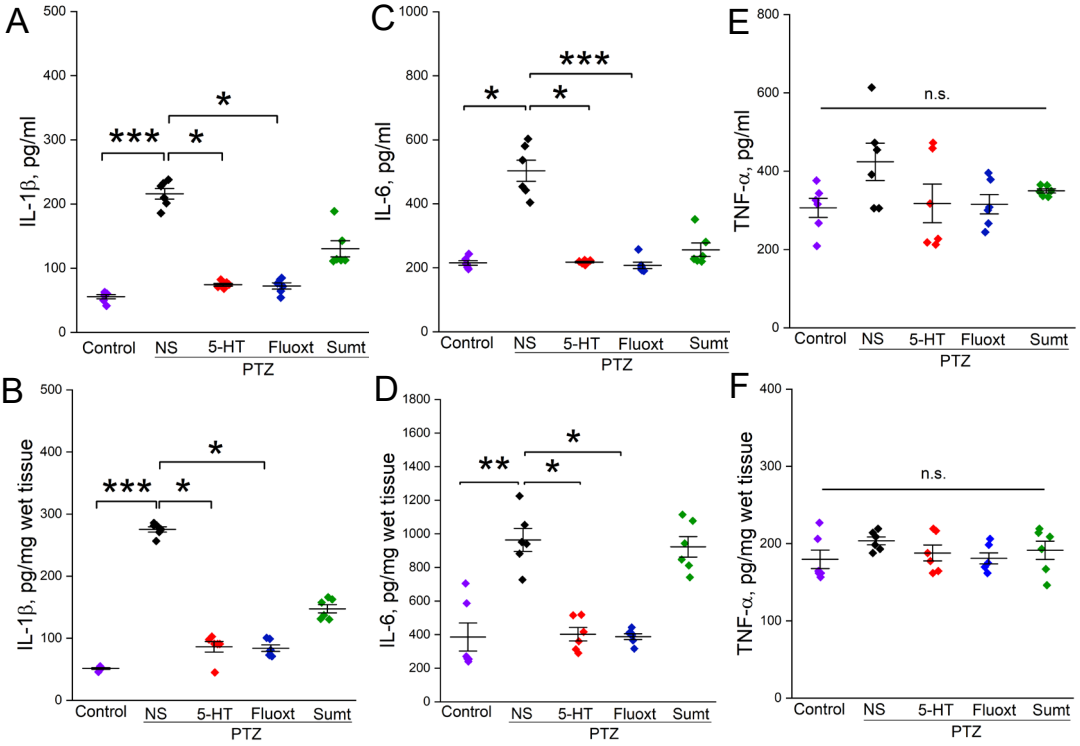
PTZ treatment significantly increased both IL-1β and IL-6 concentrations in both serum (P=0.0001 for IL-1β, Figure 3A and P= 0.014 for IL-6, Figure 3C) and brain tissue (P=0.0001 for IL-1β, Figure 3B and P=0.006, Figure 3D) (NS+PTZ group versus Control group). Contrarily, it did not change TNF-α concentrations both in serum (P=0.145, Figure 3E) and brain tissue (P=0.897, Figure 3F).

On the other hand, pretreatment of both serotonin and fluoxetine significantly reduced the increases in concentrations of both IL-1β and IL-6 induced by PTZ in serum (P=0.033 for IL-1β, Figure 3A and P=0.039 for IL-6, Figure 3C) and brain tissue (P= 0.025 for IL-1β, Figure 3B and P= 0.048 for IL-6, Figure 3D), compared to NS+PTZ, respectively. However, sumatriptan pretreatment did not change IL-1β and IL-6 levels in serum (P=1.0 for IL-1β and IL-6, Figure 3A and C) and brain tissue (P=1.0 for IL-1β and IL-6, Figure 3B and D).

Table 3. Mean values for effects of the drugs on behavioral seizure parameters.

Groups	Behavioral seizure parameters			
	Onset time of first myoclonic jerk	onset time of generalized tonic-clonic seizure	duration of generalized tonic-clonic seizure	average seizure score
NS+PTZ	63.3±3.8	81.2±4.4	41.4±3.2	5±0.0
5-HT+PTZ	117.1±8.2	146.1±9.8	36.6±4.5	4.7±0.1
Fluoxt+PTZ	145.5±16.1	199.0±14	39.6±3.4	4.7±0.1
Sumt+PTZ	65.1±3.3	91.5±5.2	50.7±3.9	5±0.0

Values are presented as mean ± SEM. SEM: standard error of the mean; NS: normal saline; 5-HT: serotonin; fluoxt: fluoxetine; sumt: sumatriptan; PTZ: pentylenetetrazole; GTCS: generalized tonic-clonic seizures.



*P < 0.05, **P < 0.01, and ***P < 0.001. Kruskal-Wallis followed by Dunn's test. NS: normal saline; 5-HT: serotonin; fluoxt: fluoxetine; sumt: sumatriptan; PTZ: pentylenetetrazole; n.s.: non-significance.

Figure 3. Effects of serotonin, fluoxetine, and sumatriptan on concentrations of pro-inflammatory cytokines in serum and brain tissue in PTZ-induced epileptic rats. Effects of serotonin, fluoxetine, and sumatriptan on concentrations of IL-1β in serum (A) and brain tissue (B), on the concentrations of IL-6 in serum (C) and brain tissue (D), on the concentrations of TNF-α in serum (E) and brain tissue (F). N=6 for each group.

Similar to PTZ treatment, pre-treatments with serotonin, fluoxetine and sumatriptan did not affect the concentrations of TNF-α in serum and brain tissue, (P>0.05 for all comparisons, Figure 3E and F). Data from pro-inflammatory cytokines were analyzed by Kruskal-Wallis followed by Dunn's multiple comparison test. Mean values for drug effects on the pro-inflammatory cytokines' parameters are given in Table 4.

Table 4. Mean values for effects of the drugs on biochemical parameters.

Groups	Biochemical parameters					
	IL-1 beta		IL-6		TNF alpha	
	Plasma (pg/mL)	Brain (pg/mg wet tissue)	Plasma (pg/mL)	Brain (pg/mg wet tissue)	Plasma (pg/mL)	Brain (pg/mg wet tissue)
Control	55.5±3.3	51.3±1.2	215.2±7.0	385.7±83.7	306.4±24.3	179.6±12.0
NS+PTZ	215.8±8.2	275.2±4.3	503.2±33.2	963.1±68.2	423.9±47.7	203.6±5.0
5-HT+PTZ	74.2±2.0	86.3±8.5	217.7±2.3	402.3±40.3	317.7±49.3	187.9±10.2
Fluoxt+PTZ	72.3±4.7	84.0±5.2	207.3±10.2	387.8±17.5	315.5±24.6	180.9±7.1
Sumt+PTZ	130.2±12.6	147.4±6.6	256.4±21.0	922.3±61.0	349.6±5.3	191.4±11.8

Values are presented as mean ± SEM. SEM: standard error of the mean; IL: interleukin; NS: normal saline; 5-HT: serotonin; fluoxt: fluoxetine; sumt: sumatriptan; PTZ: pentylenetetrazole; GTCS: generalized tonic-clonic seizures.

DISCUSSION

In the current study, we showed that both serotonin and fluoxetine, but not sumatriptan, alleviated PTZ-induced seizures by prolonging the onset-times of myoclonic jerks and generalized tonic-clonic seizures, respectively. In addition, the effect of fluoxetine on the generalized tonic-clonic seizures was greater than that of serotonin. On the other hand, PTZ elevated the levels of pro-inflammatory cytokines IL-1β and IL-6, without changing TNF-α levels, in serum and brain tissue. However, pre-treatments with serotonin and fluoxetine, but not sumatriptan, reduced the increases in the levels of IL-1β and IL-6 in serum and brain tissue evoked by PTZ.

Accumulating preclinical and few clinical evidence indicates that extracellular serotonin enhancement by 5-hydroxytryptophan and SSRIs exhibits anticonvulsant effects[10]. Fluoxetine diminished the spontaneous seizure rate in pilocarpine-induced epilepsy rat model[18] and reversed status epilepticus-evoked augmentation in brain excitability in lithium-pilocarpine-induced rat model of epilepsy[19]. Direct intrahippocampal administration of exogenous serotonin also suppressed seizures in pilocarpine-induced seizure model[20]. Additionally, a clinical study reported that frequency of seizures was decreased in patients with epilepsy who received fluoxetine or citalopram[21].

Our findings regarding the anticonvulsant effects of serotonin and fluoxetine on the seizures are in line with those previous studies. However, the vast majority of previous studies focused on the effects of endogenous serotonin enhanced by SSRIs rather than exogenous serotonin. Herein, we further confirmed the anticonvulsant action of exogenous serotonin treatment by demonstrating that it extended the onset-times of myoclonic jerks and generalized tonic-clonic seizures in PTZ-induced seizure model. In addition, we found that the anticonvulsant effect of endogenous serotonin enhanced by fluoxetine on generalized tonic-clonic seizures was greater than that of exogenous serotonin. This may be due to the fact that fluoxetine may elevate the extracellular serotonin concentration in the brain more than exogenous administration of serotonin. Additionally, the intraperitoneal application of serotonin may preclude the substance to reach the brain due to enzymatic degradation.

Increasing evidence suggests that the anti-seizure actions of serotonin are mostly mediated by 5-HT1A, 5-HT2C, and 5-HT3 receptors[10,22,23]. For instance, a preclinical study demonstrated that two 5HT1A receptor agonists, 8-OH-DPAT and indorenate, exhibited therapeutic effects against epileptic activity depending on the type of seizure in three different animal models of epileptic seizures[23]. However, activation of 5-HT1B/D receptors were reported to exert dual effects on seizures[24,25]. 5-HT1B/D receptor agonist sumatriptan exhibited biphasic effect on seizures in a dose-dependent manner in PTZ-evoked seizure model in mice[25]. In the current study, although we chose the most probable dosage for potential anticonvulsant effect[15,25], activation of 5-HT1B/D receptors by sumatriptan did not exert pro-convulsant or anti-convulsant action. Thus, more studies are needed to clarify these dilemmas.

On the other hand, it is well established that neuroinflammation, including enhanced release of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α, plays a central role in epileptogenesis[3-6]. It was stated that IL-1β increases neuronal over-excitability by promoting glutamate release from astrocytes, and by decreasing its re-uptake[26]. It was shown that intranasal treatment of IL-6 exerted pro-convulsive impacts in PTZ-induced seizure model[27]. Additionally, TNF-α increased the expression of AMPA receptors and triggered GABA receptor endocytosis in hippocampal neuronal cultures[28], thus facilitating seizure generation by enhancing the excitatory tone in the brain. Moreover, it was found that lasting febrile seizures

elevated cerebrospinal fluid levels of IL-1β, IL-6, and TNF-α in patients[29]. Enhanced concentrations of IL-1β in epileptogenic brain tissue specimens of patients with temporal lobe epilepsy lowered GABA-mediated neurotransmission and stimulated the initiation of seizures[30].

Studies on whether the serotonergic system modulation exerts its anticonvulsant effects through neuroinflammatory processes are very limited. We found that serotonin and fluoxetine, but not sumatriptan, decreased PTZ-induced increases in IL-1β and IL-6 levels in serum and brain tissue. In addition, although not statistically significant, 5-HT and fluoxetine decreased seizure severity. Therefore, we can speculate that depending on the decrease in seizure severity, IL-1β and IL-6 levels may have decreased in both 5-HT and fluoxetine groups. Furthermore, the seizure severity was stage 5 in the sumatriptan-pretreated group and sumatriptan did not decrease the levels of these pro-inflammatory cytokines. Hence, these findings also clearly support our speculation. Our findings are in line with the previous studies mentioned above. Moreover, this anti-neuroinflammatory effect of serotonin further strengthens our findings regarding its anti-seizure effects and opens new insights about potential mechanisms of action of serotonergic modulation on the epileptic seizures.

Serotonin is a high affinity natural ligand for 5-HT receptors including 5-HT1B/D receptors. In addition to their neuropsychiatric effects such as major depressive disorder and anxiety states, activation of 5-HT1B/D receptors mediates anti-neuroinflammatory effects mainly through inhibition of vasoactive neuropeptide calcitonin and gene-related peptide release from trigeminal sensory fibers[31,32,33]. On the contrary, in the present study, activation of 5-HT1B/D receptors by sumatriptan did not display anti-neuroinflammatory effects. This may be due to the lower expression of 5-HT1B/D receptors in neurons in the region of seizure generation. However, endogenous or exogenous serotonin exhibited anti-neuroinflammatory effects, suggesting that this effect may be a common consequence of activation of multiple 5-HT receptors by serotonin.

Our findings regarding anti-inflammatory effects of serotonin and fluoxetine are in accordance with previous studies reporting their potential immunoregulatory functions. It was reported that serotonin represses the release of TNF-α and IL-1β through 5-HT receptors in monocytes/macrophages[34]. Moreover, it was demonstrated that serotonin inhibited lipopolysaccharide-stimulated pro-inflammatory cytokine production from human macrophages by 5-HT7-PKA axis[35].

SSRI sertraline reduced PTZ-induced increases in IL-1β and TNF-α mRNA expressions in rat hippocampus[36]. In contrast, in our study, PTZ did not lead to an increase in TNF-α levels in serum or brain tissue. Likewise, the other administrations also showed no effect. We measured the TNF-α peptide, but not mRNA. Therefore, the reason for this difference may be that TNF-α peptide may degrade faster than its mRNA. On the other hand, sumatriptan showed no effect on PTZ-induced increases in IL-1β and IL-6 levels as well as on PTZ-induced behavioral seizures.

Compared to the PTZ group, these unchanged IL-6 and IL-1β levels in the sumatriptan plus PTZ group may be due to the seizure effect, since seizure severity did not decrease in this group. Moreover, we measured these pro-inflammatory cytokines in plasma and brain tissue after PTZ injections following pretreatment of serotonergic drugs rather than shortly before PTZ injection. Therefore, PTZ administered after sumatriptan pretreatment may have suppressed the effect of sumatriptan. However, our current findings suggest that anticonvulsant and anti-neuroinflammatory effect of serotonin may not be mediated by 5-HT1B/D receptors.

Taken together, our findings are of great importance in terms of treatment of epilepsy and its neuropsychiatric comorbidities, as epilepsy patients experiencing long-lasting active epilepsy have higher rates of neuropsychiatric comorbidities such as depression, bipolar disorders, and anxiety[13]. Drugs targeting monoamines such as serotonin are commonly used in the treatment of these neuropsychiatric comorbidities. Therefore, drugs targeted at increasing serotonin levels in the synaptic cleft, such as SSRIs, may be useful for treatment of both epilepsy and its neuropsychiatric comorbidities by acting as anticonvulsant and antidepressant.

In conclusion, our findings suggest that endogenous and exogenous serotonin exhibit anticonvulsant effects by suppressing neuroinflammation in PTZ-induced seizure model. It seems that 5-HT1B/D receptors are not responsible for these effects of serotonin.

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ARTICLE

The prevalence of impulsive compulsive behaviors in patients treated with apomorphine infusion: a retrospective analysis

Prevalência de comportamentos impulsivo-compulsivos em pacientes tratados com infusão de apomorfina: análise retrospectiva

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ABSTRACT

Background: Impulsive compulsive behaviors (ICBs) can affect a significant number of Parkinson's disease (PD) patients. **Objective:** We have studied brain samples from a brain bank of PD patients who received apomorphine via continuous infusion in life to assess the prevalence and outcome of ICBs. **Methods:** A search on the Queen Square Brain Bank (QSBB) database for cases donated from 2005 to 2016 with a pathological diagnosis of idiopathic PD was conducted. Notes of all donors who used apomorphine via continuous infusion for at least three months were reviewed. Clinical and demographic data were collected, as well as detailed information on treatment, prevalence and outcomes of ICBs. **Results:** 193 PD cases, 124 males and 69 females, with an average age at disease onset of 60.2 years and average disease duration of 17.2 years were reviewed. Dementia occurred in nearly half of the sample, depression in one quarter, and dyskinesias in a little over 40%. The prevalence of ICBs was 14.5%. Twenty-four individuals used apomorphine infusion for more than three months. Patients on apomorphine had younger age at disease onset, longer disease duration, and higher prevalence of dyskinesias. The prevalence of *de novo* ICB cases among patients on apomorphine was 8.3%. Apomorphine infusion was used for an average of 63.1 months on an average maximum dose of 79.5 mg per day. Ten patients remained on apomorphine until death. **Conclusions:** Apomorphine can be used as an alternative treatment for patients with previous ICBs as it has low risk of triggering recurrence of ICBs.

Keywords: Parkinson Disease; Compulsive Behavior; Impulsive Behavior; Disruptive, Impulse Control, and Conduct Disorders; Apomorphine.

RESUMO

Antecedentes: Comportamentos impulsivo-compulsivos (CICs) podem acometer uma parcela significativa de indivíduos com doença de Parkinson (DP). **Objetivo:** Nós estudamos amostras de tecido cerebral de uma população de pacientes com DP de um banco de cérebros que receberam apomorfina por infusão contínua em vida, com a finalidade de avaliar a prevalência e o desfecho dos CICs. **Métodos**: Uma pesquisa no banco de dados do Banco de Cérebros de Queen Square foi conduzida à procura de doações recebidas entre 2005 e 2016 com diagnóstico anatomopatológico de DP idiopática. Os prontuários de todos os doadores que usaram apomorfina por infusão contínua por um período mínimo de três meses foram revisados. Dados clínicos e demográficos foram coletados, assim como informações detalhadas sobre o tratamento, prevalência e desfecho dos CICs. **Resultados:** 193 casos de DP, 124 do sexo masculino e 69 do sexo feminino, com idade média de início da doença de 60,2 anos e tempo médio de duração da doença de 17,2 anos, foram revisados. Aproximadamente metade dos casos apresentaram demência, um quarto depressão, e um pouco mais de 40% discinesias. A prevalência de CICs foi 14,5%. Vinte e quatro indivíduos usaram infusão de apomorfina por mais de três meses. Os pacientes que usaram apomorfina apresentaram DP mais cedo, maior duração da doença, e uma maior prevalência de discinesias. A prevalência de novos casos de CICs entre pacientes usando apomorfina foi de 8,3%. Infusão de apomorfina foi usada em média por 63,1 meses a um dose máxima média de 79,5 mg por dia. Dez pacientes permaneceram usando apomorfina até o óbito. **Conclusões:** Apomorfina pode ser usada como opção de tratamento alternativo para pacientes que apresentarem CICs no passado considerando seu baixo risco de causar recorrência de CICs.

Palavras-chave: Doença de Parkinson; Comportamento Compulsivo; Comportamento Impulsivo; Transtornos Disruptivos, de Controle do Impulso e da Conduta; Apomorfina.

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INTRODUCTION

Impulsive compulsive behaviors (ICBs), such as dopamine dysregulation syndrome (DDS), hypersexuality, pathological gambling, compulsive shopping, compulsive eating and punding are relatively common behavioral complications that can affect from 14 to 36% of patients with Parkinson's disease (PD)[1,2]. The main risk factors for the development of ICBs are male sex, young age at PD onset, and dopaminergic treatment. Even though levodopa has also been associated with these abnormal behaviors, the main risk factor is the use of dopamine agonists[1]. In a population of PD patients receiving one dopamine agonist (DA) for at least six months, the prevalence of ICBs reached 39%[3].

Neuroimaging studies have shown that excessive dopaminergic release in the ventral striatum occurs in individuals with DDS[4] and other ICBs[5]. However, data from clinical studies suggest that excessive stimulation of dopaminergic D3 receptors, abundantly expressed in the nucleus accumbens[6], might also play a role[7].

Apomorphine is a dopamine agonist with preferential binding to D1 and D2 dopaminergic receptors[8]. Therefore, studies assessing the development of ICBs in PD patients on apomorphine via continuous infusion could shed some light on the pathophysiology of ICBs. Initial results suggest a lower proclivity of apomorphine to trigger these abnormal behaviors, indicating that either pulsatile rather than continuous stimulation of dopaminergic receptors is associated with ICBs, or that stimulation of D3 receptors is a key factor, or perhaps a combination of both[9-11].

We conducted a retrospective analysis to assess the prevalence and outcome of ICBs in brain samples of a population of PD patients treated with apomorphine continuous infusion who donated their brains to the Queen Square Brain Bank (QSBB), London, UK.

METHODS

We searched the QSBB database for consecutive cases donated from 2005 to 2016 with a pathological diagnosis of idiopathic Parkinson's disease. Subsequently, all donors who had received treatment with apomorphine via continuous infusion for at least 3 months were identified and case files separated for a detailed review of notes. All files were reviewed by a neurologist with expertise in movement disorders (PB). Clinical and demographic data were collected with emphasis on dopaminergic treatment and neuropsychiatric complications, as well as indication for apomorphine, dose changes, pre-existing ICBs and outcome after apomorphine, and new-onset ICBs.

The diagnosis of impulse control disorders was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the diagnosis of DDS was based on previously published diagnostic criteria[1].

All variables were tested for normality and statistical tests were chosen accordingly. Parametric data were compared using the unpaired t-test and non-parametric data, the Mann-Whitney U test. Proportions were analyzed using the chi-square test. Data was analyzed using SPSS 22®.

RESULTS

The database search returned 193 cases with a pathological diagnosis of idiopathic PD from 2005 to 2016, 124 males and 69 females. Clinical and demographic data are summarized in Table 1.

Table 1. Clinical and demographic characteristics of the entire cohort.

	N = 193
Females (%)	69 (35.8%)
Age at PD onset (years)	60.2 (±10.9; 28 – 88)
Disease duration (years)	17.2 (±8; 3 – 39)
Age at death (years)	77.5 (±7.7; 52 - 96)
Dementia (%)	87 (45%)
Depression (%)	47 (24.4%)
Dyskinesias (%)	80 (42%)
ICBs (%)	28 (14.5%)
Apomorphine infusion (%)	24 (12.4%)

PD: Parkinson's disease; ICBs: impulsive compulsive behaviors.

Twenty-eight patients were diagnosed with ICBs: 22 with one ICB (12 with DDS, 9 with hypersexuality, 1 with pathological gambling, and 1 with compulsive shopping) and 6 with multiple ICBs (3 with DDS and hypersexuality, 1 with DDS and pathological gambling, and 1 with hypersexuality and punding).

Twenty-four patients used apomorphine infusion for more than three months. Another 5 patients underwent an apomorphine trial: 2 could not tolerate the drug because of side effects, 2 were unable to operate the pump, and one had a negative apomorphine challenge.

For statistical analysis, patients were divided into two groups based on the use of apomorphine infusion for more than three months (APO+ and APO-). Sex distribution was similar in both groups. Compared to the patients who did not use apomorphine, the patients on the APO+ group had younger age at disease onset, longer disease duration, and died at an earlier age. There was no difference in the prevalence of dementia and depression between groups, but dyskinesias were significantly more prevalent in the APO+ group (Table 2).

All patients who used apomorphine infusion for more than three months had their full set of notes reviewed. Apomorphine pump was used for an average of 63.1 months. The maximum dose of apomorphine reached was on average 77.9 mg per day.

Apomorphine was discontinued prematurely in 14 cases: in 2 because of inadequate control of PD symptoms, in 1 because of excessive dyskinesias, in 8 because of side effects, in 1 because of technical issues, and in 2 because of lack of benefit. Ten patients remained on apomorphine until death (Table 3).

Three patients in the APO+ group received surgical treatment for PD, 2 pallidotomy and 1 deep brain stimulation (DBS), initially of the subthalamic nucleus and 2 years later of the globus pallidus internus. One patient received an experimental treatment with fetal mesencephalic transplant. In the APO+ group, thirteen patients also received treatment with intermittent injections of apomorphine. Most used the pen only before being prescribed the pump but 3 patients continued with the pen after being prescribed apomorphine via continuous infusion (Table 3).

Only 3 patients in the APO+ group did not use oral/transdermal dopamine agonists. Of the 21 patients that used dopamine agonists, 11 used it concomitantly with apomorphine infusion. The most common agonist used in the APO+ group was pergolide (used by 10 patients), followed by ropinirole (8 patients), rotigotine (7 patients), cabergoline (7 patients), pramipexole (2 patients), and lysuride (1 patient). DA dose was calculated in levodopa equivalent daily dose (LEDD) as previously described[12]. Regarding pathological diagnosis, 8 patients were classified as Braak stage 5 and 16 as Braak stage 6 (Table 3)[13].

Table 2. Comparison between groups that used or not apomorphine infusion for more than 3 months.

	APO+ (N = 24)	APO- (N = 169)	p
Females (%)	9 (37.5%)	60 (35.5%)	0.824*
Age at PD onset (years)	51.33 (±8)	61.56 (±10.7)	**<0.001****
Disease duration (years)	22.88 (±6.25)	16.49 (±7.9)	**<0.001*****
Age at death (years)	74.2 (±7.5)	78 (±7.6)	**0.016*****
Dementia (%)	11 (45.8%)	76 (44.9%)	1.000*
Depression (%)	9 (37.5%)	38 (22.4%)	0.092*
Dyskinesias (%)	23 (95.8%)	58 (34.3%)	**<0.001***

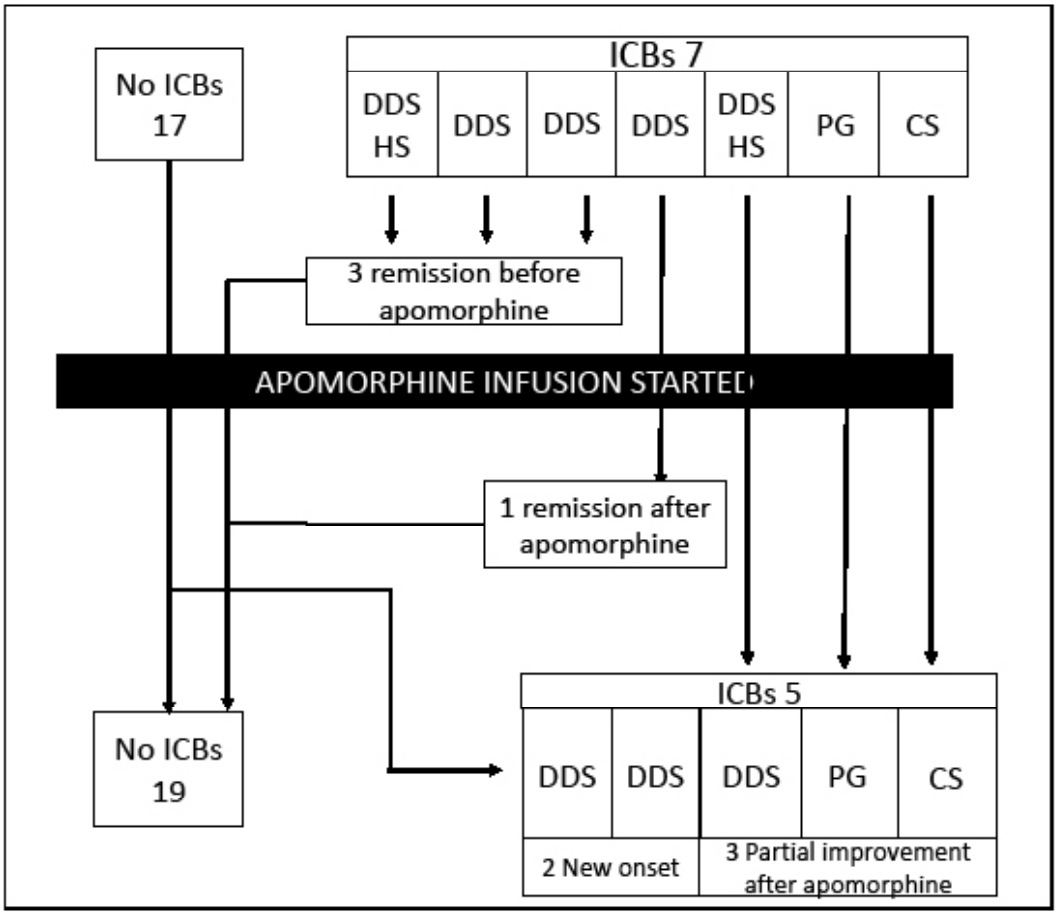
PD: Parkinson's disease; *Chi-square test; **unpaired t-test; ***Mann-Whitney test; Significant results are in bold.

Table 3. Data on apomorphine use by Parkinson's disease patients.

	N = 24
Apomorphine treatment duration	63.1 months (±54.2; 3 – 216)
Apomorphine maximum daily dose	77.9 mg (±36.9; 15 – 150)
Apomorphine discontinued	14 (58.3%)
Use of intermittent injections of apomorphine	Total – 13 (54.1%) Concomitant – 3 (12.5%)
Use of dopamine agonists	Total – 21 (87.5%) Concomitant - 11 (45.8%)

Although a larger number of individuals in the APO+ group developed ICBs, there were only 2 *de novo* cases of ICBs during apomorphine use. Seven patients developed behavioral addictions before starting treatment with the apomorphine pump: two of them had DDS and hypersexuality, one improved completely before starting the pump and another improved partially, remaining with mild DDS after apomorphine; two other patients with DDS improved completely before the pump and did not experience recurrence on apomorphine; one patient with DDS improved completely after starting apomorphine infusion; one patient with pathological gambling improved partially before apomorphine and did not worsen with the pump; and one patient with compulsive shopping improved partially after treatment with apomorphine infusion (Figure 1).

Two patients developed new onset DDS after being prescribed the pump. In one case, the abnormal behavior started during the first six months of continuous apomorphine infusion and led to a confusional state after a large dose increase by the patient. DDS improved completely after adjustment of the medications and did not recur during another five years of pump use. The other new onset DDS case was a patient that started to overdose on levodopa approximately 6 years after the pump was prescribed. At that time, he was taking up to 48 tablets of levodopa/carbidopa 50/12.5 mg per day. This was the only patient with ICBS that had never been exposed to an oral or transcutaneous DA and remained symptomatic until death (Figure 1).



ICBs: impulsive compulsive behaviors; DDS: dopamine dysregulation syndrome; HS: hypersexuality; PG: pathological gambling; CS: compulsive shopping.

Figure 1. Patients on apomorphine infusion and development of ICBs. Seven patients had ICBs before apomorphine. Three improved completely and 3 improved partially before starting this medication, and none of these patients worsened after the pump was prescribed. One patient with DDS improved completely after apomorphine treatment. Two patients had new onset DDS during apomorphine treatment.

One patient developed DDS nine years after discontinuing treatment with apomorphine infusion while receiving treatment with levodopa and cabergoline. Details on the patients who developed ICBs are shown in Figure 1.

DISCUSSION

A retrospective analysis of the prevalence and outcomes of ICBs among PD patients from the QSBB that used apomorphine via continuous infusion for more than three months was conducted.

PD affects men more than women, but the male to female ratio of 1.8:1 was slightly higher than that published in the literature[14]. Although the average age at PD onset of the entire cohort was compatible with the literature, patients that used apomorphine infusion developed PD much earlier, at approximately 50 years of age. This is similar to other cohorts of PD patients on apomorphine[15,16] and probably reflects the fact that younger patients are more likely to develop motor fluctuations earlier, one of the main indications for apomorphine continuous infusion[17]. Disease duration of the APO+ group was six years longer than the average of the entire cohort. The longer disease duration probably reflects the predominance of younger patients in the APO+ group as these patients may have slower disease progression[18].

Life expectancy in the UK in 2014 was 79.5 years for males and 83.2 years for females (https://www.ons.gov.uk/), while the average age at death in this cohort was 77.5 years, slightly lower than the national average. This is compatible with previous published research showing that PD patients have increased mortality rates after 10 years of disease progression compared to the general population[19]. Age at death was lower in the APO+ group but this was partly compensated by the longer disease duration in this group.

Dementia developed in 45% of patients, a similar prevalence to that found in the CamPAIGN study[20] but slightly higher than a meta-analysis published in 2005[21]. Depression was present in approximately 24% of individuals, in line with previously published data[22]. The prevalence of both dementia and depression was not influenced by the use of apomorphine.

Levodopa-induced dyskinesias affected 42% of the patients, less than what is expected for a population with more than 17 years of disease progression[23]. It is possible that this finding is an underestimate associated with retrospective data collection. Of the APO+ group, all patients but one developed dyskinesias, a much higher prevalence than what is expected for PD patients. Data from the literature shows that younger age at PD onset, longer disease duration, and longer exposure to levodopa are risk factors for the development of dyskinesias and could explain this finding[23]. A recently published study found that patients with PD and dyskinesias have a higher prevalence of ICBs than the general PD population, suggesting the presence of shared mechanisms between both phenomena[24].

The mean maximum daily dose of apomorphine in this study was 77.9 mg per day, higher than the dose reported by another study we conducted with living patients[25] but still lower than the 98 mg reported in the early 2000s in our centre[15]. The pump was used for an average of 5.2 years and was well tolerated by the majority of patients. However, a little over half of the patients had to discontinue apomorphine, a third of them because of side effects. The fact that nearly 40% of the patients remained on the pump until death shows that for some patients apomorphine remains a reliable treatment option until final stages of the disease.

The prevalence of ICBs found was lower than that published in the literature[2]. Even though only donations received after the year 2005 when clinical awareness of ICBs was more widespread were included, it is possible that some ICB cases in our cohort were not detected, as patients with ICBs are less likely to spontaneously disclose these abnormal behaviours[26]. Another possible explanation for the lower prevalence of ICBs is the relatively high number of patients with cognitive impairment, since a previous study has reported a lower prevalence of impulse control disorders in individuals with Parkinson's disease dementia[2].

Data from studies on addiction show that drugs that can cause a rapid increase in dopamine release in the dopaminergic reward pathway have stronger reinforcing properties and are more likely to cause addiction[27]. Whether the different methods of apomorphine delivery, intermittent injections or continuous infusion, are more or less likely to cause DDS or other ICBs is still unclear. Nearly half of the patients in the APO+ group received treatment with apomorphine intermittent injections at some point of their disease course. However, only 3 remained on this medication after starting the pump. The literature lacks data on the propensity of apomorphine delivered as intermittent injections to trigger ICBs and our small sample does not allow us to draw any conclusions.

ICBs have also been associated with excessive stimulation of D3 receptors, but this conclusion has been drawn mainly by findings from clinical studies showing that DAs are the main risk factor for the development of ICBs[1,3] and that these drugs have strong affinity for D3 receptors[7]. Apomorphine is a dopamine agonist with different pharmacological profile as it stimulates mainly D1 and D2 receptors, akin to levodopa[8]. A few studies with PD patients on apomorphine infusion have been published and the initial results indicate a lower prevalence of ICBs compared to oral DAs[10,11,25,28]. However, these results need to be confirmed with randomized clinical trials.

Our finding that patients on apomorphine had a lower prevalence of ICBs suggests that apomorphine infusion is not commonly associated with ICBs. The majority of patients that used apomorphine infusion did not develop ICBs. In three patients in whom ICBs had improved before apomorphine infusion, the problem did not recur during treatment, and in 4 patients that were previously symptomatic, the situation improved after apomorphine infusion, completely in 1 and partially in 3. Both the pharmacological profile and delivery by continuous infusion might contribute to apomorphine being less likely to trigger ICBs.

We report 2 new-onset DDS in patients on continuous infusion of apomorphine. Although the prevalence of ICBs was similar to what has been found by other authors studying infusion therapies in PD[11,28], it is possible that other dopaminergic medication contributed to the development of DDS, as levodopa use appears to be the most important risk factor for the development of DDS[29]. The fact that complete improvement occurred in one of the cases despite remaining on apomorphine infusion, and that ICBs occurred in another case 6 years after the pump was prescribed, supports this hypothesis. One limitation of this paper was the inclusion of DDS and other types of ICBs under the same group. While there are pathophysiological features common to these conditions[3], DDS and other types of ICBs have different risk factors.

The main advantage of using a brain bank cohort is the ability to confirm the diagnosis of PD through *postmortem* examination. It is known that even in specialized centers, a small proportion of patients can be misdiagnosed with PD[30]. The main disadvantage is that clinical information is acquired retrospectively, and the quality of data is heavily dependent on the thoroughness of hospital records. Considering that all patients in this cohort were seen by consultant neurologists regularly, we believe that the quality of the data was appropriate for the purposes of this study. Another potential issue is the small sample of patients using apomorphine infusion. Even though our data suggests that apomorphine is not usually associated with ICBs, larger studies are needed to confirm these findings.

In conclusion, continuous infusion of apomorphine can be used as an alternative treatment option for patients with advanced PD who previously developed ICBs, as it has a low risk of triggering recurrence of ICBs.

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ARTICLE

Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS): discrete and regression-based norms for the Brazilian context

Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS): normas discretas e regressivas para o contexto brasileiro

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ABSTRACT

Background: The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) has been recently developed as a brief, practical, and feasible tool for cognitive impairment in multiple sclerosis (MS). **Objective:** This study aimed to provide continuous and discrete normative values for the BICAMS in the Brazilian context. **Methods:** Normatization was achieved using six hundred and one healthy controls from the community assessed at five Brazilian geopolitical regions. **Results:** Mean raw scores, T scores, percentiles, and Z scores for each BICAMS measure are provided, stratified by age and educational level. Regression-based norms were provided by converting raw scores to scaled scores, which were regressed on age, gender, and education, yielding equations that can be used to calculate the predicted scores. Regression analyses revealed that age, gender, and education significantly influenced test results, as in previous studies. **Conclusions:** The normative data of the BICAMS to the Brazilian context presented good representativeness, improving its use in daily clinical practice.

Keywords: Multiple Sclerosis; Cognitive Dysfunction; Neuropsychology.

RESUMO

Antecedentes: O BICAMS foi desenvolvido como uma ferramenta breve, prática e confiável para avaliar o comprometimento cognitivo na esclerose múltipla (EM). **Objetivo:** Neste estudo, objetivamos fornecer dados normativos para o BICAMS. **Métodos:** Normatização foi realizada com seiscentos e um controles saudáveis da comunidade avaliados das cinco regiões geopolíticas brasileiras. **Resultados:** Escores brutos médios, escore T, percentil e escore Z para cada medida do BICAMS são fornecidos e estratificados por idade e nível educacional. Normas baseadas em regressão foram obtidas através da conversão dos pontos brutos em pontos ponderados, produzindo parâmetros de regressão que podem ser usados para calcular os escores preditos. As análises de regressão revelaram que idade, gênero e educação influenciaram significativamente nos resultados do teste, assim como em estudos prévios. **Conclusão:** Normas do BICAMS para o contexto brasileiro apresentaram boa representatividade, contribuindo para a utilização na prática clínica diária.

Palavras-chave: Esclerose Múltipla; Disfunção Cognitiva; Neuropsicologia.

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INTRODUCTION

Over 40% of multiple sclerosis (MS) patients can present cognitive impairment (CI)[1-4]. CI often manifests in decreased processing speed, learning and memory deficits, and less frequently in executive dysfunction[2,3]. Cognitively disabled patients are more likely to be unemployed and report fewer extra-curricular and social activities[5,6]. Appropriate test measures for the identification of CI are essential for the clinical management of the disease. Ideally, all MS patients would be routinely evaluated and/or monitored for CI, with similar measures being employed across specialized care centers.

An extensive neuropsychological assessment can be costly and time-consuming, with standards for the cognitive evaluation varying between providers. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) is a collection of tests chosen by an international panel to standardize and facilitate routine monitoring of cognition in MS patients[7]. Transcultural studies between BICAMS from Brazil and the United States (US) have demonstrated its reliability and validity[8].

The present study was conducted to establish the discrete and regression-based norms of the BICAMS to the Brazilian context.

METHODS

Participants

Six hundred and one healthy control volunteers were recruited. The healthy controls were from the five Brazilian regions (north, northeast, south, southeast, and central-west), as recommended by the Brazilian Institute of Geographic and Statistics[9]. The Ethics Committee of the Medical School of Ribeirão Preto, University of São Paulo, approved all research procedures for this study.

Quality control of data acquisition

Qualification procedures were required from all the examiners. Psychologists and health professionals participated in an interactive training on administration and scoring procedures of the BICAMS. The protocol was administered in a standardized manner following commonly used manual-based instructions[10]. The two sub-scales of the Hospital Anxiety and Depression Scale (HADS)[11] were also administered as markers of major depression and generalized anxiety disorder. The Mini-Mental State Examination test (MMSE)[12] was administered for screening and to exclude cognitive impairment and possible dementia. No healthy controls were excluded based on their HADS or MMSE performance.

BICAMS standardization and scoring procedures

In brief, the Symbol Digit Modalities Test (SDMT)[13] assesses complex scanning, visual tracking[14], processing speed, and attention. The SDMT oral version was employed in this study, following previous validation studies[4,15] and consensus opinion papers[16]. The task consists of a series of symbols presented at random, each with a blank space below, and participants are asked to name the number that matches each symbol. The maximum duration of the test is 90 seconds for the participant to complete each assessment (oral and written). When both forms of the test are administered, it is recommended that the written version be given first. It takes about five minutes to complete the test. The number of correct substitutions within the 90-second interval is recorded, with 110 being the maximum score for each form (written and oral). The translated standardized instructions of the SDMT for the Brazilian context are provided in the Technical and Interpretative Manual.

The California Verbal Learning Test – Second Edition (CVLT-2)[17] is a commonly used test of auditory/verbal learning and memory[18,19]. The total CVLT-2 raw score is obtained by the sum of the correct words said in the five learning trials (T1 to T5). The total raw score for the learning trial obtained for the CVLT-2 is 80 points. The translated standardized instructions of the CVLT-2 to the Brazilian context are: *"Eu vou ler uma lista de palavras para você. Preste atenção porque quando eu terminar de ler eu quero que você me diga o máximo de palavras que puder. Você pode repeti-las em qualquer ordem me dizendo o máximo de palavras que você se lembrar. Você está pronto?* Leia a lista (A) de palavras em um mesmo ritmo, utilizando um pouco mais do que 1 segundo de intervalo entre as palavras. Dessa forma, a lista completa deve levar entre 18 e 20 segundos. E então diga: *Pode começar***."**

Instructions for the trials 2 to 5 (T2 to T5) in Brazilian Portuguese are: *"Eu vou ler para você novamente a mesma lista de palavras. Como da primeira vez, eu quero que você me diga o máximo de palavras que puder se lembrar e em qualquer ordem. Procure repetir as mesmas palavras que você me falou na primeira vez".*

The Brief Visual Memory Test-Revised (BVMT-R)[20] is a visual/spatial memory test wherein subjects view a stimulus card with six figures for 10 seconds, and then render the figures from memory. There are three learning trials, which are summed to produce the final BVMT-R score (maximum score 36). The scores reflect visuospatial memory. The translated standardized instructions of the BVMT-R to the Brazilian context are: *"Agora eu vou mostrar para você uma página com alguns desenhos. Eu preciso que você olhe atentamente para cada um deles durante 10 segundos. Procure prestar atenção no formato e na posição deles na folha. Eu vou te mostrar uma vez, daí retiro os desenhos e você os fará de memória aqui nesta folha (mostrar uma folha de sulfite A4 em branco). Nós faremos um treino, ou seja, vou te mostrar os desenhos e você irá desenhá-los por três vezes para você poder aprender e memorizar os desenhos."*

Instructions for the trials 2 and 3 (T2 and T3) in Brazilian Portuguese are: *"Muito bem, agora vou mostrar mais uma vez porque quero ver se você aprendeu mais alguma figura".* Present the page with the stimuli for 10 seconds, then remove and deliver the blank sheet.

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (v21.0, SPSS Inc, Chicago). Normality tests for each variable were performed with the Shapiro-Wilk test.

To the regression-based norms, the same methodology employed previously[21,22] were applied in the present study. Each raw value was rank-ordered, converted to a proportion estimated, and then multiplied by 100 to derive percentile ranks. The ranks were then converted to scaled scores using the same conversion for all variables (mean=10, standard deviation=3). Thus, these steps allowed to convert the raw scores to a scaled score metrics based on a cumulative frequency distribution. The new variables are the Scaled Scores (SS) that were carried forward to the next step.

The SSs were inspected to ensure if the data were normally distributed. The scaled scores were then entered one at a time, as the dependent variables in multiple regression analyses used to model the proportion of variance in performance accounted for by the block entry of four demographic variables: age, age^2, gender, and years of education. Age and age^2 were coded in years. The b weights for each demographic variable, a predictive constant, and the standard deviation of the group's raw residuals were derived for each test.

RESULTS

Demographics of the normative sample are shown in Table 1. The sample consisted of 65.6% (n=394) females, and age between 18 to ≥ 70 years. Most participants were between 30 and 39 years old (30.1%, n=181) and had a high educational level (59.6%, n=358, >12 years). The MMSE and HADS scores were classified as normal.

In the present paper, the discrete and regression-based norms are provided, either of which can be used by the examiner.

Using the discrete norms

The discrete norms, stratified by age and educational level, are shown in Tables 2 and 3.

Using the regression-based norms

- Step 1: To obtain the predicted scores from raw scores, the examiner must convert the raw scores to scaled scores derived from the healthy controls using the data provided in Table 4.
- Step 2: To obtain the predicted scaled score (pss), the examiner must employ the predictive equation model. It is necessary to use the formula below (in gender, please use 1 for male and 2 for female) and the data from Table 5 (final regression models and standard deviation of the residual for BICAMS measures).

Table 1. Demographic characteristics of the normative sample (n=601).

Demographic data		Percentage (freq.)	Mean±SD (95%CI)
Gender	Female	65.6 (394)	–
	Male	34.4 (207)	–
Region	Central West	32.1 (193)	–
	Northeast	6.5 (39)	–
	South	35.3 (212)	–
	Southeast	26.1 (157)	–
Age groups (years)	18 to 29	22.3 (134)	–
	30 to 39	30.1 (181)	–
	40 to 49	17 (102)	–
	50 to 59	17.5 (105)	–
	60 to 69	53 (8.8)	–
	≥70	26 (4.3)	–
Classes of education (years)	1 to 8	10.8 (65)	–
	9 to 11	29.6 (178)	–
	>12	59.6 (358)	–
MMSE		–	28.46±3.55 (13 to 30)
HADS-A		–	6.27±3.92 (0 to 21)
HADS-D		–	4.85±2.05 (0 to 19)

SD: standard deviation; IC: confidence interval; freq.: frequency; MMSE: Mini Mental State Examination; HADS-A: Hospital Anxiety and Depression Scale, anxiety measure; HADS-D: Hospital Anxiety and Depression Scale, depression measure.

Table 2. Discrete norms: BICAMS scores stratified by age and educational level.

Age	BICAMS tests	Educational level									
		1-11 years					>12 years				
		Mean	±SD	Percentile			Mean	±SD	Percentile		
				5th	10th	50th			5th	10th	50th
18-29 (n=134)	CVLT-II T1	8.1	2.8	4	4	8	7.7	2.2	5	5	7
	CVLT-II T2	10.4	2.6	5	6	11	10.6	2.3	7	8	10
	CVLT-II T3	12.2	2.3	8	8	13	12.4	2.5	8	9	13
	CVLT-II T4	12.8	2.5	7	9	13	13.4	2.5	10	11	14
	CVLT-II T5	13.4	2.2	8	10	14	14.1	2.2	10	11	15
	CVLT-II Total	56.8	10	36	40	57	58.2	9.3	41	45	59
	CVLT-II Total Rep.	3	4.7	-	-	-	3.3	3.7	-	-	-
	CVLT-II Total Intr.	1.5	2.8	-	-	-	1.5	4.1	-	-	-
	BVMT-R T1	7.4	2.9	2	3	8	7.3	2.9	2	3	7
	BVMT-R T2	9.3	2.4	4	6	10	9.5	2.2	4	7	10
	BVMT-R T3	10.3	2.3	4	7	12	10.6	1.8	6	8	11
	BVMT-R Total	27	7	10	17	27	27.5	5.9	15	19	28
	Oral SDMT	55	14	32	39	52	60	15.7	36	45	57
30-39 (n=181)	CVLT-II T1	7.6	2.4	4	5	8	7.4	2.2	4	5	7
	CVLT-II T2	10.2	2.4	6	7	10	10.6	2.6	6	7	10
	CVLT-II T3	11.7	2.4	8	8	12	12.4	2.8	6	9	13
	CVLT-II T4	12.3	2.4	8	9	12	13.1	2.4	9	10	13
	CVLT-II T5	12.9	2.1	10	10	13	13.9	2.2	9	11	15
	CVLT-II Total	54.8	9.1	35	39	53	57.4	10.2	38	44	58
	CVLT-II Total Rep.	5.6	5.4	-	-	-	4.8	5.9	-	-	-
	CVLT-II Total Intr.	1.1	1.8	-	-	-	1.3	2.1	-	-	-
	BVMT-R T1	6.1	3.6	2	2	5	6.7	2.9	2	3	6
	BVMT-R T2	8.4	3	3	4	8	9.3	2.4	5	6	10
	BVMT-R T3	10	2.5	5	6	11	10.5	1.9	6	8	11
	BVMT-R Total	24.4	8.1	10	13	26	26.6	6.3	15	19	27
	Oral SDMT	48.8	15	23	31	49	60.6	15.6	33	40	60
40-49 (n=102)	CVLT-II T1	6.5	2	4	4	6	7	2.2	4	5	7
	CVLT-II T2	9.8	2	7	7	10	9.9	2.6	5	6	10
	CVLT-II T3	11	2	7	8	11	11.7	2.4	8	9	11
	CVLT-II T4	11.9	2.5	5	9	12	12.8	2.3	8	10	13
	CVLT-II T5	12.9	1.8	10	10	13	13.2	2.3	9	10	14
	CVLT-II Total	52	8.3	35	30	51	54.5	9.3	39	42	55
	CVLT-II Total Rep.	5.2	3.7	-	-	-	5.4	6.4	-	-	-
	CVLT-II Total Intr.	1.1	1.3	-		-	1.2	1.9	-	-	-
	BVMT-R T1	5.6	3.3	0	1	5	5.7	2.5	2	2	6
	BVMT-R T2	8	2.9	2	4	9	8.4	2.7	3	5	9
	BVMT-R T3	9.1	31	1	4	11	10.1	2.4	4	6	11
	BVMT-R Total	22.8	8.4	6	12	23	24.2	6.6	10	13	26
	Oral SDMT	39.2	14.8	14	27	45	55.3	15.4	31	36	56

±SD: standard deviation; n: sample size; CVLT-II T1: California Verbal Learning Test second edition, trial 1; CVLT-II T2: California Verbal Learning Test second edition, trial 2; CVLT-II T3: California Verbal Learning Test second edition, trial 3; CVLT-II T4: California Verbal Learning Test second edition, trial 4; CVLT-II T5: California Verbal Learning Test second edition, trial 5; CVLT-II Total: California Verbal Learning Test second edition, Total sum score; CVLT-II Total Rep.: California Verbal Learning Test second edition, Total of Repetitions; CVLT-II Total Intr.: California Verbal Learning Test second edition, Total of Intrusions; BVMT-R T1: Brief Visuospatial Memory Test Revised, Trial 1; BVMT-R T2: Brief Visuospatial Memory Test Revised, Trial 2; BVMT-R T3: Brief Visuospatial Memory Test Revised, Trial 3; BVMT-R Total: Brief Visuospatial Memory Test Revised, Total Sum Score; Oral SDMT: Symbol Digit Modalities Test oral form.

Table 3. Discrete norms: BICAMS scores stratified by age and educational level (continuation).

Age	BICAMS tests	Educational Level									
		1-11 years					>12 years				
		Mean	±SD	Percentile			Mean	±SD	Percentile		
				5th	10th	50th			5th	10th	50th
50-59 (n=105)	CVLT-II T1	7.1	2.2	4	5	7	6.9	2.4	3	4	7
	CVLT-II T2	9	2.4	5	6	9	9.3	2.4	6	6	9
	CVLT-II T3	10.6	2.4	7	8	10	11	2.6	6	7	12
	CVLT-II T4	11	2.7	5	7	12	12	2.3	6	9	12
	CVLT-II T5	12.3	2.7	8	9	13	13.4	2.3	9	10	14
	CVLT-II Total	50	9.6	35	32	49	52.5	8.3	38	42	53
	CVLT-II Total Rep.	4.9	4.4	-	-	-	4,1	3.7	-	-	-
	CVLT-II Total Intr.	1.4	2	-	-	-	1.3	2.3	-	-	-
	BVMT-R T1	3.5	2.3	0	1	4	5.4	3.0	0	1	5
	BVMT-R T2	5.4	3.2	0	1	5	7.3	2.8	3	4	7
	BVMT-R T3	7	3.3	2	2	8	9.3	2.4	3	5	10
	BVMT-R Total	16	8	4	6	18	22	7.3	8	13	24
	Oral SDMT	36.9	14	12	20	33	46.4	14.9	26	28	47
60-69 (n=53)	CVLT-II T1	6.2	2.1	1	4	6	6	1.7	3	3	6
	CVLT-II T2	8.5	2.7	2	6	9	8.7	1.6	6	6	9
	CVLT-II T3	9.8	2.8	2	7	10	10.4	2.4	5	6	11
	CVLT-II T4	10.3	3.4	2	7	11	12	2.2	8	8	12
	CVLT-II T5	10.9	3.3	1	6	12	13.2	2.2	8	10	13
	CVLT-II Total	45.6	12.9	30	31	48	50.2	7.9	32	37	52
	CVLT-II Total Rep.	6	3.2	-	-	-	6.3	6.2	-	-	-
	CVLT-II Total Intr.	1.5	2.2	-	-	-	1.6	1.7	-	-	-
	BVMT-R T1	3.8	2.7	0	1	3	4.2	3.4	1	2	4
	BVMT-R T2	5.5	2.8	1	2	6	6.5	3.5	1	3	6
	BVMT-R T3	6.5	3.7	0	1	7	8.3	2.8	1	5	8
	BVMT-R Total	15.8	8.4	1	5	16	22	9.1	2	8	17
	Oral SDMT	29.5	12.9	10	12	30	44	14.4	23	26	40
>70 (n=26)	CVLT-II T1	5.2	2.0	1	3	5	6.6	1.8	5	5	6
	CVLT-II T2	7.5	2.2	4	4	7	8.1	2.3	4	4	9
	CVLT-II T3	8.7	2.3	5	5	9	8.4	1.6	6	6	8
	CVLT-II T4	9.8	2.6	6	6	10	9.7	2.2	6	6	10
	CVLT-II T5	10.3	2.7	5	6	10	12.1	2.5	8	8	13
	CVLT-II Total	41.5	9.7	21	30	42	45	8,2	29	29	47
	CVLT-II Total Rep.	6.0	4.6	-	-	-	5	4.6	-	-	-
	CVLT-II Total Intr.	1.1	1.7	-	-	-	3.4	4.7	-	-	-
	BVMT-R T1	2.5	2.5	1	1	2	6	3.7	1	1	5
	BVMT-R T2	3.9	3.2	1	1	3	7.9	3.7	2	2	7
	BVMT-R T3	4.6	3.6	1	1	4	8.4	3.7	2	2	9
	BVMT-R Total	11.1	8.5	1	1	10	19	10.7	5	5	20
	Oral SDMT	23.7	9.8	9	9	26	40.1	8.6	23	26	37

±SD: standard deviation; n: sample size; CVLT-II T1: California Verbal Learning Test second edition, trial 1; CVLT-II T2: California Verbal Learning Test second edition, trial 2; CVLT-II T3: California Verbal Learning Test second edition, trial 3; CVLT-II T4: California Verbal Learning Test second edition, trial 4; CVLT-II T5: California Verbal Learning Test second edition, trial 5; CVLT-II Total: California Verbal Learning Test second edition, Total sum score; CVLT-II Total Rep.: California Verbal Learning Test second edition, Total of Repetitions; CVLT-II Total Intr.: California Verbal Learning Test second edition, Total of Intrusions; BVMT-R T1: Brief Visuospatial Memory Test Revised, Trial 1; BVMT-R T2: Brief Visuospatial Memory Test Revised, Trial 2; BVMT-R T3: Brief Visuospatial Memory Test Revised, Trial 3; BVMT-R Total: Brief Visuospatial Memory Test Revised, Total Sum Score; Oral SDMT: Symbol Digit Modalities Test oral form.

Table 4. Regression-based norms: BICAMS raw-to-scaled scores conversions.

Scaled scores	Raw Scores			Classification
	CVLT-II	BVMT-R	SDMT	
1	<20			Extremely low
2	20-28			
3	29-31	1-2	1-9	
4	32-35	3-5	10-17	
5	36-39	6-8	18-23	Borderline
6	40-41	9-12	24-29	
7	42-44	13-17	30-36	Low average
8	45-48	18-20	37-43	
9	49-52	21-23	44-49	Average
10	53-56	24-26	50-53	
11	57-60	27-28	54-58	
12	61-64	29-30	59-62	High average
13	65-66	31-32	63-68	
14	67-69	33-34	69-74	Superior
15	70-71	35	75-79	
16	72	36	80-93	Very superior
17	73-74		94-107	
18	75		>107	
19	>75			

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; SDMT: Symbol Digit Modalities Test; CVLT-II: California Verbal Learning Test second edition; BVMT-R: Brief Visuospatial Memory Test Revised.

Table 5. Final regression models and standard deviation of residuals for the BICAMS measures.

CVLT2 Residual SD		BVMT-R Residual SD		SDMT Residual SD	
	2.527166		2.626665		2.48323
CVLT-2 Reg Model		BVMTR Reg Model		SDMT Reg Model	
Predictor	B	Predictor	B	Predictor	B
(constant)	8.512324	(constant)	11.58455	(constant)	9.248778
Age	-0.14798	age	-0.14752	age	-0.01094
age^2	0.001373	age^2	0.000896	age^2	-0.00086
Sex	0.176426	sex	-0.19042	sex	-0.4714
education	0.364315	education	0.22895	education	0.263055

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; SD: standard derivation; CVLT-2: California Verbal Learning Test second edition; SDMT: Symbol Digit Modalities Test; BVMT-R: Brief Visuospatial Memory Test Revised; Reg. Model: Regression Model.

$$\text{Predicted Scaled Score (pss)} = \text{Constant} + \beta_{age}(\text{age}) + \beta_{age^2}(\text{age}^2) + \beta_{gender}(\text{gender}) + \beta_{ed.}(\text{ed.})$$

- Step 3: In sequence, the examiner must calculate the Z-score using the formula:

Z-score = (Actual scaled score - Predicted scaled score) / SD of residuals (provided in Table 5).

DISCUSSION

The present study aimed to provide both discrete and regression-based norms for the BICAMS. This study followed the recommendations of the international validation protocol for the BICAMS[10,16] and is the first to publish in the Brazilian Portuguese the discrete and regression-based norms for BICAMS with age, gender and education corrections in the Brazilian population.

The BICAMS is a validated and reliable brief protocol for monitoring the CI of MS patients. In several countries, efforts are being made to establish it as a psychometrically valid and reliable tool that is internationally applicable. This protocol was optimized for small MS centers so it can be administered by health care professionals without specific expertise in neuropsychological testing and without high costs. Its clinical use allows large-scale international clinical trials to have a common outcome measure of cognitive functioning[23,24]. It is recognized that assessments and follow-ups of cognition should be as much as a priority as the evaluation of physical disability.

Discrete norms have their limitations and have come under criticism over in recent years, but they facilitate clinical use. Discrete norms are easier to use, but may distort demographic variables such as age, gender, and educational level, so they should be used with caution. Regression-based norms allow control of demographic influences on test performance.

In conclusion, our results provide the normative data of the BICAMS for use in the Brazilian context. Future studies are necessary to confirm its suitability for longitudinal assessments.

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Congenital myasthenic syndrome in a cohort of patients with 'double' seronegative myasthenia gravis

Síndrome miastênica congênita em uma série de pacientes com miastenia gravis duplo soronegativa

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ABSTRACT

Background: Congenital myasthenic syndromes (CMS) have some phenotypic overlap with seronegative myasthenia gravis (SNMG). **Objective:** The aim of this single center study was to assess the minimum occurrence of CMS misdiagnosed as double SNMG in a Brazilian cohort. **Methods:** The genetic analysis of the most common mutations in *CHRNE*, *RAPSN*, and *DOK7* genes was used as the main screening tool. **Results:** We performed genetic analysis in 22 patients with a previous diagnosis of 'double' SNMG. In this study, one CMS patient was confirmed due to the presence of compound heterozygous variants in the *CHRNE* gene (c.130insG/p.Cys210Phe). **Conclusions:** This study confirmed that CMS due to *CHNRE* mutations can be mistaken for SNMG. In addition, our study estimated the prevalence of misdiagnosed CMS to be 4.5% in 'double' SNMG patients of our center. Based on our findings, genetic screening could be helpful in the diagnostic workup of patients with 'double' SNMG in whom differential diagnosis is recommended.

Keywords: Myasthenic Syndromes, Congenital; Myasthenia Gravis; Genetics.

RESUMO

Antecedentes: As síndromes miastênicas congênitas (SMC) podem ter sobreposição fenotípica com a miastenia gravis soronegativa (MG-SN). **Objetivo:** Estabelecer a prevalência mínima de SMC diagnosticada inicialmente como MG duplo soronegativa em uma série de casos brasileiros. **Métodos:** a análise genética das mutações mais comuns nos genes *CHRNE*, *RAPSN* e *DOK7* foi usada como o principal exame de triagem. **Resultados:** Vinte e dois pacientes com diagnóstico prévio de MG-SN foram geneticamente analisados, sendo que uma paciente foi confirmada com SMC devido a presença de variante em heterozigose composta no gene *CHRNE* (c.130insG/p.Cys210Phe). **Conclusões:** O presente estudo confirma que SMC devido mutação no gene *CHNRE* pode ser inicialmente diagnosticada como MG-SN. O estudo estimou como 4,5% a prevalência de diagnóstico de SMC entre nossos pacientes préviamente diagnosticados como MG-SN. Com base nesse estudo, a análise genética pode ser recomendada para investigação do diagnóstico diferencial em pacientes com MG-SN.

Palavras-chave: Síndromes Miastênicas Congênitas; Miastenia Gravis; Genética.

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INTRODUCTION

Congenital myasthenic syndromes (CMS) are heterogeneous inherited diseases caused by specific mechanisms that compromise the function of neuromuscular transmission[1,2]. Some CMS patients present clinical manifestation from birth or shortly after, whereas others, especially those with mild presentations, go undiagnosed until adolescence or adulthood[1-5]. CMS are usually identified by clinical manifestations, family history, electrophysiologic studies, and response to acetylcholinesterase inhibitors[1,2]. The presence of an affected family member seems to be the strongest indication to initially suspect of CMS. However, in sporadic patients with no reported affected family, other signs can help the diagnosis: age at onset, delayed motor development, hypotonia, ptosis, ophthalmoplegia, weakness that may worsen on exertion, skeletal deformities (e.g. arthrogryposis, lordosis, or scoliosis), standard response to the use of acetylcholinesterase inhibitors, and no response to treatment with immunosuppressants[1,2].

CMS and MG share many clinical and electrophysiological features; thus, they can be difficult to differentiate, mainly when they present in adolescents or adults[3-5]. An abnormal decrement on low-frequency repetitive nerve stimulation (RNS) or an increased jitter on single-fibre electromyography (SFEMG) confirms an underlying neuromuscular transmission defect in CMS, but these electrodiagnostic findings are similar to those in MG[6,7]. This fact makes it difficult to electrophysiologically differentiate CMS from MG[6,7]. In this situation, the presence of serum antibodies, e.g. anti-acetylcholinesterase receptor (AChR), is helpful to distinguish between the diseases. However, this situation is still challenging, especially if the initial diagnosis is seronegative MG (SNMG), which is usually one cause of the delay in the CMS diagnosis in pediatric and adult populations[4-6,8,9].

CMS was previously misdiagnosed as SNMG[3-7]. CMS and MG are treated differently, and the recognition of such cases is important in order to ensure beneficial therapy for patients and prevent the use of inappropriate immunosuppression[3,6,10]. The main objective of this study was to assess the prevalence of CMS in a Brazilian population diagnosed as 'double' SNMG (absence of serum antibodies against AChR and muscle-specific tyrosine kinase [MuSK]). To investigate this, we screened a targeted panel, including hot-spot mutations previously identified in Brazilian patients, to detect the CMS.

METHODS

We selected all cases catalogued as 'double' SNMG who visited a single neuromuscular disorder center at Hospital de Clínicas of the Universidade Federal do Paraná (Curitiba, Brazil) between 2015 and 2019. We included MG patients who met the clinical (including purely ocular symptoms), laboratorial ('double' absence of serum antibodies), and electrophysiological (compound muscle action potential with decrement greater than 10% in 3 Hz repetitive nerve stimulation in at least one site) diagnostic criteria for SNMG. We excluded patients with suspected CMS, relatives of CMS patients, relatives of MG patients, relatives of patients with known neuromuscular disorders and patients younger than 18 years.

We performed a retrospective analysis of clinical data, treatment, laboratory and electrophysiological features. Relevant data, including age, gender and repetitive nerve stimulation findings, were recorded during the investigation of MG. We reviewed clinical data when a patient had a mutation in the *CHRNE*, *RAPSN,* or *DOK7* genes.

We performed molecular analysis (genetics) for the hot-spot mutations identified in the international literature by using blood specimens. We collected blood samples from peripheral veins in ethylenediaminetetraacetic acid (EDTA)-coated vacuum tubes. We extracted DNA from peripheral blood lymphocytes using a modified phenol/chloroform method.

We analyzed the point mutations c.130insG, c.1327delG, and c.1353insG, respectively in exon 2, 11, and 12 of the *CHRNE* gene, by Sanger sequencing. In the sequencing, we used two sets of oligonucleotides to amplify the putative DNA mutations in the exon 2 (F-5'–CAGTGAGATGAGATTCGTCAG–3' and R-5'–CCTCACACAGGCACCCTGGCA–3') and exons 11 to 12 (F-5'–CTGGAGATGGGTGGGAAATTG–3' and R-5'–CACGGAGCGAGCTCGTGTTTGA–3') by two conventional polymerase chain reactions (PCRs) with Taq DNA polymerase. The PCRs produced 518 base-pair (bp; for exon 2) and 550 bp (for exons 11 and 12) fragments that were purified and sequenced.

We analyzed the point mutation p.N88K (c.264C>A; p.Asn88Lys) in exon 2 of the *RAPSN* gene by Sanger sequencing. In the sequencing, we used oligonucleotide primers (F-5'–GCCACAGGGTGTGTGCCTCA–3' and R-5'–AGGCTGGGGTCCAAGGCTCAGAGT–3') to amplify the putative DNA mutation by conventional PCR with Taq DNA polymerase. The PCR produced a 476 bp fragment that was purified and sequenced.

We analyzed the frameshift mutation c.1124_1127dupTGCC (p.Ala378SerfsTer30) in exon 7 of the *DOK7* gene by Sanger sequencing. In the sequencing, we used oligonucleotide primers (F-5'–agcaatcctcgtcgtcagccagcac–3' and R-5'AAGAAAGCCGG GGGTGGCCCCGCGTG–3') to amplify the putative DNA mutation by conventional PCR with Taq DNA polymerase. The PCR produced a 610 bp fragment that was purified and sequenced.

We used a Big Dye Terminator Cycle Sequencing Kit (Applied Biosystems) and an ABI PRISM 3100 Avant Genetic Analyzer (Hitachi High Technologies Corporation, Tokyo, Japan) for sequencing. We compared the obtained sequences with the revised genomic reference of these genes (*CHRNE*, *RAPSN* and *DOK7*). If the patient was homozygous for one of hot-spot mutations, CMS was confirmed. If the patient was heterozygous for one of the hot-spot mutations, as these CMS subtypes have autosomal recessive inheritance, we additionally amplified and sequenced the whole targeted gene (coding sequence and flanking intronic regions; methods available under request).

The local ethics committee (Hospital de Clínicas da UFPR) approved the study. We obtained the informed consents for DNA tests from participants in the out-patient clinic. We conducted all studies in accordance with ethical principles after obtaining patient informed consent.

RESULTS

We found 22 patients with 'double' SNMG from unrelated families in our center who were eligible for genetic screening for CMS. The sample population comprised 15 females and 7 males, aged 19 to 69 years (mean: 45.13 ± 13.24 years; median: 43 years). The age at onset varied between 4 and 60 years (mean: 27.81 ± 13.95 years; median: 27 years). The disease duration varied between 5 and 37 years (mean: 16.86 ± 7.98 years; median: 15.5 years). The clinical presentation of SNMG was ocular in two patients and generalized in 20 patients. The MG composite scores at the last appointment ranged from 0 and 21 (mean: 5.81 ± 6.41; median: 3.5). All patients received symptomatic treatment with the acetylcholinesterase inhibitor pyridostigmine. Twenty patients used immunosuppression concomitant to symptomatic treatment: prednisone in seven patients, azathioprine in two patients, and prednisone associated with azathioprine in eleven patients. Five patients previously underwent thymectomy; the thymus histopathology revealed thymoma in three patients and thymic atrophy in two patients.

All 22 'double' SNMG patients were genetically evaluated. Genetic analysis revealed no hot-spot mutation for the *RAPSN* and *DOK7* genes in any patients (Table 1). The heterozygous c.130insG variant in *CHRNE* exon 2 was detected in only one patient (Table 1). In this patient, we sequenced the entire *CHRNE* gene; we also found the c.630G>T variant (p.Cys210Phe; g.4901163C>A) in exon 7 (Table 1). For these *CHRNE* variants, it was not possible to analyze the segregations status.

The confirmed CHRNE-CMS patient was a 53-year-old woman who presented mild eyelids ptosis that was slowly worsening and was progressively associated with facial and proximal limb-girdle weakness since adulthood. There were no delayed motor milestones or relatives with similar symptoms. She had no osteoskeletal changes. At 33 years of age, she presented worsening of all symptoms, which were associated with dysphagia after pregnancy and a lung infection episode. At 42 years of age, the neurological examination showed eyelids ptosis, ophthalmoparesis, facial weakness, and symmetrical weakness in proximal muscles in the upper and lower limbs (Medical Research Council grade 3; Figure 1). At this time, she did not have clinical suspicion of CMS and her initial diagnosis was MG. The investigation yielded the following results: absence of serum antibodies against AChR (0.2 nmol/L; negative: < 0.45); increased serum creatine kinase (CK) levels (717 U/L; normal: < 200); normal lactic acid (1.9 nmol/L; normal: < 2); repetitive nerve stimulation with decrement response of the compound muscular action potential found in the facial, accessory spinal and ulnar nerves; and muscle biopsy with 'ragged red fibers' and sub-sarcolemmal accumulation of mitochondria that were compatible with mitochondrial dysfunction. Initial treatment for SNMG (pyridostigmine and prednisone) seemed to be beneficial, but her symptoms did not completely improve after some months. At 43 years of age, she presented mild deafness. Despite the immunosuppressive treatment, her disease was slowly progressing in the follow-up (MG composite: 21; QMG score: 21; MG-QOL15: 50). At that time, her clinical diagnosis was SNMG (possibly refractory to the immunosuppressive treatment) and she was undergoing genetic analysis for CMS because she met the inclusion criteria of this study (Figure 1). The investigation still showed repetitive nerve stimulation with a decremented pattern in the facial, accessory spinal, and ulnar nerves (Figure 1), serum antibodies against the AChR (0.11 nmol/L; negative: < 0.25), and MuSK (0.26 U/mL; negative: < 0.4) in the normal range. However, CHRNE-CMS diagnosis was confirmed by genetic analysis (compound heterozygous variants in the *CHRNE* gene - transcript ENST00000649488.2: c.130insG/p.Cys210Phe).

Table 1. Synopsis of studies in seronegative myasthenia gravis (SNMG) cohorts using genetic screening for congenital myasthenic syndromes (CMS).

Year of publication, Country	Genetic screening method	Number of investigated SNMG patients (number of confirmed CMS patients)	Misdiagnosed as CMS
2011, Norway[2]	Sanger sequencing: targeted panel for *RAPSN* (p.N88K) and *DOK7* (c.1124_1127dupTGCC) genes	74 (1): homozygous for *RAPSN* gene (p.N88K)	1.4%
2016, Australia[6]	Whole exome sequencing (followed by confirmatory Sanger sequencing)	25 (7): 3 were homozygous for the RAPSN p.N88K; 2 for *RAPSN* (S201N/E162K)*; 2 for CHRNA1 (F256L/R55H)	28%
This study, Brazil	Sanger sequencing: targeted panel for *CHRNE* (c.130insG, c.1327delG and c.1353insG); *RAPSN* (p.N88K) and *DOK7* (c.1124_1127dupTGCC) genes	22 (1): compound heterozygous for *CHRNE* gene (c.130insG/p.Cys210Phe)	4.5%
Total		121 (9)	7.4%

*One patient had a sibling with a confirmed *RAPSN* mutation (S201N/E162K), but he was not genetically tested.

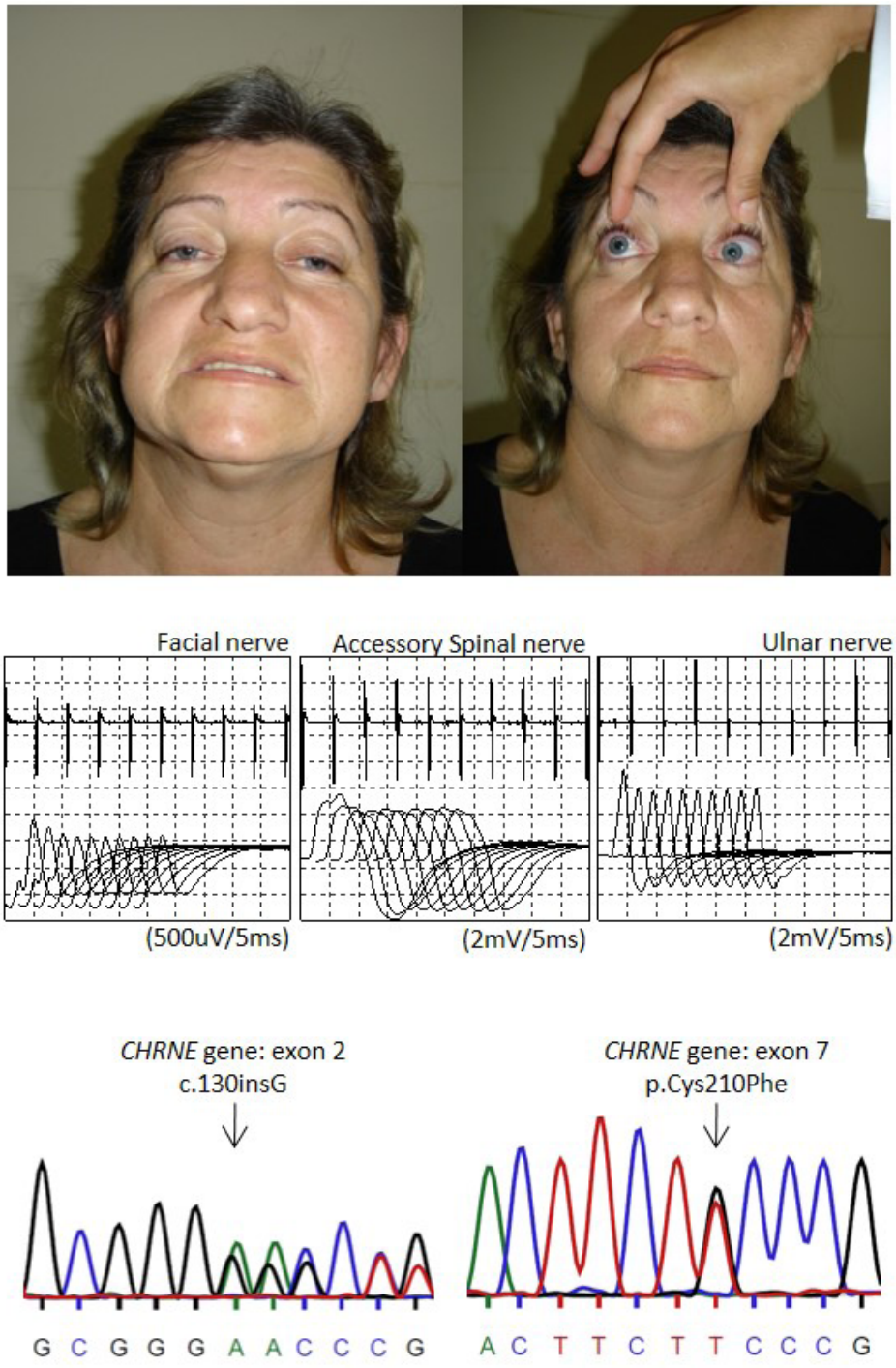

Figure 1. Patient with CHRNE-congenital myasthenic syndrome (CMS) showing eyelid ptosis associated with ophthalmoparesis (published with written patient consent); repetitive nerve stimulation at 3 Hz with decrement greater than 10% in the compound muscular action potential; and Sanger sequencing (electropherogram) with compound heterozygous pathogenic variants (c.130insG/p.Cys210Phe) in *CHRNE* gene.

DISCUSSION

Clinical and electrophysiological features of CMS can easily be mistaken for MG[5,6]. Hence, it is well-established that CMS is a differential diagnosis of MG, mainly for SNMG and pediatric MG[3,8-10]. Although the worldwide prevalence of misdiagnosis is not fully known, CMS was provisionally misdiagnosed with SNMG in 9% of a pediatric cohort in England and in up to 47% of an adult cohort in North America [6,8]. Some CMS subtypes have been highlighted as mimicking SNMG, particularly late-onset CMS due to mutations in the *RAPSN* gene (RAPSN-CMS) or limb-girdle CMS due to mutations in the *DOK7* gene (DOK7-CMS)[3,4,6,9]. Indeed, RAPSN-CMS has been reported as the most common CMS subtype that is misdiagnosed as SNMG in some cohorts[3,5,7].

There are few studies on the prevalence of CMS that is misdiagnosed with SNMG. In SNMG investigated as potential CMS, the rate of misdiagnosed CMS was 1.4 and 28% in European and Australian cohorts, respectively (Table 1)[3,7]. Our study found a prevalence of 4.5% in adult Brazilian 'double' SNMG patients of our center (Table 1). In the European cohort, as in our cohort, the proportion of misdiagnosed CMS was lower than in the Australian cohort[3,7]. However, only SNMG patients with an affected sibling underwent genetic analysis in the Australian study[7]. Thus, we speculate that there may be a bias that caused the higher proportion of CMS patients with misdiagnosis in that center. In our study, we only included patients from unrelated families to avoid initially suspected CMS. In addition, as these data are usually from tertiary centers experienced in disorders that affect neuromuscular transmission, the lower proportion of misdiagnoses could be related to the high index of suspicion of CMS in the initial evaluation of the patients by these centers.

The most common form of CMS is caused by autosomal recessive mutations in the *CHRNE* gene, with hundreds of patients reported in the literature and gene-specific databases[11]. The majority of the post-synaptic CMS result from mutations within the *CHRNE* gene[11]. CHRNE-CMS mistaken for SNMG has been reported[4]. Given that CMS and MG share clinical manifestations (especially eyelids ptosis, ophthalmoparesis, and generalized weakness), our finding of a CHRNE-CMS patient mistaken for SNMG is not surprising. The c.130insG mutation, which was found as a compound heterozygous variant in our patient, is one of the most common mutations in the *CHRNE* gene for Brazilian CMS patients[12,13]. The p.Cys210Phe mutation in the *CHRNE* gene is not common; it has only been published once in association with the CMS phenotype[11]. This mutation has been described at a very low allelic frequency (ExAC Consortium: 0.000008485), predicted to be damaging by *in silico* analysis (PolyPhen-2, Mutation Tasting, UMD-Predictor) and reported to be pathogenic in gene-specific databases (LOVD, HGMD). However, *CHRNE* mutations were not found in adult patients from an Australian SNMG cohort investigated by whole exome sequencing (WES)[7].

RAPSN-CMS has been mistaken for SNMG in European and Australian populations[3-5,7]. In a Norwegian SNMG cohort investigated for CMS, misdiagnosis occurred in 1.4%, in whom the p.N88K mutation was found to cause CMS[3]. In an Australian SNMG cohort, pathogenic variants in the *RAPSN* gene were the most frequent, and p.N88K was the commonest pathogenic variant in this gene[7]. Although none of our previous CMS cohorts of southern Brazilian patients had RAPSN-CMS, CMS cases due to a p.N88K mutation were recently reported in Brazilian patients[12,14]. Hence, we also screened p.N88K in our SNMG cohort. However, our study suggests that RAPSN-CMS mistaken for SNMG is not common in southern Brazilian patients.

The c.1124_1127dupTGCC mutation is the most common pathogenic variant worldwide in the *DOK7* gene[15,16]. This mutation was also previously reported in Brazilian CMS patients[12]. However, we found no SNMG patients with the c.1124_1127dupTGCC mutation in our study, a result that is similar to the Norwegian and Australian cohorts[3,7]. The clinical manifestation of DOK7-CMS can appear more like a myopathy[15,16]. Therefore, DOK7-CMS has been described more as a misdiagnosis of myopathies rather than a SNMG misdiagnosis[17,18]. This factor could be one of the reasons why DOK7-CMS was not found in the published SNMG cohorts screened to CMS.

Muscle histology of CMS patients often shows only non-specific myopathic changes[18-20]. Our patient had mitochondrial dysfunction in her muscle biopsy, which has not been reported in patients with CHRNE-CMS. Indeed, there are other CMS subtypes that are often associated with mitochondrial abnormalities in muscle biopsy (e.g. *SLC25A1*, *GFPT1* or *ALG2* genes)[21-23].

The advent of next generation sequencing (NGS) for the genetic diagnosis of CMS is reducing the use of Sanger sequencing as the main diagnostic tool. However, Sanger sequencing is still being performed in the investigation of CMS mostly when hot-spot mutations are previously detected in a specific population, when familial segregation is mandatory, or when NGS analysis is not available. Our study still used Sanger sequencing, which proved to be a cost-effective strategy for initial screening of our patients, as a targeted panel including the hot-spot mutations previously identified in Brazil[12-14]. Sanger sequencing as screening strategy in our study was limited to the most common mutations, i.e., the limitation of our study would be that patients with mutations that are not as common may not have been diagnosed.

In our study, the prevalence of adult CMS was 4.5% in patients with an initial diagnosis of 'double' SNMG. This finding is consistent with smaller published studies, with a combined prevalence of 7.4% (Table 1)[3,7]. These differences may reflect country-specific variations in the frequency of a rare disease or bias in the selection of the SNMG patients who underwent genetic screening. Based on our findings, genetic screening by Sanger sequencing could still be helpful in the diagnostic workup of patients with 'double' SNMG in whom differential diagnosis is recommended.

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Olfactory nerve: from ugly duckling to swan

Nervo olfatório: de patinho feio a cisne

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ABSTRACT

Background: The olfactory nerve has never been the shining star of neurological examination. Quite the contrary, examining the first cranial nerve is often an overlooked step. As cases of anosmia secondary to COVID-19 infection continue to rise, the 2020 pandemic has shed new light on this much-forgotten nerve, its value as an aid to diagnosis of several diseases and its central role in our daily lives. **Objective:** We aimed to emphasize how essential and simple clinical examination of the olfactory system can be by highlighting practical techniques and clinical tips for its assessment. We also share pearls and pitfalls in localization and differential diagnosis, which may prove valuable to busy clinicians. **Methods:** A broad review of the literature was conducted by searching PubMed, Cochrane and Google Scholar for articles and books containing topics regarding examination of the olfactory nerve and its anatomy, physiology and pathology. No particular inclusion or exclusion criteria were used. **Results:** Forty different works were found, between books and articles, from which 20 were selected after careful analysis. **Conclusions:** Despite the tragedy and adversity that followed the COVID-19 pandemic, its legacy has taught us a crystal-clear lesson: olfaction should no longer be neglected in clinical practice.

Keywords: Clinical Neurology; Smell; Infectious Disease; Olfactory Nerve.

RESUMO

Antecedentes: O nervo olfatório nunca foi a estrela do exame neurológico. Pelo contrário, o exame desse nervo craniano é um passo frequentemente ignorado. No entanto, o aumento exponencial de casos de anosmia secundária a COVID-19 o colocou sob os holofotes, tanto em relação á sua função para o ser humano em sociedade, como seu papel no auxílio do diagnóstico de diversas patologias. **Objetivos:** Enfatizar quão importante é examinar o nervo olfatório e compreender as desordens do seu sistema. Ressaltamos pérolas clínicas e erros comuns no exame deste nervo, além dicas que possam auxiliar no diagnóstico de uma série de doenças neurológicas e sistêmicas. **Métodos:** Uma ampla revisão da literatura foi conduzida por meio de busca no PubMed, Cochrane e Google Acadêmico por artigos e livros relacionados aos tópicos do exame físico, fisiologia, anatomia e patologia do nervo olfatório. Não foram utilizados critérios específicos de inclusão ou exclusão. **Resultados:** Foram encontrados 40 artigos itens relacionados na língua inglesa, dentre os quais livros e artigos, tendo sido analisados e selecionados um a um até o total de 20 referências. **Conclusões:** Apesar da tragédia e adversidade trazidas pela pandemia de COVID-19, uma lição clara permanece: o olfato não deve mais ser negligenciado na prática clínica.

Palavras-chave: Neurologia Clínica; Olfato; Doenças Infecciosas; Nervo Olfatório.

INTRODUCTION

Intrinsically different, as primitive as it is sophisticated, the olfactory system does not play by the book. One example of its uniqueness is the fact that olfaction is the only human sense not to be firstly processed by the thalamus before reaching the cerebral cortex. However, olfaction does share similarities with other parts and properties of the human body, as it may benignly lose its function with age (presbyosmia) or reveal life-threatening organic diseases, intracranial lesions, systemic disorders or neurodegenerative conditions[1].

Human olfaction has played such an admirable role during evolution that 2% of the entire human genome is concerned solely with expression of unique and distinct olfactory

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receptors[2]. Some vertebrate animals with highly developed olfactory systems may even have an "olfactory area" in their brains, occupying a proportionally identical space to that of the visual system.

Throughout history, the task of uncovering the mysteries of olfaction was not lost to humanity. Hippocrates' account was the earliest basic anatomical description of the nose, followed by Leonardo da Vinci's (1452-1519) description of the nasal conchae and sinuses[3]. Joseph-Hippolyte Cloquet (1787-1840) was the first physician to suggest, in his doctoral thesis "*On odours, the sense of olfaction and the olfactory organs*" (1815), the molecular nature of the odorous substrate, stating that*: 'Olfaction can be seen at every turn of the labyrinth'*. More recently, in 1862, Max Schultze (1825-1874), an anatomy professor in Bonn, uncovered the olfactory sensory cell[4], and in 1991, Richard Axel and Linda Buck's work shed light on the hundreds of genes responsible for the odorant sensors in the olfactory neurons of the nose, for which they won the Nobel Prize in 2004[5].

Despite several breakthroughs in the science of olfactory chemical stimuli, the mysteries of olfaction are probably still beyond the scope of modern scientific understanding. Smell plays an irreplaceable part in human communication, interaction, memory and emotion that is yet to be explained. This should not come as a surprise, considering the shared anatomical pathways between the olfactory and limbic systems within the brain.

Smell evokes memories as complex as living sensations of experiences from the past. This connection intrigued and mesmerized the author of one of the greatest novels ever written: *"In Search of Lost time"*, Marcel Proust (1871-1922), who wrote about a vivid involuntary autobiographical memory triggered by the smell and taste that resulted from dipping a madeleine into a cup of tea, which henceforth became known as the "petit madeleine phenomenon"[6]. He beautifully wrote: *"But when from a long-distant past nothing subsists, after the people are dead, after the things are broken and scattered, taste and smell alone, more fragile but more enduring, more immaterial, more persistent, more faithful, remain poised a long time, like souls, remembering, waiting, hoping, amid the ruins of all the rest; and bear unflinchingly, in the tiny and almost impalpable drop of their essence, the vast structure of recollection"*[7].

The importance of olfaction is, therefore, unquestionable. It is as central to many activities of daily living as it is to clinical practice. For example, smell can provide crucial sensory information in life-threatening situations like detecting the presence of smoke or toxic gas, or even interpreting taste stimuli in poisonous or spoiled food[8].

Bedside assessment of the olfactory system remains incredibly simple and straightforward, dispensing the need for expensive ancillary examinations. Despite the inherent importance and ease of examination of the olfactory nerve, it undoubtedly remains the most neglected cranial nerve in neurological practice[9]. As modern physicians looking back in history, we may even hypothesize about extent to which this omission might have impacted Neurology. Could it have been the explanation behind such curiosities as the fact that motor manifestations of Parkinson's disease were described before prodromal non-motor manifestations like olfactory loss[10]?

Our main purpose in writing this review was also a plea to all neurologists: we aimed to disseminate the practice of quick and objective examination of olfaction. We thus hoped to shed light on what the most important facts to be gathered from the clinical history might be, the pearls and pitfalls to avoid in examinations, some tips concerning localization and the clinical reasoning behind the myriad of differential diagnoses that may be causing olfactory deficits. In this manner, we expect to encourage further clinical study of the first cranial nerve, which could both facilitate discoveries in this field and improve our own diagnostic accuracy as practicing neurologists.

OLFACTORY NERVE EVALUATION: HOW TO APPROACH IT?

What to ask? The clinical history

Opening and chief complaints

One of the main agreed-upon rules of general Neurology is that the patient's history should be the cornerstone, providing a guide to all subsequent clinical reasoning. This also applies to olfactory evaluation. However, although patients with olfactory deficits often present with complaints of either loss of or diminished sense of smell (or even altered discrimination of different odors), this is not always the case. The assumption that normal smelling is so intuitive that the perception of any slight dysfunction must be readily evident to anyone is false and should work as a turning point in the mindset of the clinician taking the patient's history. It is essential to remember that only 40% of patients with olfactory dysfunction will ever even notice it and, therefore, refer to it. Consequently, the absence or presence of spontaneous clinical complaints regarding loss of olfaction does nothing to absolutely exclude or confirm the existence of smell dysfunction.

Another (often forgotten) caveat is that most patients who do complain of anosmia actually suffer from bilateral olfactory lesions. This is because unilateral lesions most often cause subclinical deficits, since contralateral olfactory function is preserved and can partially compensate for unilateral loss. This information is paramount, especially if a central nervous system mass lesion is suspected, which usually only injures the ipsilateral olfactory nerve. Consequently, unilateral deficits will probably only be detected through neurological examination, not from the patient's history[2].

A lack of spontaneous olfactory complaints does not mean that the clinical history is in any way dispensable. Faced with any evidence of memory loss, rigidity, tremor or parkinsonism (symptoms and signs that could be accompanied by subclinical olfactory deficits), detailed questioning and thorough examination of smell function is always mandatory[11].

It is sometimes important to understand and evaluate disorders of smell and taste as a whole. Many patients who seek medical attention complaining of "loss of taste" or of "food tasting bland" actually have an underlying olfactory dysfunction. This results from the direct influence that our ability to distinguish between different types of odors has on our sense of taste.

So, anosmia will actually often be presented to clinicians as a complaint of ageusia (loss of taste, not smell). More often than not, an organic loss of smell, even without true hypogeusia, is indeed associated with a subjective feeling that the food has become tasteless. However strong this sensation may be, it should not impair a patient's ability to distinguish between the five most elementary tastes: savory, sweet, sour, bitter and umami. If this distinction is lost, the patient probably does suffer from true ageusia or hypogeusia. Therefore, it is essential to determine which systems are affected: is the patient presenting with smell loss alone? Is it taste loss alone? Is it both, or neither? This information is useful not only with regard to differential diagnosis, but also when dealing with functional or simulating patients, as they may complain of complete loss of smell but with a completely unaltered sense of gustation, which, as we have stated, is very uncommon[8].

Pearls in the history: etiology and topography

Also in agreement with neurological clinical reasoning, olfactory dysfunction can result from either a central or a peripheral cause. One should always bear in mind when thinking about differential diagnosis that the second of these is more frequently observed than the first. Akin to hearing loss, a peripheral olfactory loss might be due to a neurosensorial or conductive problem. In conductive disorders, resulting most frequently from hypertrophy of the nasal mucosa, the pathway of odorants to the receptors in the olfactory cleft is obstructed, while in neurosensorial causes, it is the receptors themselves, not the pathway, that are damaged[12].

Some elements in the patient's history, such as epistaxis, nasal discharge or obstruction, are suggestive of conductive causes. Periods of worsening and improvement (fluctuation) of smell function during the course of a day, with remissions during physical activity, after taking a warm shower or through improvement with corticosteroid therapy (given that this reduces edema of the submucosal tissue, thus improving nasal congestion), also point to an obstructed pathway.

One exception to the "fluctuating symptoms rule" in conductive causes is hyposmia secondary to viral upper respiratory tract infections (URTI). Albeit a "nasal cause", hyposmia is usually continuous and is probably explained by concomitant neurosensorial dysfunction. Another clue to making the diagnosis is seasonality, since cases of smell loss due to URTI are more common during "flu seasons". Moreover, as these patients start to recover, they characteristically present distortion of the perception of smell (dysosmia) or a sensation of smelling "ghost" odors that are not there (phantosmia)[13]. Likewise, we speculate that olfactory dysfunction secondary to SARS-CoV-2 behaves similarly.

Conversely, strictly neurosensorial etiologies often present with continuous and progressive symptoms, while complaints of nasal obstructions will mostly be absent. With regard to the time taken from onset of symptoms to progression to complete anosmia, neurosensorial peripheral disorders will usually evolve more rapidly and acutely than will dysfunction secondary to a central etiology, which often has a slower clinical course. In order to explain the reason behind this phenomenon, it is once again helpful to borrow from the example set by central hearing loss. Inside the central nervous system, bilateral connections form a dense, redundant network that compensates for any dysfunction until severe or widespread lesions are found[2].

Particular details in the patient's history can provide interesting clinical pearls that may help steer clinicians in the direction of particular etiologies. For instance, when someone reports that they do not remember ever having smelled anything in their entire life, this most likely means this person has suffered from olfactory dysfunction since birth (e.g., through congenital causes). One example is Kallmann syndrome[14].

Another syndrome worth mentioning is that of patients who complain of unilateral anosmia ipsilateral to the loss of multiple senses. They usually present with a very particular set of symptoms: anosmia on the same side as monocular visual loss, hearing loss and hemianesthesia. This should point to the diagnosis of a nonorganic olfactory dysfunction[1].

A thorough exploration of the past medical history is needed, concerning events such as URTI, head injury, nasal surgeries, chemotherapy and radiotherapy, as well as exposure to conventional drugs and toxic agents. These questions may hold the key to the diagnosis. The hazardous effects of organic solvents, heavy metals, chemotherapy, cocaine, corticosteroids, methotrexate, aminoglycosides, tetracyclines and opioids are potentially harmful to the olfactory epithelium. Similarly, many conventional drugs commonly used in neurological practice can result in reversible hyposmia (e.g., valproic acid, levodopa or phenytoin)[12].

Non-hyposmic complaints

It is important to keep in mind that not all olfactory complaints are identical, since they are not always related to diminished/loss of function (quantitative symptoms). Some patients present with "qualitative symptoms" such as olfaction distortion (e.g., dysosmia, as previously mentioned), difficulty in differentiating smells (as is the case in olfactory agnosia; see Tables 1 and 2), or even olfactory hallucinations. Whatever the nature of a particular olfactory complaint might be (qualitative or quantitative), reviewing other relevant signs and symptoms related to systemic or neurological diseases is imperative[2].

Table 1. Glossary of olfactory terms: quantitative disorders.

Loss or reduction of smelling capacity	Increase of smelling capacity
Hyposmia: increased threshold for detecting odors.	Hyperosmia: diminished threshold for detecting odors.
Anosmia: complete loss of odor perception.	
Microsmia: decreased olfactory spectrum (differentiation of distinct odors).	
e.g. allergic rhinitis, neuronal damage after upper respiratory tract infection and olfactory groove meningioma.	e.g. migraine, anxiety and pregnancy.

Table 2. Glossary of olfactory terms: qualitative disorders.

Distortion of illusion of smell	Olfactory hallucinations	Olfactory agnosia
Parosmia or dysosmia: distortion of the perception of an odor. Cacosmia: perception of unpleasant odors (coprosmia, when it is the odor of feces).	Phantosmia: smelling odors that are not there.	Incapacity to discriminate odors, with preservation of perceptual aspects of primary smell.
e.g. temporal lobe epilepsy and smell recovery after neuronal damage of any kind.	e.g. temporal lobe epilepsy, psychiatric disorders and during smell recovery after viral etiology.	e.g. cortical lesions and Korsakoff syndrome.

HOW TO EXAMINE AND INTERPRET FINDINGS? TESTING THE OLFACTORY NERVE

Obtaining the clinical history is essential, particularly in determining etiology (either in neurological diseases in general, or in uncovering the cause of olfactory dysfunction). However, attentive physicians who are determined to routinely examine olfaction will no doubt eventually be faced with the following situation: a subclinical or unreported olfactory dysfunction that was only detectable through physical examination. Hence, although neurological examination is seldom useful in pinpointing the exact site of the lesion (an exception in Neurology), meticulous testing of olfaction is rarely a futile effort, even among asymptomatic patients, considering that this may bring an otherwise unperceived smell deficit to the fore[15].

Before starting the examination, the first step is always to ensure that both nostrils are clear and unobstructed. Check whether there is any kind of nasal congestion that could potentially alter adequate evaluation of olfactory nerve (ON) function (Table 3) and search for signs of trauma or other macroscopic alterations such as polyposis and deviated septum. These could steer the diagnosis towards a conductive cause for anosmia/hyposmia. Under standard inspiration, only a small amount of air will actually reach the olfactory mucosa inside the nose. Inhaling deeply and more rapidly helps to better direct the air towards the olfactory crypt and its receptors. Patients always need to be instructed in this regard and there is also a need to double check that they did not just "breathe on top" of the object that is being used in the test. Deep inspiration is critical in order to avoid false-negative findings[2].

There is still ongoing discussion regarding the merits of testing each nostril individually. Some groups have argued against this, claiming that there is a large degree of mixing of the inhaled air in the nasopharynx, thus making separate nostril testing a pointless practice. Others have suggested that there is brief segregation of the stimulus in situations of quick inspiration, which adds value to individual nostril testing for detection of unilateral lesions[8]. Until this matter is settled, we advocate for the latter technique.

Table 3. Key points during the neurological examination.

Key points during neurological examinations
1) Check that nostrils are unobstructed and that the airflow is normal.
2) Present different odors to the patient, while closing one nostril at a time with your finger on the ipsilateral upper lateral cartilage. Ask for a quick and deep inhalation and then for identification of the odors.
3) Preferably, formally validated psychophysical tests should be performed (for example: UPSIT test).
4) Avoid using irritating substances like alcohol and ammonia.
5) Do not forget to examine all cranial nerves, with particular attention to the facial nerve (especially the gustatory portion), trigeminal nerve and optic nerve (fundoscopy should always be performed).
6) During the examination, search for signs of neurological or systemic diseases that may be commonly associated with olfactory loss (e.g. cleft lip in Kallmann syndrome, nystagmus due to phenytoin use, rigidity and tremor from Parkinson's disease, muscular atrophy from amyotrophic lateral sclerosis or motor impersistence from Huntington's disease).

UPSIT: University of Pennsylvania Smell Identification Test.

Most clinicians examine the ON through presenting patients with one or two odors (e.g., coffee or cinnamon) and asking them if they can accurately identify these odors. Should physicians choose this method of examination, they must keep in mind that this provides a very rudimentary assessment of smell function. It is comparable to testing visual acuity only by flashing a simple white light once in the direction of each eye, asking if the patient saw the light beam and believing that a thorough visual assessment was made. Although this method is certainly better than not testing at all, practical methods with much higher sensitivity are now available for evaluating the ON[16].

Independently of which method is chosen, i.e. whether subjective and straightforward, like two-odor testing, or whether formal, like psychophysical olfactory tests, avoidance of irritant odorants should be an inflexible rule. Inhalation of particles such as alcohol (unfortunately, in our experience, often erroneously used for testing the ON) or ammonia stimulates trigeminal receptors, which both interferes with proper olfactory evaluation and generates a false sense of odor perception[8].

Olfactory testing

Modern psychophysical olfactory tests are the method most widely used in clinical practice. These are done by presenting several different types of odors to patients, who then, in turn, provides responses regarding smell identification, discrimination, threshold detection and memory. Odor identification tests (OITs) are the most reliable among these, since they are less cognitively demanding for patients[2].

Despite the immensely vast number of distinct smells in nature, these tests only use a small number of them. The theoretical basis for this approach comes from knowledge of the close proximity of olfactory pathways: lesions anywhere along the olfactory system pathways lead to impairment of the perception of multiple smells simultaneously, regardless of site. This precludes the need for testing with a thousand different odors while still giving the examiner an excellent general idea about patients' ON function[16].

OITs are valuable for providing an idea of the patient's olfactory spectrum, i.e. how many different types of smells they can accurately identify and discriminate between. This correlates remarkably well with the olfactory threshold, i.e. the amount of stimulus needed to create the sensation of smell. In other words, loss of ability to discriminate between different types of smells (microsmia) is also an indication that the patient has some degree of hyposmia (loss of function). So, this method serves to evaluate olfactory function quantitatively as well, and it has proved to be more reliable for detecting hyposmia than has subjective information gathered using one or two odors alone[17].

UPSIT (University of Pennsylvania Smell Identification Test) is the most popular OIT[18]. It consists of 40 different odors and is administered in a multiple-choice format of questioning. There is also a smaller version of the test called BSIT (Brief Smell Identification Test)[19], consisting of 12 smells. UPSIT is not only reliable (with adjustments for age and sex) but also simple, such that it can be self-administered, thus enabling home testing in extensive populations, in a trustworthy "do-it-yourself" system[2]. These characteristics make it an ideal method for testing patients in quarantine or who are socially distancing themselves, through online consultations: in short, in the situations that we have been facing during the SARS-CoV-2 pandemic.

Moreover, UPSIT helps in differentiating organic from functional olfactory loss, since it is mathematically expected that subjects should get at least ten questions right (25% of the test), out of the 40 questions presented (each question poses a choice between four options), even if they are entirely anosmic or are guessing at random. Patients with functional anosmia tend to give wrong answers to most or all of the questions, thus amounting to a score of fewer than ten correct answers. There are, however, some disadvantages to this method: the smells are exposed to both nostrils simultaneously, which theoretically makes it more challenging to detect unilateral loss. There is also a significant cultural bias concerning the odors selected[16].

Another well-established test is Sniffin Sticks[20], a nasal chemosensory performance test that uses pen-like odor dispensing devices. It includes 12, 16 or 32 items and, in its complete form, evaluates olfactory threshold, discrimination and identification. It correlates well with UPSIT, although it is more time-consuming and demands previously trained staff to apply it[17].

Lastly, information gathered from the remainder of the neurological examination is always extremely valuable. Every patient who comes in with olfaction complaints needs to undergo careful examination of all of the remaining cranial nerves.

Clinician should, at least, always test for deficits in the facial nerve (especially concerning gustatory function) and in the trigeminal and optic nerves. In particular, bilateral fundoscopic examination should be performed to search for optic atrophy or papilledema, which may point to an anterior frontal mass or tumor. It goes without saying that any other focal neurological signs or evidence of neurodegenerative diseases, parkinsonism or vitamin deficiencies (among others), should be explored and valued in the proper clinical context[2].

HOW TO LOCALIZE THE LESION?

Lesion localization has always been a staple of neurological practice. Precise localization not only narrows the differential diagnosis but also helps to determine which ancillary testing route will be pursued. Usually, in Neurology, clinicians will use information gathered in the physical examination to determine the lesion site and information from the history to determine etiology.

In this regard, the clinical reasoning behind diagnosing olfactory disturbance is, once again, unconventional. The clinical history plays a greater role in localization than does the neurological examination, which more frequently helps in detection and proper documentation of the nature or severity of deficits.

Olfactory dysfunction can be caused by central or peripheral nervous system lesions. Similarly to auditory lesions, conductive olfactory loss is strictly caused by peripheral lesions, while sensorineural olfactory loss might be caused by either central alone or combined central and peripheral lesions (anywhere from the olfactory receptors in the nose to the olfactory cortex) (Table 4).

Table 4. Clinical pearls.

Clinical pearls for olfactory investigation
1) Lesions in any segment of the olfactory nerve usually affect the perception of more than a single stimulus, because of the proximity of the olfactory pathways.
2) The most reliable tests are those consisting of stimulus presentation that involves odor identification. These tests are therefore preferrable for clinical practice.
3) It is indispensable to test each nostril individually, in order to detect potential unilateral problems. It is essential to point out that patients with unilateral problems usually do not complain about olfactory loss.
4) Complaints of hyposmia or anosmia indicate a bilateral lesion.

Peripheral olfactory impairment

The olfactory neuroepithelium consists of receptors and first-order neurons situated in the posterosuperior portion of both nasal cavities. This is the most common lesion site, with regard to both conductive and sensorineural olfactory loss[21].

Conductive olfactory loss results from any cause that halts inspired airflow (and, with this, odor molecules) from reaching olfactory receptors. We have mentioned that mucosal integrity and an unobstructed pathway for air inhalation are both fundamental prerequisites for physiological olfaction. The most frequent causes of conductive olfactory loss include deviated septum, osteomeatal deformity owing to trauma, nasal polyps, nasal tumors, allergic rhinitis and chronic rhinosinusitis (CR). CR is fairly common, and 80% of the patients suffering from it have had some sort of olfactory dysfunction. Loss of function in this setting can result from conductive and/or sensorineural causes, respectively due to either nasal blockage or olfactory neuroepithelium damage[21].

Peripheral damage causing sensorineural olfactory loss alone, without conductive abnormalities, is mainly secondary to viral or post-viral infections. URTI may cause olfactory dysfunction even in the absence of previous flu-like symptoms[21], which means acute anosmia could be the sole symptom of an URTI. Examples of viral agents commonly involved include rhinoviruses, coronaviruses, parainfluenza and influenza viruses and Epstein-Barr virus[22]. It is worth pointing out that individuals presenting with viral URTI-induced olfactory dysfunction might also be predisposed to other cranial neuropathies[23], which further proves the need for thorough cranial nerve examination in these patients.

Sensorineural olfactory loss can result from other types of infectious etiologies (although much less common), such as bacterial pathogens. *Mycobacterium leprae* is a neglected, albeit common cause of anosmia in countries where this disease is prevalent. In a study conducted in Lucknow, India, it was concluded that all patients diagnosed with Hansen's disease had some level of olfactory dysfunction[24]. So, in patients with the appropriate epidemiology, leprosy should always be in the differential diagnosis of anosmia. Fungal disease is also a relevant cause, especially among immunocompromised and diabetic patients (e.g., aspergillosis and mucormycosis)[25].

Lastly, non-infectious diseases like tumors (e.g., small-cell carcinoma, adenoma or inverted papilloma) may also cause conductive or sensorineural olfactory loss. The classic example is esthesioneuroblastoma, a rare neuroepithelial tumor that arises from the olfactory neuroepithelium in the cribriform plate[26].

Central olfactory impairment

The first central nervous system structure in the olfactory pathways is the olfactory bulb. It is located in the anterior fossa, above the cribriform plate. Anterior fossa tumors and aneurysms of the anterior communicating artery or anterior cerebral artery are both central causes of anosmia or hyposmia resulting from olfactory bulb lesions[8]. The clinical presentations of these disorders are one of the better-known syndromes associated with olfactory dysfunction: ipsilateral anosmia and optic atrophy (from direct compression of the olfactory bulb and optic nerve), in association with contralateral papilledema (from increased intracranial pressure), i.e. the Foster-Kennedy syndrome[27].

From the olfactory bulb, the olfactory pathways follow through olfactory tracts and are then processed in structures collectively referred to as the primary olfactory cortex, which is responsible for more complex olfactory processing. These are the anterior olfactory nucleus, piriform cortex, anterior cortical nucleus of the amygdala, periamygdaloid complex and rostral entorhinal cortex. Depending on the nature of the injury, dysfunction of these structures can result either in olfactory loss or high-order olfactory disturbances, such as olfactory hallucinations and olfactory agnosia. The leading causes of cortical olfactory loss are neurodegenerative, demyelinating, nutritional and metabolic disorders.

Recognizing early signs of olfactory loss secondary to degeneration in olfactory areas (including the olfactory bulb)

in some neurodegenerative diseases can be very useful in clinical practice. For example, finding an olfactory deficit in a patient with mild cognitive impairment can predict progression to Alzheimer's disease[8,28]. Moreover, the prevalence of olfactory dysfunction in Parkinson's disease is so high that its absence should be a warning sign for the diagnosis[29]. The same principle can be applied to other degenerative diseases and may prove extremely helpful in the differential diagnosis. Progressive supranuclear palsy and corticobasal degeneration syndrome usually spare the sense of smell. In contrast, dementia with Lewy bodies, frontotemporal dementia, pure autonomic failure, Huntington's disease and lateral amyotrophic sclerosis usually impair it[1,21].

One must not, however, jump to hasty conclusions and assume that olfactory loss in an elderly patient necessarily equates to a neurodegenerative process. Although olfactory dysfunction is very prevalent in many neurodegenerative diseases, the opposite is not a rule: most hyposmic patients do not have life-threatening neurological conditions.

Demyelinating diseases (e.g., multiple sclerosis, neuromyelitis spectrum disorder and acute disseminated encephalomyelitis) have also been shown to be associated with olfactory dysfunction. In some exceptional cases, anosmia was the first manifestation of multiple sclerosis[21,30].

Metabolic/nutritional disorders, especially thiamine and vitamin A deficiencies, are also worth mentioning. These not only can cause olfactory loss but also, in patients with Korsakoff's psychosis, can give rise to odor discrimination deficits and olfactory agnosia. This probably results from degeneration of the medial nuclei of the thalamus[2].

Some conditions are known for their interesting and unique presentations, such as causing olfactory hallucinations without associated olfactory loss. Classical examples of this include migraine auras and temporal lobe epilepsy, with seizures presenting as positive olfactory phenomena, usually of unpleasant characteristics, like cacosmia (traditionally known as uncinate seizures)[31].

Combined central and peripheral olfactory impairment

A few conditions are responsible for olfactory deficits that combine central and peripheral mechanisms. Among these are head injury and several systemic diseases.

Head trauma can lead to an assortment of neurological conditions, such as concussion, cranial fractures, intracranial hematomas, damage to several cranial nerves, damage to arteries and intraparenchymal contusions. The olfactory system is no exception, and it can be affected in a multitude of ways. Lesions in the sinonasal area, lacerations of the olfactory nerve itself while passing through the cribriform plate, damage to the olfactory bulb through traction forces and hemorrhages of the orbitofrontal and anterior temporal lobe have all been reported as potential causes of hyposmia after traumatic head injuries. Particularly when presence of cerebrospinal fluid rhinorrhea is associated with the trauma, the risk of olfactory dysfunction seems to be higher. When the orbitofrontal cortex is concomitantly injured, associated symptoms such as dysexecutive and behavioral syndromes can occur[21]. Some patients with traumatic anosmia can also suffer from true traumatic ageusia, which, if detected on examination, could work as a clinical tip for the etiological diagnosis of olfactory loss, although the reason for this association remains unclear[8].

Although anosmia secondary to systemic disease (endocrinological, renal, hepatic or rheumatological) is a well-described entity, it results from many possible mechanisms (central or peripheral) that are not yet fully understood. Rheumatological conditions such as Sjögren's syndrome, Churg-Strauss syndrome, Behçet's disease, systemic lupus erythematosus, scleroderma, giant-cell arteritis and granulomatosis with polyangiitis may cause anosmia due to vasculitis, a phenomenon that is believed to be particularly underdiagnosed[21].

ANOSMIA FROM COVID-19

Post-viral olfactory dysfunction is a recognized cause of acute olfactory loss, and it accounts for as much as 15-20% of all anosmia cases[1]. However, over the past year, the new coronavirus pandemic (SARS-CoV-2 disease, COVID-19) has led to an exponential rise in acute anosmia cases and may have significantly increased the incidence of this already common condition. It is estimated that anosmia can occur in up to 60% of COVID-19 cases[32,33].

The clinical presentation of anosmia secondary to SARS-CoV-2 is not particularly different from that of many other previously known causes of viral/post-viral olfactory loss. But, since acute anosmia can likewise present without any respiratory/flu symptoms, it is now considered to be an important symptom of SARS-CoV-2 infection, which motivates testing and even social isolation measures among these patients[34]. Recovery of olfactory function in these cases seems to be good, and for most patients the outcome is complete spontaneous recovery[21].

Olfactory nerve infection may also form a route for the virus to spread to the central nervous system (trans-cribriform spread), thus possibly explaining cases of acute encephalitis following documented infection. The mechanism of central nervous system damage is believed to be related to immune-mediated effects induced by the virus[35].

GENERAL PROGNOSIS AND TREATMENT

The olfactory nerve has a well-known reputation for having great power of regeneration. This happens continuously, through basal stem cells located on the olfactory epithelium.

The prognosis for recovery after olfactory dysfunction depends on the underlying cause of injury. Usually, acute injury to the olfactory nerve (e.g., URTI) that spares the basal stem cells is followed by spontaneous recovery of olfactory function in most individuals. However, this is not true for many other

causes of olfactory loss such as neurodegenerative diseases, trauma and compressive lesions of the olfactory bulb, which can result in persistent olfactory dysfunction[8].

There are plenty of types of treatment available for anosmia, which are beyond the scope of this review. Regarding treatment options for patients with acute olfactory loss related to SARS-CoV-2 infection, the treatment strategy classically used for other forms of viral anosmia, consisting of use of topical corticosteroids, is currently being avoided due to the risk of immunosuppression[14,34].

During the pandemic, smell training techniques have gained ground as a simple and cheap type of "physical therapy". This form of rehabilitation consists of olfactory stimulation using four different odors, in which the patient smells each one for at least ten seconds, two times a day over a four-month period. Studies have shown this technique to be beneficial in both post-viral and post-traumatic cases of olfactory loss, leading to improvement of wellbeing and depression among these patients[36,37].

In conclusion, over the course of human history, tragedies such as disease and war have frequently been powerful driving forces for mankind. Scientific advances driven by calamity have transformed previously well-established points of view and have often illuminated subjects that were traditionally overlooked. Some such advances have even been responsible for entirely resetting society, thereby leaving long-lasting legacies.

This new virus is no different. The 2020 pandemic brought with it a crystal-clear fact: olfaction should no longer be neglected, either in clinical practice or in research.

We hope that this misfortune will result in a new legacy for future generations of neurologists, through promotion of novel habits of careful physical examination and clinical reasoning, thus placing olfaction under the spotlight that it has always deserved. This is important not only in our day-to-day clinical practice, but also for further research, in order to enable new discoveries in the field of human olfaction. How many conquests could, literally, be under our noses?

KEY POINTS

1. Information from the clinical history is better than data gathered from physical examinations for locating and diagnosing the cause of olfactory lesions.
2. Less than half of all patients with olfactory loss will complain of it. Therefore, active searching is mandatory.
3. Evaluating a small sample of odors gives us a good general idea of patients' olfactory capacity.
4. Olfactory dysfunction can be of either central or peripheral origin; the latter is most common.
5. Smell training techniques are an effective treatment for post-viral olfactory loss.

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VIEW AND REVIEW

An overview of dysphagia rehabilitation for stroke patients

Uma revisão das terapias de reabilitação para disfagia em pacientes com acidente vascular cerebral

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ABSTRACT

Background: Dysphagia is characterized by difficulty in the swallowing pattern at any stage of this neuromuscular process. It is a frequent symptom after stroke. **Objective:** This study aimed to investigate the most commonly used phonoaudiological interventions as therapy for the treatment of swallowing disorders in patients with dysphagia after stroke. **Methods:** We performed a review of studies indexed in MEDLINE-PubMed, LILACS, Cochrane, and Clinical trials.gov focusing on speech-language interventions for adult dysphagic patients after stroke between January 2008 and January 2021. **Results:** Thirty-six articles of clinical trials were selected. Eleven different types of therapies have been studied. Studies on the efficacy of therapeutic interventions for the rehabilitation of adult patients with dysphagia after stroke are still scarce. Most techniques are combined with conventional therapy, so the effectiveness of the other techniques alone cannot be assessed. **Conclusions:** Therapeutic interventions should be selected in accordance with the possibilities and limitations of the patients, and especially with the findings of the clinical evaluation and with its objective.

Keywords: Deglutition Disorders; Stroke; Speech Therapy; Rehabilitation.

RESUMO

Antecedentes: A disfagia é caracterizada como uma dificuldade no padrão de deglutição em qualquer fase desse processo neuromuscular. É um sintoma frequente após o Acidente Vascular Cerebral. **Objetivos:** O objetivo deste estudo foi investigar as intervenções fonoaudiológicas mais utilizadas como terapia para o tratamento dos distúrbios da deglutição em pacientes com disfagia pós AVC. **Métodos:** Realizamos uma revisão dos estudos indexados no MEDLINE-PubMed, LILACS, Cochrane e Clinical trials.gov com foco nas intervenções fonoaudiológicas em pacientes adultos e disfágicos após AVC entre janeiro de 2008 e janeiro de 2021. **Resultados:** Foram selecionados trinta e seis artigos de ensaios clínicos e estudados onze tipos de terapia. Os estudos sobre a eficácia de intervenções terapêuticas para a reabilitação destes pacientes adultos ainda são restritos. A maioria das técnicas é aplicada em combinação com a terapia convencional, tornando inconclusiva a medição da eficácia de outras técnicas isoladamente. **Conclusões:** As intervenções terapêuticas devem ser escolhidas de acordo com as possibilidades e limitações dos pacientes e, principalmente, com os achados da avaliação clínica e seu objetivo.

Palavras-chave: Transtornos de Deglutição; Acidente Vascular Cerebral; Fonoterapia; Reabilitação.

INTRODUCTION

Dysphagia is characterized by difficulty or discomfort in swallowing. The swallowing process ensures the transit of food and saliva from the oral cavity to the stomach providing metabolic balance, nutrition, and hydration to the human body[1]. Stroke is the main cause of neurogenic dysphagia[2]. Depending on the affected area and the extent, stroke can lead to damage to the neurological control areas of swallowing, which may cause dysphagic disorders[1].

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Authors' contributions: KCM, VFO, PLCO, PBN: study conception and design and data collection; KCM, VFO, PBN: analysis and interpretation of results; KCM, VFO: drafting of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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Dysphagia after stroke carries the risk of aspiration pneumonia, malnutrition, dehydration, and death[3]. Dysphagia is a major complicating factor in the rehabilitation of such patients or of neurological patients in general. If associated with other risk symptoms such as drowsiness, disorientation or incontinence it may indicate an even worse prognosis[4,5]. Recent studies indicate an average frequency of dysphagia of 50% after stroke. It causes a large increase in hospital costs per patient. Patients with stroke who develop dysphagia have a longer length of hospital stay when compared to not dysphagic patients, requiring additional care for enteral diets and are more likely to need home care after discharge[6].

Considering the need for early intervention for dysphagia in post-stroke patients to improve their quality of life and reduce sequelae, complications, hospital costs and hospitalization time, it is necessary to find effective treatment interventions. The objective of this study was to investigate the most commonly used phonoaudiological interventions as therapy for swallowing disorders in patients with dysphagia after stroke. In this review, we provided the most relevant information of dysphagia treatment after stroke published in recent years.

METHODS

Eligibility criteria

Studies were selected according to predefined inclusion and exclusion criteria. "English-language full-text articles on clinical and controlled trials indexed in the previously selected electronic databases with adult populations presenting with oropharyngeal dysphagia as a symptom after stroke" was defined as inclusion criteria. Studies involving (1) pediatric population, (2) analysis of the application of evaluation protocols, (3) studies aiming at decannulation of tracheotomized patients, (4) studies involving esophageal dysphagia, and (5) studies in which the primary outcome was not related to the degree of dysphagia and improvement of the swallowing pattern were excluded.

Review question

The guiding question for the research was: "What interventions are reported as effective treatments for the rehabilitation of adult patients with dysphagia after stroke?".

Search strategy, study selection and data extraction

A review of articles published between January 2008 and January 2021 in indexed scientific journals was carried out in the following electronic databases: MEDLINE-PubMed, LILACS, Cochrane, and Clinical Trials.gov. The selection of descriptors was performed through consultation in a Brazilian platform for descriptors in health sciences (DeCS – Descritores de Ciências em Saúde). The selected English descriptors were: "dysphagia" AND "therapy" AND "stroke".

The articles were selected based on the screening of titles or abstracts. However, when title, keywords, and abstract did not have sufficient information to determine the inclusion according to the established criteria, a full-text review was conducted. After that, all the remaining papers were fully read, evaluated, and cataloged. All steps in this study were performed independently by two researchers following the protocol described above. Individual results were assessed and compared, and a consensus was reached through discussion.

The following data were extracted after the assessment of full text of all selected articles: country, number of patients, study design, outcome measures, types of intervention groups, intervention time, summary of the results, and conclusions. These data were then compiled into a standard table.

RESULTS

The search identified 154 references (117 in MEDLINE-Pubmed, 31 in Cochrane, 3 in Clinical trials, and 3 in LILACS) of which 90 were excluded based on the title and 4 were duplicates. Therefore, 60 studies were selected for inclusion according to their titles and abstracts, of which 38 clinical trials that met the inclusion criteria were included in this review. A flow diagram showing the study selection process is presented in Figure 1.

All included studies evaluated patients diagnosed with stroke. A total of 12 different therapies have been studied with a variety of study designs: [1] electrical stimulation (n = 14; 36.8% of the total)[7-20], [2] transcranial magnetic stimulation techniques (n = 3; 7.9%)[21–23], [3] active pharyngeal electrostimulation (n = 3; 7.9%)[24–26], [4] exercises with Mendelsohn maneuver (n = 2; 5.3%)[27,28], [5] transcranial direct current stimulation (n = 3; 7.9%)[29–31], [6] CTAR exercise (n = 5; 13.6%)[32–36], [7] Shaker exercise (n = 2; 5.3%)[33,37], [8] acupuncture (n = 3; 7.9%)[38–40], [9] resistance to tongue pressure (n = 2; 5.3%)[41,42], [10] modified jaw opening exercise (n = 1; 2.6%)[43] and [11] cervical isometric exercises (n = 1; 2.6%)[44].

Even among studies focusing on the same type of therapy a wide variety of outcome measures were found to assessing dysphagia. The sample sizes varied from 4[22] to 250[40]. More than half of the studies were from Asia, but some were from Europe and North America.

The following sections present a summary of the articles' results by type of interventions.

Electrotherapy (NMES)

Electrotherapy is a technique that can be used with motor stimuli, sensorial stimuli, or both. In addition, depending on the muscular function affected in the swallowing process and the degree of this change, variations in intensity, electric current pulse duration, electrodes number and position are applied. Despite all these factors, there is still little scientific evidence of the effectiveness of electrotherapy in improving the swallowing pattern in oropharyngeal dysphagia, especially when this technique is associated with conventional exercise therapy.

The Neuromuscular Electrical Stimulation (NMES) technique combined with Endoscopic Evaluation of Swallowing

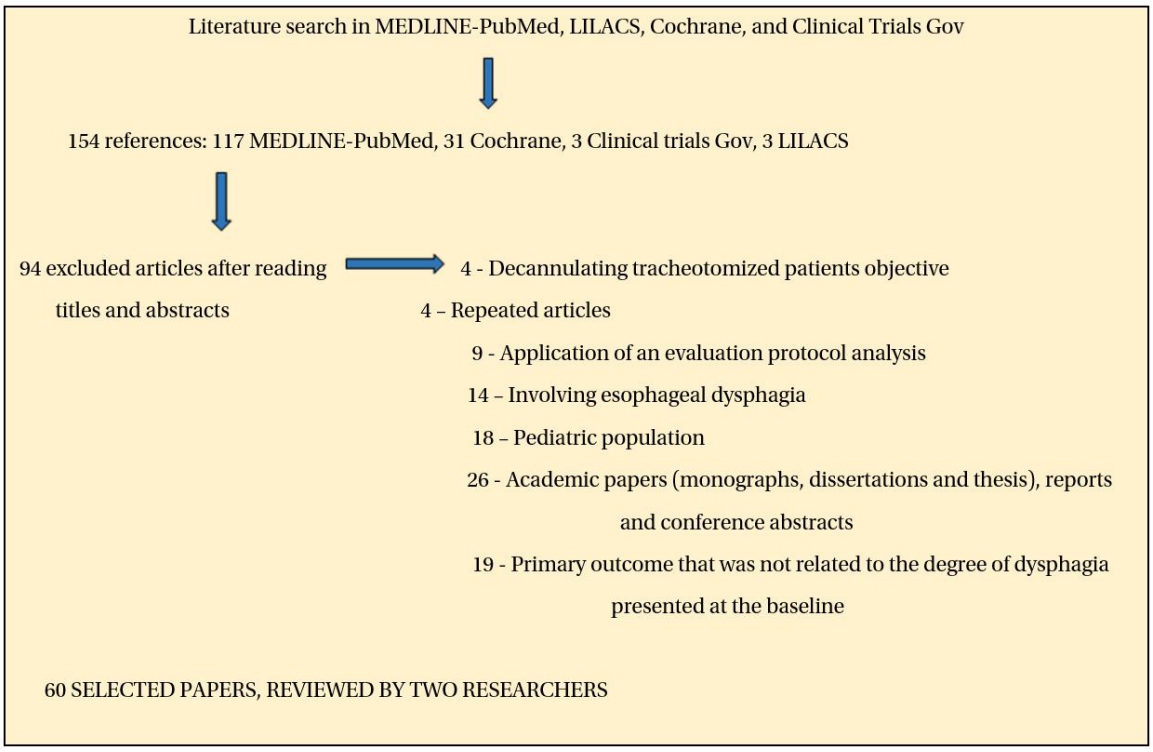

Figure 1. Flow chart of the search strategy.

(EES) and traditional swallowing rehabilitation improved the swallowing quality in a study involving thirty-two patients with moderate to severe post-stroke dysphagia. In addition, patient satisfaction was high and there were no serious adverse events. Thus, the implementation of this promising combination in clinical practice was recommended[7]. Similarly, the effects of applying sensory-level electrical stimulation (SES) on masseter muscles in patients with acute stroke were evaluated in another study[8]. Applying SES (based on its oral and pharyngeal functions) on masseter muscles and using SES to generate cortical reorganization was effective in treating dysphagia in stroke patients.

In another study[17], selected patients were randomly assigned to a VitalStim electrotherapy group, a conventional swallowing therapy group, and electrotherapy plus conventional therapy group. The results suggested that VitalStim combined with conventional therapy is capable of improving dysphagia after stroke. Xia et al.[18] also evaluated the effects of VitalStim in their patients and confirmed its effectiveness. A limitation of this study, however, was the absence of a placebo stimulation group.

The combined application of electrical stimulation and conventional therapy in patients with acute oropharyngeal dysphagia secondary to acquired brain injury[9] resulted in better outcomes than when conventional therapy with placebo stimulation was adopted. A study conducted by Rofes et al.[10] evaluated and compared the efficacy and safety of a 10-day surface electrical stimulation (e-STIM) treatment in sensory and motor intensities in patients with chronic oropharyngeal dysphagia after chronic stroke. This study showed that e-STIM is a safe and effective therapy to improve swallowing. However, further investigation involving a control group, a larger number of patients, a prolonged follow-up, and the effect on clinical outcomes is needed to confirm the clinical utility of this therapy.

Konecny and Elfmark (2018) showed that after four weeks of standard therapy with suprahyoid muscles electrical stimulation, the duration of oral and pharyngeal transit time was statistically improved[11]. In another study, electrical stimulation associated with conventional therapy was performed. Electrodes were placed adjacent to the suprahyoid and upper and lower parts of the thyroid, in the geniohyoid region, and in the mylohyoid region. When compared to conventional therapy, a significant improvement was noted. However, the position of electrodes did not generate significant differences[12].

Another study investigated the effects of forced swallowing combined to neuromuscular electrical stimulation on the hyoid bone movement and on the swallowing function in stroke patients[13]. The experimental group showed an increase in the anterior and superior movement of the hyoid bone and an improvement in the pharyngeal phase swallowing function. The neuromuscular electrical stimulation combined with thermal-tactile stimulation were found to be a better treatment for patients with deglutition disorders after stroke than isolated thermal-tactile stimulation therapy[14].

Electrical stimulation was performed by Park et al.[15] using two sets of electrodes placed in the segmentation area of the infrahyoid and sternum-hyoid muscles. When using sensorial EE with forced swallowing, no significant improve was observed in any of the evaluated parameters. However, the

studied methodology can only be applied to selected patients, as many patients with dysphagia fail to elevate the hyolaryngeal complex during motor electrical stimulation.

The effects of NMES associated with electromyographic biofeedback (EMG-BF) were also investigated[19]. EMG-BF is known to be an effective therapy for stroke rehabilitation. In this pilot study, all subjects received NMES combined with EMG-BF in the suprahyoid area. The results demonstrated that NMES combined with EMGBF had the potential to improve oropharyngeal swallowing in stroke patients with dysphagia.

In a more recent study, the effects of neuromuscular transcutaneous electrical stimulation (NMES) in 33 patients affected by dysphagia after sub-acute stroke were evaluated. Both groups showed improvements[16]. Another recent study analyzed the McNeill's dysphagia therapy (MDTP) with NMES for the treatment of post-stroke dysphagia[20]. MDTP showed a greater positive change than the NMES group, including increased oral intake and improved functional outcome three months after the stroke. These data support the inclusion of intense short-term behavioral interventions for an efficient allocation of resources for acute stroke rehabilitation.

Studies that used electrotherapy as a therapeutic approach are detailed in Table 1.

Neuromodulation

The nervous system has the ability to modulate and modify itself in response to external stimuli. The term neuromodulation has been used to describe procedures in which electrical stimulation is applied directly to structures of the nervous system for therapeutic purposes. A summary of these approaches is shown in Table 2.

Repetitive Transcranial Magnetic Stimulation

Repetitive Transcranial Magnetic Stimulation (rTMS) has been proposed as an alternative treatment for dysphagia after stroke. It is a noninvasive technique that modulates brain activity using electromagnetic induction and thus induces physiological changes. An advantage of rTMS is that patients do not need to be actively engaged during treatment[21].

One of the included studies indicated that 5 Hz rTMS applied over the tongue area of the motor cortex for 10 days was not effective in improving the swallowing function in patients with stroke and chronic dysphagia. However, given he small and unbalanced sizes of the groups in this study, the therapeutic effects of the protocol remain uncertain[21]. Another study also evaluated the therapeutic effect of 5 Hz high-frequency rTMS on the unaltered pharyngeal motor cortex in 4 post-stroke dysphagic patients. In disagreement with the previous study, the authors indicated that 5Hz high-frequency rTMS applied to the tongue region of the motor cortex may be beneficial for patients with dysphagia after hemispheric unilateral stroke and with dysfunction in the swallowing phase. Further investigations with larger samples are required to support the benefit of this protocol[22]. Finally, a study of 40 patients showed that the use of high frequency (3 Hz) and low frequency (1 Hz) rTMS improved dysphagia (after 5 days) more than the simulated group, with the effects remaining for at least 3 months after the intervention[23].

Transcranial direct current stimulation (tDCS)

tDCS is a non-invasive brain stimulation method based on the principle of neuroplasticity. It provides a constant low-intensity electric current between the anode and the cathode applied to the scalp area associated with the segmentation of the cerebral cortex. In general, cathodic tDCS decreases cortical excitability and anodic tDCS increases cortical excitability[29]. Recently, noninvasive cortical stimulation has been used to improve neural plasticity and treat hemiplegia and aphasia. However, little is known about the possible effects of tDCS on swallowing function[30], and few studies were conducted on the mater.

The association of the tDCS technique with conventional therapy was evaluated in patients with chronic post-stroke dysphagia. Although the result of this study shows that the bihemispheric anodic tDCS group did not have a statistically superior improvement compared with the control group, the detailed dysphagia outcome scale (using videofluoroscopy), patient symptom report, or patient and caregiver satisfaction may reflect the clinical improvement of dysphagia[29]. The study conducted by Shigematsu et al.[30] investigated the effects of cerebral pharyngeal cortex noninvasive stimulation combined with intensive swallowing therapy on dysphagia recovery and found that the combined therapies effectively improve post-stroke dysphagia compared to isolated therapy.

Krueger et al.[31] evaluated patients with acute and dysphagic stroke that received contralesional anode stimulation or placebo tDCS for 4 consecutive days. Applying objective instrumental diagnosis in parallel with functional neuroimaging, a greater improvement in the swallowing function was observed after tDCS compared with the placebo intervention. Thus, tDCS seems to be a safe and beneficial therapeutic option for patients with oropharyngeal dysphagia during the early stage of stroke.

Pharyngeal electrical stimulation (PES)

In one of the included studies, PES interventions were performed at the bedside. The effects of PES on dysphagia in stroke patients remained inconclusive because the recruitment goal was smaller than predicted. Despite this, there is an indication for the use of this treatment considering some potentially favorable results, such as the observed improvement in the number of safe swallows. In addition, PES was well tolerated without any adverse effects[25]. In another study with the same objective, it was found that PES did not reduce radiological aspiration or clinical dysphagia[24].

Table 1. Clinical studies using electrotherapy for patients after stroke or TBI.

References	Country	Patients	Diagnosis	Study design	Outcomes	Intervention	Intervention time	Results	Follow-up
Terré,R.; Mearin, F., 2014[9]	Spain	20	STROKE and TBI	Randomized; controlled; prospective	VFSS; FOIS	GI- EE and TC GC - EE placebo eTC	20 sessions/60 min-5 times a week	FOIS increased 4.9 points (GI); 3.1 points (GC).	1, 3 months
Sun, S.F et al., 2013[7]	Taiwan	29	STROKE	Clinic; prospective	FOIS; Dysphagia scale	EE e TC separately	NMES and TC 12 sessions/60 min - 3 times a week	FOIS and dysphagia scale improved after NMES, for 6 months and 2 years (p \ 0.001, each)	6 months, 2 years
Rofes, L. et al., 2013[10]	Spain	20	STROKE	Randomized; double-blind	VFSS (PAS)	Motor EE group Sensory EE group	10 sessions/ 30 min - 5 times a week	Sensory and motor EE reduced the insecure deglutition number in (p < 0.001), and (p = 0.002)	No follow-up
Park, J. S. et al., 2016[13]	Korea	50	STROKE	Randomized; Controlled; Single-blind	VFSS (PAS e VDS)	GI - EE and forced swallowing exercise GC - EE placebo and forced swallowing exercise	30 sessions/30 min - 5 times a week	GI increased oral and pharyngeal phase in VDS (P < 0.00, P = 002 and P < 0.00), and PAS (P < 0.00).	No follow-up
Park, J. W. et al., 2012[15]	Korea	20	STROKE	Randomized; Controlled; Double-blind	VFSS (PAS; UES)	GI - Motor EE and forced swallowing GC- Sensory EE and forced deglutition	12 sessions/20 min - 3 times a week	GI increased vertical larynx movement (p\0.05).	No follow-up
Konecny, P.; Elfmark, M., 2018[11]	Czech Republic	108	STROKE	Randomized; Controlled; Prospective	VFSS	GI - Motor EE and TC GC – TC	20 sessions/20 min - 5 times a week	The difference in the oral and pharynx transit time after therapy between the GI and the GC (P = 0.01 e P= 0.009)	No follow-up
Lim, K. B. et al., 2009[14]	Korea	28	STROKE	Randomized; Controlled	VFSS	GI - EE muscular and tactile-thermic stimulation GC - Tactile-thermic stimulation	20 sessions/60 min - 5 times a week	GI with higher scores in PAS; 2 in semi-solid (p < 0.05) and 2.5 in liquids (p < 0.05)	No follow-up
Meng, P. et al., 2017[12]	China	30	STROKE	Randomized	VFSS; DOSS	GA - EE with electrodes along the suprahyoid and along with the superior and inferior thyroid parts and TC GB - EE with 1 pair of electrodes in the geniohyoid region and 1 pair in the mylohyoid region and TC GC - TC	10 sessions/30 min - 5 times a week	Improvement in DOSS in groups A and B (P<0.005) in relation to GC.	No follow-up
Xia, W. et al.,2011[18]	China	120	STROKE	Randomized; prospective	SSA; VFSS	G1 – Conventional therapy G2 - EE G3 – Conventional therapy and EE	40 sessions/30 min - 2 times a day, 5 times a week for 4 weeks	SSA, VFSS increased more in G3 than in G1 and G2 (P < 0.01).	No follow-up
LI, L et al., 2015[17]	China	135	STROKE	Randomized; controlled	SSA	G1 - EE G2 - TC G3 - EE and TC	20 sessions/60 min - 5 times per week for 4 weeks	SSA improved in G3 (P <0.01)	4 weeks
Ploumis, A. et al., 2018[44]	Greece	70	STROKE	Randomized, controlled, prospective.	VFSS; PAS	GI – Cervical exercises and conventional therapy GC – Conventional therapy	30 min daily sessions/12 weeks	Improved swallowing (P < 0.05) and PAS (P < 0.001)	No follow-up
Umay, E. et al., 2017[8]	India	98	STROKE	Randomized; controlled	MASA; SSA	GI - Sensory EE and TC GC - Sensory EE placebo and TC	20 sessions/60 min - 5 times a week for 4 weeks	All parameters improved in G1 (P <0.025).	No follow-up

Table 1. Cont.

References	Country	Patients	Diagnosis	Study design	Outcomes	Intervention	Intervention time	Results	Follow-up
Park, S.J. et al., 2019[34]	Korea	10	STROKE	Clinical; prospective	VFS; PAS	NMES and EMG-BF	20 sessions/30 min – 5 times a week	Significant differences between oral (P = 0.015) and pharyngeal (P = 0.016) VFS. Improved PAS (P = 0.031).	No follow-up
Carnaby, G.D et al., 2020[20]	USA	53	STROKE	Randomized; controlled; double-blind	FOIS, MASA	G1 – TC and EENM G2 – TC and EENM placebo G3 - TC	15 sessions/60 min – 3 weeks	MASA was different among groups different (p ☞ 0.0001) G2 had the best FOIS result (p☞0.0001).	3 months

DOSS: Dysphagia Outcome and Severity Scale; EE: Electrical Stimulation; NMES: Neuromuscular Electrical Stimulation ; FOIS: Functional Oral Intake Scale; GA: Group A; GB: Group B; GC: Control group; GI: Intervention group; MASA: Mann Assessment of Swallowing Ability; PAS: Penetration-Aspiration Scale; SSA: Standardized Swallowing Assessment; TC: Conventional therapy; TBI: Traumatic Brain Injury; VDS: videofluoroscopic dysphagia scale; UES: Upper esophageal sphincter; VFSS: Video Fluoroscopic Swallowing Study.

Table 2. Intervention clinical studies using neuromodulation for stroke patients.

Reference	Country	Patients	Diagnosis	Study design	Outcomes	Intervention	Intervention time	Results	Follow-up
Hyun, Y. et al., 2017[29]	Korea	26	Stroke	Randomized; multicenter controlled; prospective; double-blind.	DOSS	GI - ETCC and TC. GC - Placebo ETCC and TC	10 sessions/20 min - 5 times a week	DOSS - Significant improvement (0.62 points on GI)	No follow-up
Cheng, I. K. Y. et al., 2017[21]	China	15	Stroke	Randomized; controlled; double-blind.	VFSS; IOPI	GI - Active EMTr GC - Simulated EMTr	10 applications - 5 times a week	No significant results	2, 6 and 12 months
Cheng, I. K. Y. et al., 2014[22]	China	4	Stroke	Randomized; controlled.	VFSS; IOPI	GI - Active EMTr/ Tongue motor cortex stimulation GC - Simulated EMTr	10 sessions/30 min - 5 times a week	No significant deglutition improvement on GI	1 week, 1 month
Du, J. et al., 2016[23]	China	40	Ischemic stroke	Randomized; controlled; double-blind.	SSA	G1 - High-frequency EMTr (3Hz) G2 - Low-frequency EMTr (1Hz) G3 - Simulated EMTr	5 sessions	Better G1 and G2 dysphagia improvement after 5 days compared to the other group, remaining for 5 months.	1, 2 and 3 months
Park, J.W. et al., 2013[15]	Korea	18	Stroke	Randomized; controlled; double-blind.	VFSS (PAS and VDS)	GI - Contralesional pharyngeal motor cortex EMTr 5Hz GC - Placebo (same conditions)	20 sessions/10 min	VDC and PAS improved significantly on the GI (P<0.005)	2 weeks
Shigematsu, T. et al., 2013[30]	Japan	20	Stroke	Prospective; double-blind.	DOSS	GI - TC and 1-mA ETCC (contralesional pharyngeal motor cortex) GC - Simulated ETCC and TC	10 sessions/20min - Once a day	1.4 points (P=0.006) improvement and after 1 month 2.8 points (P=0.004) improvement on the GI.	1 month
Krueger, S. S. et al., 2018[31]	Germany	59	Ischemic stroke	Randomized; double-blind.	FEDSS; SSA	Contralesional pharyngeal motor cortex ETCC group Placebo ETCC group	4 sessions/20min	Significant dysphagia improvement on the ETCC group when compared to the placebo group (P<0.0005)	No follow-up

DOSS: Dysphagia Outcome and Severity Scale; ETCC: TC: Conventional Therapy; GI: Intervention group GC: Control group; VFSS: Videofluoroscopy; IOPI: Iowa Oral Performance Instrument; EMTr: PAS: Penetration-Aspiration Scale; VDS: Functional Dysphagia Scale; SSA: Standardized Swallow Assessment; FEDSS: fiberoptic endoscopic dysphagia severity scale.

In addition, there are currently a wide variety of candidate genes that can be studied in the context of brain plasticity and response to PES. BDNF is the most abundant growth factor in the brain and is involved in long-term brain plasticity. It has attracted much interest and is considered a candidate for neurological and swallowing function recovery in patients treated with electrical stimulation of the pharynx[26]. The study conducted by Essa et al.[26] aimed to test the possible influence of a single but common BDNF polymorphism on the functional recovery in a population with dysphagia after stroke. An association between the Val66Met BDNF allele and level of swallowing recovery was observed when pharyngeal stimulation was performed. On the other hand, the BDNF showed no correlation in the simulated group, suggesting that such genetic polymorphisms may be less relevant in natural recovery than in treatment-induced recovery.

A summary of studies using the pharynx electrostimulation technique is shown in Table 3.

Tongue pressure resistance exercise and precision training

Tongue function can affect both the oral and the pharyngeal stages of the swallowing process. Adequate tongue strength is vital for safe oropharyngeal swallowing. Table 3 has a summary of the studies on tongue pressure resistance exercises and precision training.

Kim et al.[42] investigated the effect of tongue-pressure resistance training (TPRT) on tongue strength and oropharyngeal swallowing function in patients with stroke and dysphagia. The results showed that TPRT increased tongue muscle strength and improved swallowing function in patients with post-stroke dysphagia. This study also confirmed that TPRT improved the oral and pharyngeal phases of deglutition. Therefore, TPRT is recommended as an easy and simple rehabilitation strategy to improve swallowing in patients with dysphagia. However, these results do not reflect a pure TPRT effect, as this therapy was conducted in conjunction with conventional therapy[42]. Another study published the following year aimed to investigate the effects of tongue pressure strength and accuracy training (TPSAT) on tongue pressure strength and its ability to improve quality of life in patients with dysphagia after stroke. TPSAT consisted of an isometric exercise of anterior and posterior tongue strength and an isometric tongue precision exercise. TPSAT combined with traditional therapy improved outcomes compared to pre-intervention levels[41].

CTAR exercise

Recently, CTAR (Chin Tuck Against Resistance) exercise has been reported as a treatment for pharyngeal dysphagia. However, clinical evidence of its effect is still unclear. Park et al.[32] investigated the effect of CTAR on the swallowing function in patients with dysphagia after subacute stroke and found that the exercise improved swallowing.

Game-based CTAR was also proposed[34]. The experimental group performed game-based CTAR, while the control group performed traditional head lifting exercises. The LES 100 (Cybermedic Inc., Iksan in South Korea) consists of a tablet screen, a resistance bar, and a Bluetooth connector, and it implements a game-based exercise in which the chin is tucked down against a bar in order to strengthen suprahyoid muscles. The game-based CTAR not only has a similar effect on the swallowing function of patients with dysphagia as the lifting exercise, but is also a less rigorous, more enjoyable and interesting rehabilitation method.

Because the CTAR involves hand-holding a device, physically weak patients may find it difficult. A study investigated the effect of modified CTAR (mCTAR) in patients with post-stroke dysphagia[35] and found that it reduced aspiration and improved nutritional levels of patients. I can thus be assumed that the mCTAR is beneficial for physically vulnerable patients with dysphagia who have limited hand strength and movement.

The aim of the study was to investigate the effect of jaw opening exercise (JOE) and hyoid bone movement compared to head lifting exercise, or Shaker exercise (HLE) in patients with dysphagia after stroke. The JOE/CTAR group performed an exercise using a resistance bar. The Shaker group performed traditional exercises. The total duration of the intervention was 6 weeks. The thickness of the digastric and mylohyoid muscles was measured by ultrasound. The CTAR and Shaker had similar effects in increasing the thickness of the suprahyoid muscle and improving the movement of the hyoid bone. However, CTAR required less perceived effort than Shaker[36].

Shaker exercise

The Shaker exercise (SE) has been considered a popular rehabilitation training for dysphagia[33]. This is an isometric and isotonic exercise based on the upward and forward movement of the larynx structures resulting from the traction of the thyroid, mylohyoid, and geniohyoid muscles and the anterior belly of the digastric muscle. First, patients perform 3 head raises for 60 s in a supinated position without movement; there is a 60 s pause between the elevations. Next, participants perform 30 repeated head raises in the supine position. Participants raise their head high enough to observe the toes without raising the shoulders[37].

Gao & Zhang[33] compared the effects of Shaker exercises, CTAR and conventional exercises on dysphagia and psychological status. Traditional rehabilitation included tongue exercises such as tongue extension movement and mouth exercises such as mouth opening, teeth clicking, and voluntary swallowing. The main conclusion of this study was that the CTAR exercise has a similar effect on improving swallowing function as the Shaker exercise. However, the rehabilitation effect of CTAR exercises on dysphagia should be more explored in younger patients with stroke, since all patients assessed in this study were 60 years old or older.

Choi et al.[37] investigated the effects of the Shaker exercise on aspiration and oral diet level in stroke survivors with dysphagia. This study suggested that the SE is an effective exercise for swallowing function recovery in stroke survivors, reducing aspiration and improving oral diet level. As aspiration severity is closely related to the feeding tube and to the oral diet level, the results of this study indicate that performing SE can lead to tube withdrawal in stroke survivors with dysphagia. Some limitations, such as a relatively small sample, no follow-up after the intervention, and failure to observe long-term effects prevent the results of this work from being generalized.

Important data from the articles about CTAR and SE are shown in Table 4.

Modified jaw opening exercise (MJOE)

The viability and effectiveness of a new method (modified jaw opening exercise - MJOE) for promoting anterior displacement of the hyoid bone during swallowing was studied. The MJOE differs from the conventional JOE, in which an upward vertical resistance is applied to the jaw while the mouth is closed with the tongue held in the swallowing tilting position to prevent mouth opening. In the MJOE, surface electrodes connected to the sternohyoid muscle in the mandibular midline were connected to the biofeedback equipment. The results showed that MJOE is feasible in elderly post-stroke patients, without adverse events and promotes anterior displacement of the hyoid bone during swallowing[43].

Mendelsohn maneuver

The Mendelsohn maneuver, a voluntary prolongation of laryngeal elevation during swallowing, has been widely used as a compensatory strategy to improve the opening of the upper esophageal sphincter (UES) and bolus flow. When used as a rehabilitation exercise, it significantly improves the duration of the hyoid movement and the duration of the UES opening[27].

McCullough et al.[28] performed a research to determine if the intensive exercise using the Mendelsohn maneuver would improve swallowing physiology. The Mendelsohn maneuver, used as a rehabilitation exercise, improved the duration of the anterior and superior maxillary movement of the hyoid and the duration of the UES opening. With a similar goal, McCullough et al.[27] stated that it seems possible that the use of the Mendelsohn maneuver as a rehabilitation exercise may have a greater impact on swallowing durations than on structural movements. Changes in the coordination of structural movements with duration measures, however, require further investigation. When the Mendelsohn maneuver was used as a compensation mechanism, duration measures also appeared to be more affected than measures of structural movements. Thus, the data reported in this research support the use of the Mendelsohn maneuver as an exercise to improve the swallowing physiology[27].

A synthesis of the results discussed above is shown in Table 5.

Acupuncture

Acupuncture is a simple, inexpensive, primary medical procedure that has been widely used in China and other parts of East Asia for many years. Needles are inserted at acupuncture points to produce a "qi" response in which the patient feels pain or heaviness in the area around the needle[38].

Xia et al.[38] evaluated the effect of acupuncture on swallowing function in patients with dysphagia after stroke. The intervention group received standard therapy and acupuncture and the control group received only standard therapy. Although it was concluded that acupuncture combined with conventional swallowing therapy may be beneficial, the study had a significant limitation due to the lack of a control group for acupuncture alone. In addition, short-term evaluation and lack of follow-up were factors that prevented the evaluation of a long-term therapeutic effect.

Another study found that acupuncture combined with swallowing therapy can improve the swallowing function in post-stroke patients[39]. The study conducted by Mao et al.[39] proved that acupuncture in combination with standard swallowing therapy was effective for post-stroke dysphagia, corroborating the findings presented by Xia et al.[38]. However, several limitations prevent this conclusion from being generalized, so it cannot be said that acupuncture alone is capable of providing a high level of rehabilitation.

A similar study was conducted by Chen et al.[40]. This study has shown that acupuncture is safe and has several additional effects in improving neurological deficits, swallowing disorder, cognitive impairment, and lower limb function. However, no significant improvement in the upper limb function was observed during this short-term study.

A summary of the results in the articles using acupuncture techniques is shown in Table 5.

Cervical isometric exercises

Cervical isometric exercises to improve dysphagia and cervical spine malalignment was applied in 70 patients in a randomized controlled trial. The exercises were carried out in all 4 directions (by placing their hand or the hand of their personal assistant on their head and contracting their neck muscles under forward-backward-sideward resistance). Swallowing was improved in the experimental group compared to the control group[44].

DISCUSSION

The purpose of this review was to assess recently studied therapies for dysphagia rehabilitation. Numerous studies of a wide range of interventions were included. However, they differed not only in terms of the therapy conducted, but also in terms of sample size, outcome measurement methods, intervention times and follow-up time. These differences presented a challenge to combine and summarize the results, and to compare and define which is the most effective treatment for post-stroke dysphagia.

Table 3. Interventional clinical studies using electrostimulation of the larynx, tongue pressure resistance exercise and precision training for patients after stroke.

References	Country	Patients (n)	Diagnosis	Study Design	Outcomes	Intervention	Intervention time	Results	Follow-up
Bath, P. M. et al., 2016[24]	United Kingdom	162	Stroke	Multicenter; Randomized; Controlled; Double-blind	VFSS (PAS)	GI – active PES GC – simulated PES	3 sessions/10 min	No GI improvements in relation to the GC	2,6 and 12 weeks
Vasant, D, H et al., 2016[25]	United Kingdom	36	Stroke	Multicenter; Randomized; Controlled	DSR	GI – active PES GC – simulated PES	3sessions/10 min	In relation to the simulated group, a probability ratio (OR)> 1 indicated a favorable outcome for the active group in DSR punctuations.	2 weeks and 3 months
Essa, H., 2017[26]	United Kingdom	38	Stroke	Randomized; Controlled; Double-blind	DRS	GI – active PES GC – simulated PES	3 sessions/10 min	In the GI, patients with the allele Met BDNF showed improvements in DERD after 3 months in relation to patients in the GC (P = 0.009)	2 weeks and 3 months
Moon, J. H et al., 2018[41]	Korea	16	Stroke	Randomized; Controlled	IOPI; MASA	GI - TPSAT in the morning and TC in the afternoon GC - TC	80 sessions/30 min - 2 times a day, 5 times a week for 8 weeks	Anterior (P = 0.001) and posterior (P = 0.001) PMI improvement in the GI in relation to the GC; GI and GC MASA improvement (P = 0.012)	No follow-up
Kim, H. D. et al., 2016[35]	Korea	35	Stroke	Randomized; Controlled	IOPI; VFSS (VDS and PAS)	GI - TPRT and TC GC - TC	20 sessions - 5 times a week	GI tongue strength improvement (anterior and posterior, p = 0.009, 0.015) and oral and pharynx phases punctuations improvement in VDS (p = 0.029, 0.007), but not in PAS (p = 0.471) in relation to the control group.	No follow-up

VFSS: Video Fluoroscopic Swallowing Study; PAS: Penetration-Aspiration Scale; DSR: Dysphagia Gravity Scale; DERD/DSRS: Dysphagia Severity Rating Scale; GI: Intervention Group; GC: Control Group; PES: Pharyngeal electric stimulation; BDNF: brain-derived neurotrophic factor; DRS: Dementia Rating Scale; PMI: maximum isometric pressure; VDS: videofluoroscopic dysphagia scale; TPRT: tongue to palate resistance training; IOPI: Iowa Oral Performance Instrument.

Table 4. Intervention clinical studies using CTAR and Shake exercises for patients after stroke.

Reference	Country	Patients	Diagnosis	Study design	Outcomes	Intervention	Intervention time	Results	Follow-up
Gao, J.; Zhang, H.J., 2017[33]	China	90	Ischemic stroke	Clinical; Random	VFSS (PAS)	GC – TC Shaker - TC and Shaker exercise CTAR - TC and CTAR	42 sessions - 3 times a day	A better swallowing improvement in the CTAR group when compared to the Shaker group	2, 4 and 6 weeks
Park, J. S. et al., 2018[32]	Korea	22	Stroke	Randomized; Controlled	VFSS (PAS; FDS)	GI - CTAR and TC GC - TC	20 sessions/30 min - 5 times a week	Significant improvement in the PAS and FDS in the GI when compared to the GC	No follow-up
Choi, J. B. et al., 2017[37]	Korea	31	Stroke	Randomized; Controlled; Double-blind	VFSS (PAS); FOIS	GI - TC and Shaker exercise GC - TC	20 sessions/30 min - 5 times a week	PAS and FOIS significantly improved the GI in relation to the GC	No follow-up
Park, J. S et al., 2019[34]	Korea	37	Stroke	Randomized; Controlled	VFSS (PAS); FOIS	GI – Game-based CTAR GC – CTAR	20 sessions/30min – 5 times a week	There were no differences in improvement between groups	No follow-up
Kim, H. H.; Park, J. S, 2019[35]	Korea	30	Stroke	Clinical; Randomized	PAS; FOIS	GI – CTAR and TC GC - TC	30 sessions/30 min – 5 times a week	GI had a significant improvement in PAS and FOIS (P <0.001, both)	No follow-up

VFSS: Videofluoroscopy; PAS: Penetration-Aspiration Scale; FDS: Functional Dysphagia Scale; GI: Intervention group; GC: Control group; TC: Conventional therapy; FOIS: Functional Oral Intake Scale; CTAR: Chin Tuck Against Resistance.

Table 5. Interventional clinical studies using the Mendelsohn maneuver and EMG with biofeedback and acupuncture for stroke patients.

Reference	Country	Patients	Diagnosis	Study design	Outcomes	Intervention	Intervention time	Results	Follow-up
McCullough, G.H. et al., 2012[28]	USA	18	Stroke	Randomized	VFSS (DOHME and DOHAME)	Group A - 2 weeks of treatment with the Mendelsohn maneuver and EMG with feedback and 2 weeks without treatment. Group B - 2 weeks without treatment and 2 weeks with treatment.	45 min sessions, 2 times a day	DOHME and DOHMAE significantly improved (P = 0.011 and 0.009) after treatment.	No follow-up
McCullough, G.H; Kim, Y., 2013[27]	USA	18	Stroke	Randomized	VFSS (HME, HMAE, UES)	Group A - 2 weeks of treatment with the Mendelsohn maneuver and EMG with feedback and 2 weeks without treatment. Group B - 2 weeks without treatment and 2 weeks with treatment.	45 min sessions, 2 times a day	No significant improvement after treatment	1 month, 1 year
Xia, W. et al., 2015[38]	China	124	Stroke	Clinical; Randomized; Double blind	SSA; DOSS	GI- TC and acupuncture GC – TC	24 sessions/30 minutes - 6 times a week	SSA and DOSS GI improvement in relation to the GC (P<0.01)	No follow-up
Mao, L. et al., 2016[39]	China	98	Stroke	Prospective	VFSS; SSA	GI - TC and acupuncture GC – TC	20 sessions/30 minutes - 5 times a week	VFSS and SSA GI improvement in relation to the GC (P=0.007 and P=0.007)	No follow-up
Chen, L. et al., 2016[40]	China	250	Stroke	Randomized; Double-blind; Controlled	NIHSS; VFSS; SSA	GI - TC and acupuncture GC – TC	18 sessions/30 minutes - 6 times a week	GI improvement in relation to the GC: NIHSS ($p < 0.001$), VFSS ($p < 0.001$) and SSA ($p = 0.037$)	1, 3, 7 weeks

VFSS: Videofluoroscopy; DOHME: Duration of Hyoid Maximum Elevation; DOHAME: Duration of Hyoid Maximum Anterior Excursion HME: Hyoid Maximum Elevation; HMAE: Hyoid Maximum Anterior Excursion; UES: Upper Esophageal Sphincter; EMG: Surface Electromyography; SSA: Standardized Swallow Assessment; NIHSS: NIH Stroke Scale; DOSS: Dysphagia Outcome and Severity Scale; GI: Intervention group; GC: Control group; TC: Conventional Therapy.

Considering that this neuromuscular process is complex and involves dozens of muscles and six pairs of cranial nerves, there are many symptoms that affect a dysphagic individual. Therefore, it is difficult to elaborate a single exercise protocol (in the case of conventional therapy) that will effectively improve the condition. Scientific evidence highlights the benefits of conventional therapy in improving the swallowing pattern of a dysphagic individual. However, the search for new therapeutic techniques that can increase this benefit is constant.

Studies on the efficacy of therapeutic interventions for rehabilitation of adult patients with dysphagia after stroke are still limited. Most techniques are used in combination with conventional therapies, which makes measuring the efficacy of other techniques alone inconclusive. Among the reviewed therapies, electrotherapy, associated or not with conventional therapy, was the most frequently used. In both cases, it proved to be a method with significant results for the rehabilitation of dysphagia. Similarly, neuromodulation applied in areas such as the motor cortex of the tongue and pharynx, as mentioned in the included studies, also lead to an improvement in the swallowing pattern. Tongue pressure resistance exercises and precision training, the Shaker exercise and acupuncture also showed significant results for rehabilitation.

Neuromodulation is not a possibility in many healthcare institutions that admit patients with acute stroke, making this therapy technique difficult to access, especially for low-income patients. An advantage of the SE is that it is a non-invasive therapy, does requires no any additional cost or equipment and can be easily performed at the bedside with the assistance of a caregiver[37]. However, a limitation of the SE is that coordinated movements and resistance are required, and many patients in the acute phase of stroke do not have this capability. Pharyngeal electrical stimulation (PES) is also considered a promising treatment for dysphagia after stroke. However, the results of the studies included in this review are contrary to this. With regard to tongue pressure resistance exercise, it is important to emphasize that isometric and isotonic exercises are commonly used in conventional therapy to improve the amplitude and increase the force of tongue movements. The tongue is an essential organ for the proper functioning of the safe swallowing process.

The majority of the studies used videofluoroscopy of swallowing as the gold standard evaluation method. The method allows the swallowing dynamics to be visualized from the preparatory phase to the opening of the upper esophageal sphincter. It is also possible to identify the tracheal aspiration, laryngeal penetration, and oral and pharyngeal residues, which is important for a detailed analysis of the various changes that may occur in a dysphagia disorder of any degree. Videofluoroscopy helps in selecting the most appropriate technique and therapeutic plan to improve the swallowing pattern. Ideally, this examination should be available in all health centers admitting patients in the acute phase of stroke.

In conclusion, this review highlights the main interventions for dysphagia of patients after stroke. Among the techniques used, conventional therapy remains the best strategy, achieving positive results alone or combined with various rehabilitation therapies. However, greater consistency between science and clinical practice is needed to allow a comparison between different techniques. Dysphagia is a potentially treatable symptom in post-stroke patients and deserves attention, and its treatment may increase patients' quality of life. In addition, even if conventional therapy is empirically considered essential for the rehabilitation process, its effect would be strengthened by studies that scientifically support this technique.

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"But man is not made for defeat": insights into Ernest Hemingway's dementia

"Mas o homem não foi feito para a derrota": visões sobre a demência de Ernest Hemingway

Léo COUTINHO[1,2], Hélio Afonso Ghizoni TEIVE[1,2]

ABSTRACT

Ernest Hemingway is widely regarded as one of the greatest fiction writers of all time. During his life, he demonstrated several signs of psychological suffering with gradual worsening and presentation of cognitive issues over his late years. Some of his symptoms and the course of his disease suggest that he might have suffered from an organic neurodegenerative condition that contributed to his decline, which culminated in his suicide in 1961. In this historical note, we discuss diagnostic hypotheses compatible with Hemingway's illness, in light of biographical reports.

Keywords: History of Medicine; Neurology; Art; Dementia; Neurodegenerative Diseases.

RESUMO

Ernest Hemingway é considerado um dos escritores mais lidos de todos os tempos. Durante sua vida, ele demonstrou diversos sinais de sofrimento psicológico com piora gradual durante seus últimos anos, associado à apresentação de distúrbios cognitivos. Alguns de seus sintomas, assim como o curso da doença, sugerem que ele talvez tenha padecido de uma condição neurodegenerativa orgânica que contribuiu para o seu declínio, culminando em seu suicídio em 1961. Nesta nota histórica, discutimos hipóteses diagnósticas compatíveis com a doença de Hemingway, à luz de relatos biográficos.

Palavras-chave: História da Medicina; Neurologia; Arte; Demência; Doenças Neurodegenerativas.

INTRODUCTION

Ernest Hemingway (1899–1961) (Figure 1) is one of the world's most praised literary writers. His objective prose created masterpieces such as *For whom the bell tolls and The old man and the sea*[1-4].

Born in 1899 in Oak Park, Illinois, Hemingway began writing in journalism and war correspondence. He married four times and had three children.

Hemingway was given the ultimate accolades in literature: the Pulitzer in 1953 and the Nobel Prize in 1954[5,6]. Despite an achieved life, Hemingway presented signs of psychiatric suffering[7-12], which culminated in his suicide in 1961 in Ketchum, Idaho. Recent evidence suggests that in his late years he presented neurological signs attributable to dementia[3].

At the 60th anniversary of Hemingway's death, we discuss his neurological condition, emphasizing organic hypotheses based on his biographic reports.

COGNITIVE AND BEHAVIORAL DECLINE

Hemingway presented early signs of a psychiatric condition, possibly bipolar disorder, with documented maniac and depressive episodes, in addition to a significant family history of suicide (Figure 2), although only his father had committed suicide before him[1-3,7]. Many patients with this condition share outstanding creativity[7,8]. Patients with bipolar disorder have an increased dementia risk with an incidence of 25.2% in a recent cohort[9]. Previous papers detailed his psychological ailment[10-13].

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Authors' contributions: LC: organization, execution, writing of the first draft, writing of the final manuscript; HAGT: conception, review and critique, writing of the final manuscript.

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Source: Ernest Hemingway Collection. John F. Kennedy Presidential Library and Museum, Boston. Licensed under a Public Domain Mark.

Figure 1. Ernest Hemingway in the cabin of his boat, *Pilar* (circa 1950s).

The following evidence supports the presence of dementia:

1. Hemingway's decline was inexorable, despite electroconvulsive therapy carried in the Mayo Clinic.
2. In his last years, his cognition sharply declined, impairing his writing.
3. He presented risk factors for dementia, namely alcoholism, sexual risk behavior, and repeated head trauma[3].

The precise onset of Hemingway's decline is unclear, but it possibly initiated during his fifth decade of life[1-3]. The disease was marked by a primacy of behavioral symptoms with late cognitive issues, raising several hypotheses (Table 1)[1-3].

Hemingway experienced progressive disinhibition. He would often say inappropriate things during social gatherings and engage in more sexually liberated experiences. This disinhibition can be perceived in the sexual themes present in his last works, ***A moveable feast*** and G***arden of Eden***[1-3]. The former cruelly depicts his first two wives and his friendship with Scott Fitzgerald, possibly motivated by disinhibition.

His paranoia and delusions increased, with a belief that he was under FBI surveillance. Other sources of paranoia were his hypochondria, fear of impoverishment, and the possibility of arrest for illegal hunting and for "taking liberties with a minor"[1-3].

Hemingway would present frequent and unpredictable bursts of aggressiveness, particularly towards his last wife, Mary, who endured significant abuse[1-3].

After his first admittance to the Mayo Clinic (1960), Hemingway presented amnestic symptomatology. This would be a burden to his writing, and he would consider finishing *A moveable feast* impossible. He needed help with the manuscript revision from his wife and editor and his last works would be published only posthumouslly[1-3].

DISCUSSING THE POSSIBILITIES

Frontotemporal dementia (FTD)

Hemingway´s clinical features are compatible with the behavioral variant of frontotemporal dementia (bvFTD). FTD presents an earlier onset than other neurodegenerative etiologies, as seen in the writer's case. Genetics plays a significant role in FTD, and up to 40% of patients present a family history of dementia. However, other bvFTD features, such as lack of empathy, obsessive behavior, and a dysexecutive syndrome were not present[14].

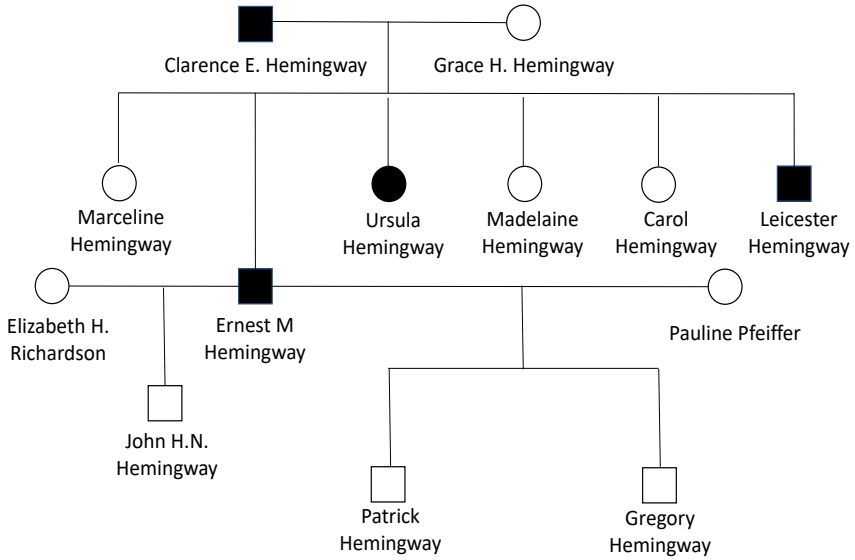

Figure 2. Pedigree chart for the Hemingway family, showing first-degree relatives to Ernest[3,7]. Icons in black represent family members who committed suicide. Marriages with Martha Gellhorn and Mary Welsh were omitted, as they did not have children.

Table 1. Diagnostic possibilities compatible with Ernest Hemingway's condition and epidemiology.

Condition	Arguments in favor	Arguments against
Behavioral variant Frontotemporal Dementia (bvFTD)	Disinhibition. Early onset. Late cognitive disability.	Absence of other features (lack of empathy, obsessive behavior, problems in executive function).
Lewy Body Dementia (LBD)	Psychosis. Delusions. Fluctuations.	Absence of Parkinsonism. Lack of well systematized hallucinations.
Vascular dementia	Multiple risk factors. Family history of vascular. complications.	No history of strokes.
Chronic traumatic encephalopathy (CTE)	Multiple concussions. He was a notorious brawler. Predominantly behavioral presentation.	None.
Alcohol toxicity/Vitamin deficiency	Heavy alcohol consumption. Other documented complications of alcohol intake (hepatopathy, withdrawal syndrome).	Lack of early amnestic symptomatology.
Neurosyphilis	Risk sexual behavior.	Lack of other neurosyphilis hallmarks (motor symptoms, cranial nerve palsy). Lack of a well-documented primary treponemal infection.
Huntington's disease (HD)	Phenotypes with pure behavioral/cognitive symptomatology.	Rare presentation. No members of the Hemingway family presented motor phenomenology compatible with HD.

Lewy body dementia (LBD)

Hallucinations and psychosis with marked fluctuations are the hallmarks of LBD[15]. This diagnosis was recently proposed as etiology for Hemingway's decline[3]. However, parkinsonism was never described in his case. Moreover, Hemingway's psychosis presented more delusions than well-substantiated hallucinations, making LBD an unlikely diagnosis[1-5].

Vascular dementia

In the Mayo Clinic, Hemingway was diagnosed with severe hypertension, prediabetes, and dyslipidemia. He was under suspicion of hemochromatosis, but a liver biopsy was contraindicated considering his precarious health[1-5]. Hemingway had a family history of vasculopathy, particularly related to diabetes[1-5].

Although Hemingway's biography reports no strokes, these comorbidities are risk factors for small vessel disease and subcortical ischemic vascular dementia. As clinical presentation is variable and overlapping with other dementia etiologies is common, this is a consistent hypothesis[16].

Chronic traumatic encephalopathy (CTE)

Hemingway endured nine major head traumas during his war service, including a mortar blast. In 1954, he survived two plane crashes. He practiced football and boxing from an early age, acted as an amateur bullfighter, and was a reckless driver[1-5]. CTE is a plausible hypothesis, as this condition often presents with behavioral symptomatology, particularly aggressiveness and mood changes, while cognition is of late affection[17].

Alcohol toxicity/Vitamin deficiency

To say Hemingway was a heavy drinker would be an understatement. He spent a significant part of his time in Havana at the bar *La Floridita*, being served with *Papa Dobles* (the Hemingway daiquiri) by the bartender[2,3]. The role of alcohol consumption in dementia is documented, being a risk factor for vascular dementia and Alzheimer's disease. The proposed mechanisms include direct neuronal toxicity and secondary vitamin deficiencies[18].

Neurosyphilis

Hemingway had multiple sexual partners, including extramarital relationships. Although he was at risk for syphilis, a more diverse clinical picture would be expected. The absence of motor symptomatology, cranial nerve palsy, and other hallmarks of neurosyphilis, besides the absence of a well-documented primary treponemal infection, make this diagnosis improbable[19].

Huntington's disease (HD)

Certain phenotypes of HD have a predominance or exclusivity of non-motor symptomatology, presenting behavioral and cognitive symptoms, such as the exhibited in Hemingway's case and family history; motor phenomena may have a late onset or never occur. However, this is a rare presentation and an unlikely hypothesis. Phenotypic variability occurs within the same family, and other members of the Hemingway family would present motor symptomatology[20].

In conclusion, Hemingway's case would remain a challenge in modern days. His personality traits would pose an obstacle for the detection of behavioral symptoms of neurodegeneration.

Although a psychiatric condition is acknowledged, Hemingway's symptomatology is compatible with organic dementia. In the author's opinions and in accordance with recent literature[3], bvFTD and CTE, possibly associated with a vascular component, might have contributed to his decline.

Remarkably, Hemingway tried to write to his very end despite his cognitive impairment; a display of tenacity worthy of Santiago, the main protagonist of *The old man and the sea.*

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A rare case of intraventricular gangliocytoma

Um caso raro de gangliocitoma intraventricular

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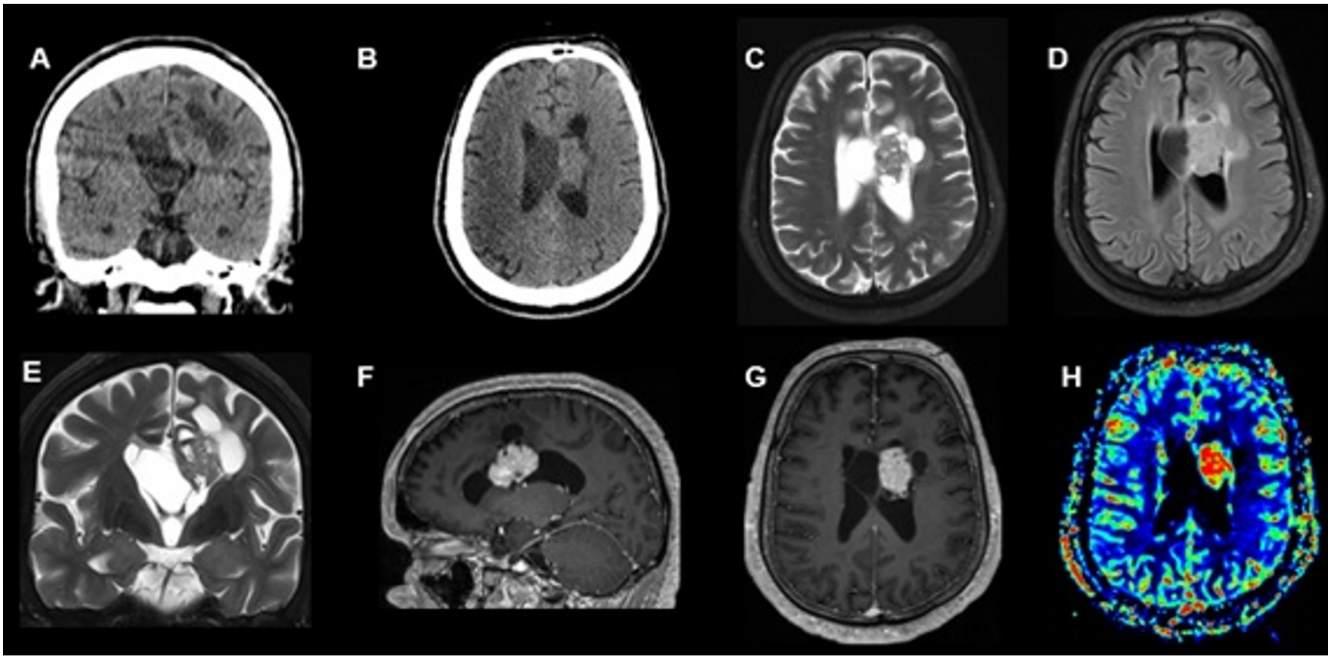
A 49-year-old man presented to the emergency department after cranioencephalic trauma with an intraventricular tumor detected in the computed tomography (CT) scan (Figure 1). An magnetic resonance image (MRI) showed a heterogeneous expansive lesion with enhancing solid components and peripheral cysts located in the left lateral ventricle (Figure 1). The patient underwent excision of the lesion. Histopathologic (Figure 2) and immunohistochemical (Figure 3) analysis revealed the diagnosis of gangliocytoma. Gangliocytomas are rare low-grade central nervous system tumors composed of dysplastic ganglion cells, usually presenting in children or young adults and located in the cerebral hemispheres[1,2]. Until now, there are no case reports of intraventricular gangliocytoma.



FLAIR: fluid attenuated inversion recovery; rCBV: relative cerebral blood volume; DSC: differential scanning calorimetry.

Figure 1. Coronal (A) and axial (B) nonenhanced brain CT shows a solid and cystic lesion within the lateral left ventricle and infiltrating adjacent white matter. Coronal and axial T2 (C, D), axial FLAIR (E) shows a well-demarcated, isointense and heterogeneous lesion with predominantly peripheral cysts located within the left lateral ventricle with infiltration of its lateral wall and the septum pellucidum. Sagittal and axial post-contrast T1 (F, G) sequence shows intense enhancement of the solid portion and increased rCBV on DSC perfusion (H).

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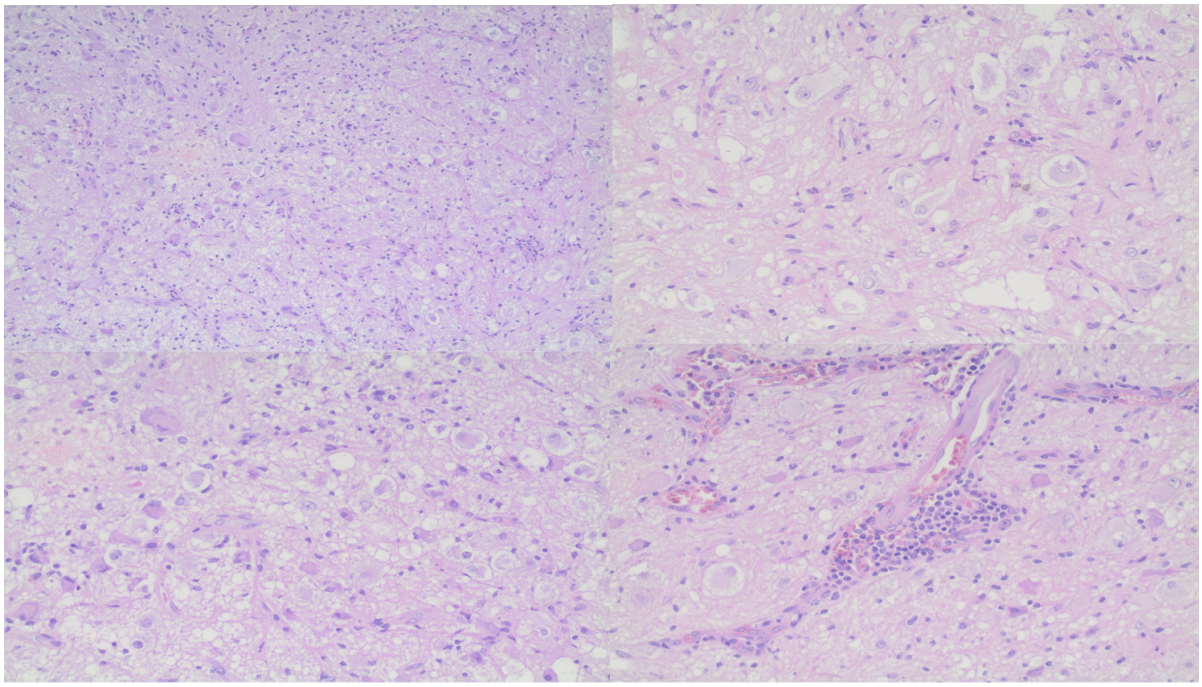

Figure 2. Clusters of atypical pleomorphic ganglion cells embedded in a haphazard manner within a delicate neuropil matrix. No neoplastic glial cells are present.

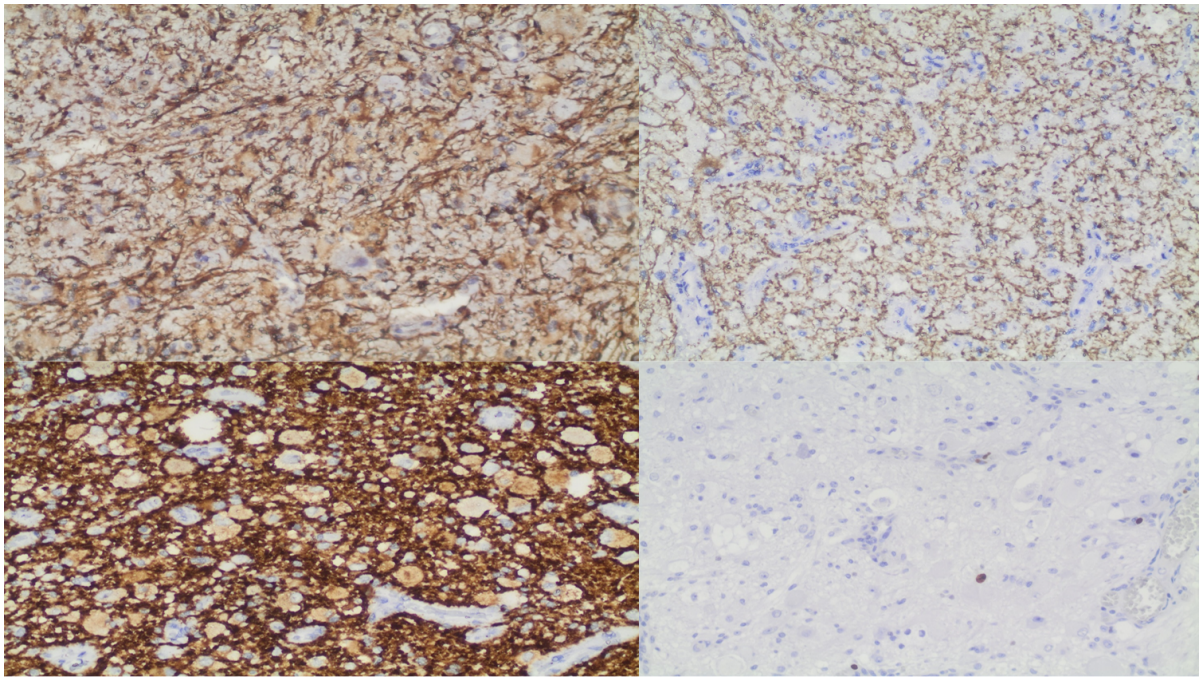

Figure 3. Immunohistochemical (IHC) studies. Glial fibrillary acidic protein (GFAP) positive in normal astrocytes with positive ATRX and negative isocitrate dehydrogenase. Neurofilament (NF) and synaptophysin (SYN) were positive in the neuropil. Ki-67 (Ki67), which determines the proliferative index, was low (< 2%).

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Demyelinating sentinel lesion preceding a primary central nervous system lymphoma

Lesão desmielinizante sentinela precedendo linfoma primário do sistema nervoso central

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A 29-year-old man presented with tonic-clonic seizures. Initial MRI showed a lesion centered on the white matter of the left frontal lobe, with restricted diffusion and contrast enhancement on its margins and low rCBV and hypometabolismon PET-CT, suggestive of a tumefactive demyelination lesion (Figure 1). Patient underwent surgical biopsy, with no signs of malignancy (Figure 2). Two months later, control MRI showed a new lesion on the brainstem, with solid enhancement and hypermetabolism on PET-CT, compatible with lymphoma (Figures 3 and 4).

Demyelinating sentinel lesions preceding CNS lymphomas are a rare entity and its pathophysiology is not fully understood[1,2].

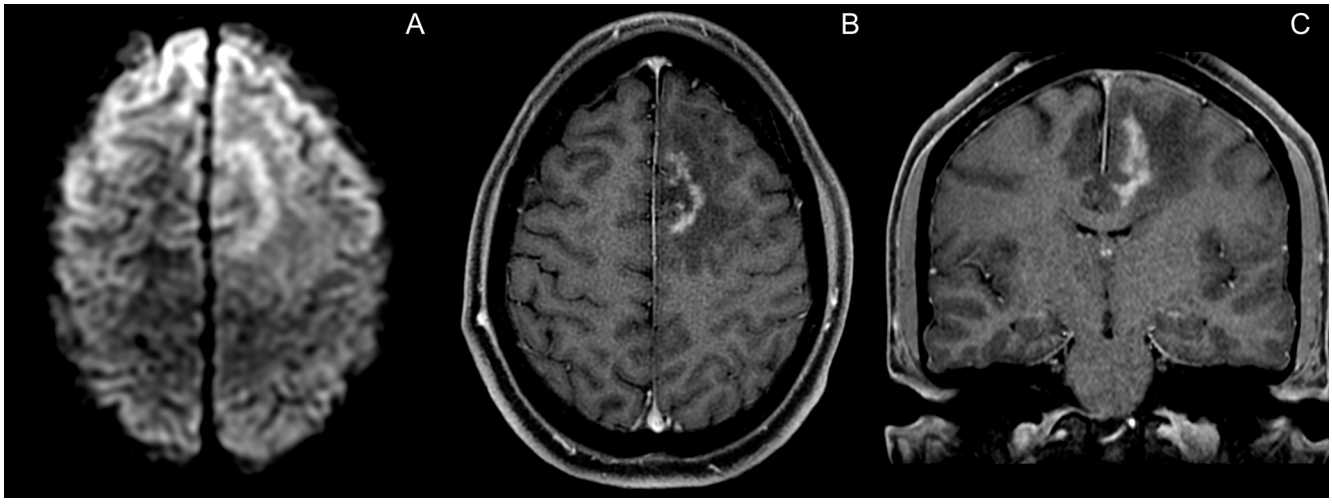

Figure 1. A: Axial diffusion weighted imaging (DWI), showing a left frontal lesion with restricted diffusion on the lesion's free margin, oriented towards the white matter, suggestive of demyelinating nature. B: Axial post-gadolinium T1, showing contrast enhancement on the lesions free margin. C: Coronal post-gadolinium T1 shows the left frontal lesion, insinuating towards the corpus callosum, but with no frank signs of invasion. Notice the spared brainstem.

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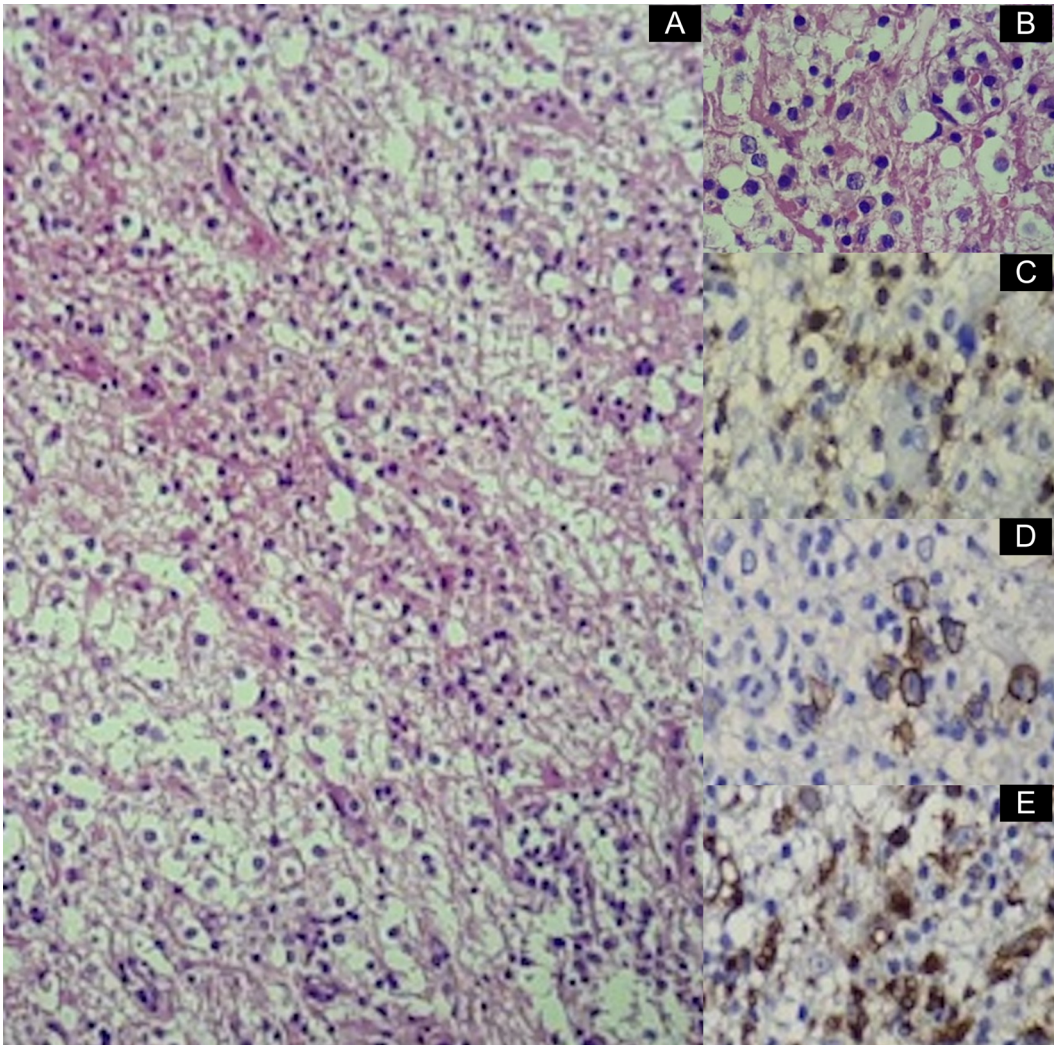

Figure 2. Histopathological findings from surgical biopsy. A: Hematoxicilin-eosin 100x, amplified on B, shows a diffuse inflammatory infiltrate composed by T-lymphocytes, confirmed by immunohistochemistry for CD3 marker on C, plasmacytes (CD138 on D) and foamy macrophages (CD68 on E). The sample was negative for malignancy and markers for B cells were negative (not shown).

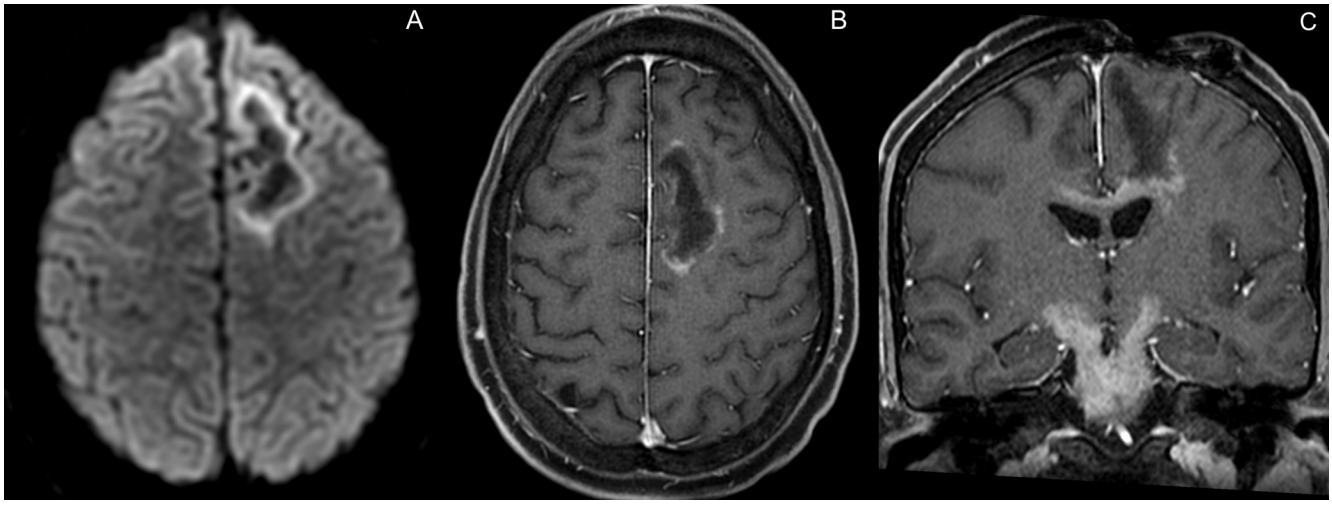

Figure 3. Control MRI two months later, demonstrates persistent restricted diffusion (A), but less enhancement of the left frontal lesion (B). C (coronal post-gadolinium T1): Its caudal aspect extends and invades the corpus callosum. Notice the development of a new and solid-enhancing lesion on the brainstem, extending along the cerebral peduncles and the postoperative changes on the left frontal lobe.

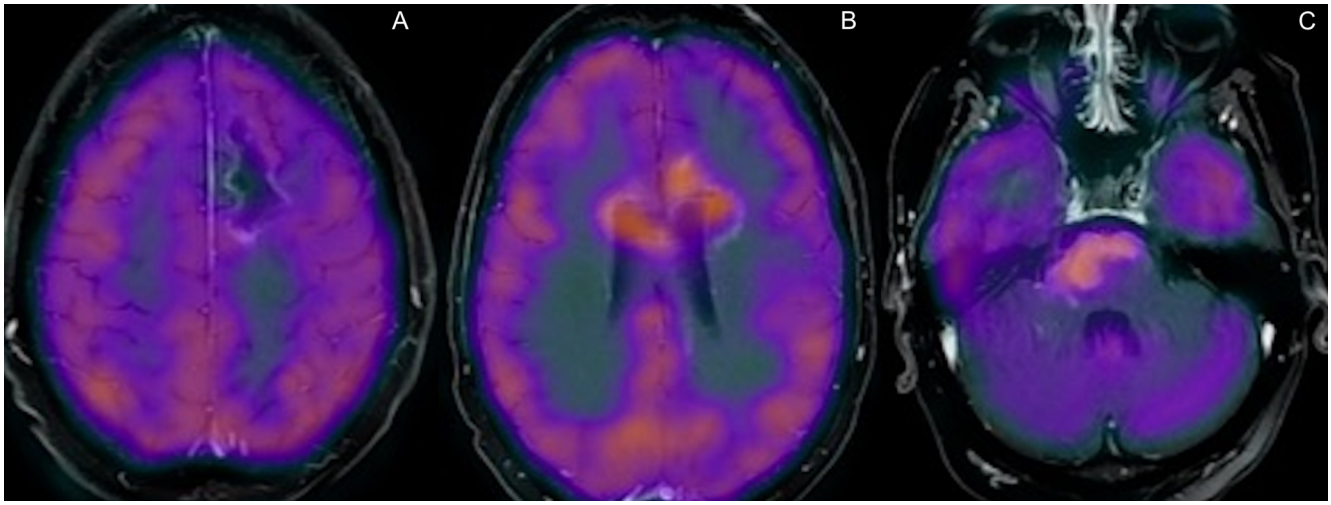

Figure 4. PET-CT and MRI fusion, showing the hypometabolic behavior of the original left frontal lesion (A), in contrast with hypermetabolism on the corpus callosum (B) and brainstem (C) lesions, inferring different etiologies.

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