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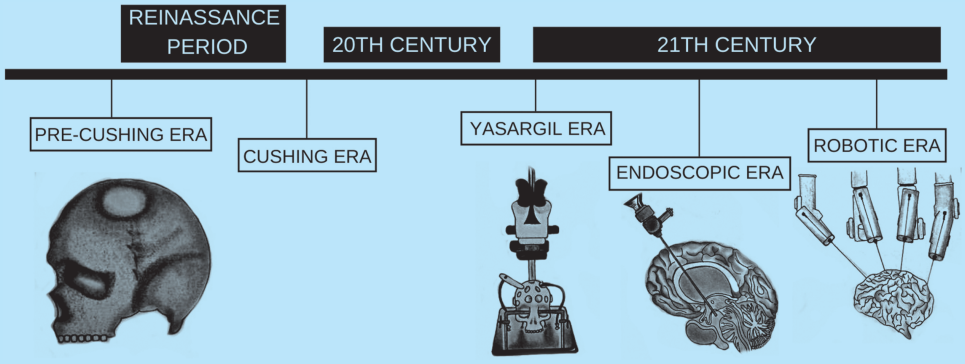

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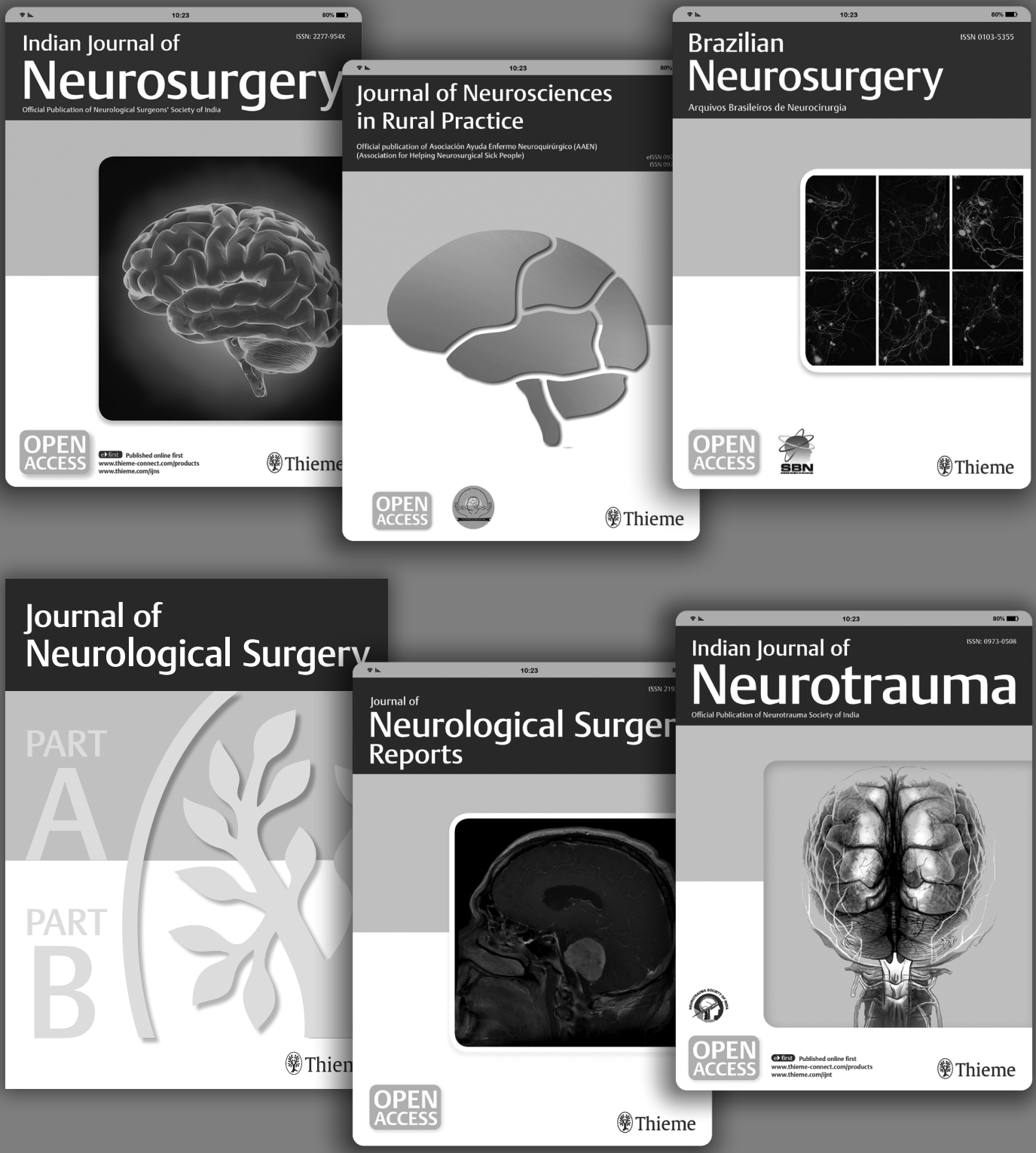

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[1] Neulen et al. Avaliação de eficácia e biocompatibilidade de uma nova matriz semissintética de colágeno como enxerto de restauração de dura-máter em um modelo animal de grande porte.
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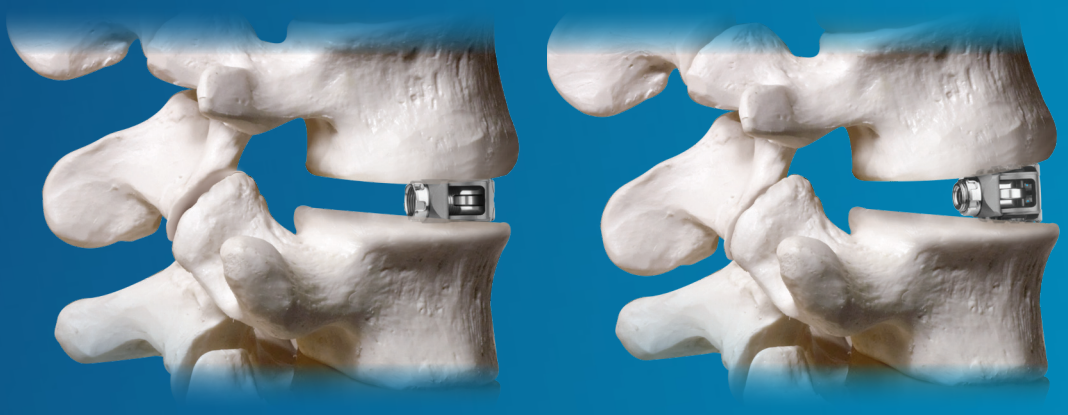

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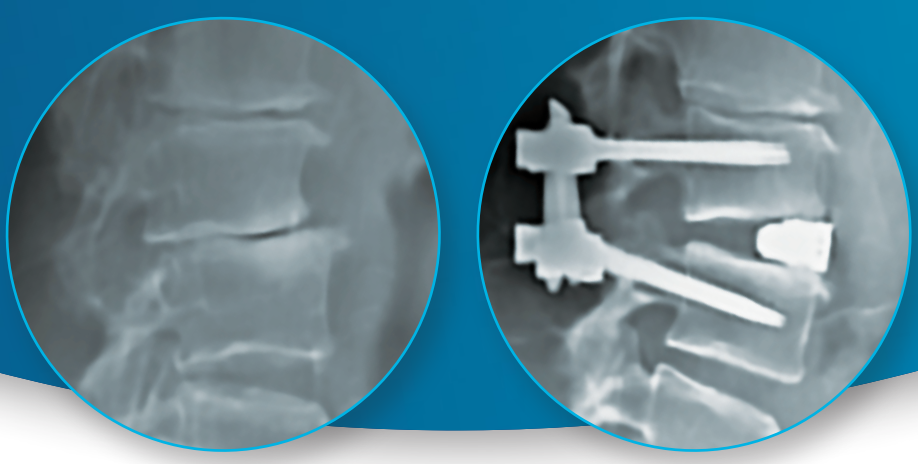

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Predictive Mortality Factors after Decompressive Craniectomy in Ischemic Stroke

Fatores preditivos de mortalidade após craniectomia descompressiva em acidentes vasculares cerebrais isquêmicos

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Abstract

Background Decompressive craniectomy is a consolidated method for the treatment of malignant ischemic stroke (iS) in the territory of the middle cerebral artery. Thus, factors contributing to mortality constitute an important area of investigation.

Objective To evaluate the epidemiological clinical profile and predictors of mortality in a single-center population of patients undergoing decompressive craniectomy for the treatment of malignant iS.

Methods A single-center retrospective study was performed in 87 patients with malignant iS subjected to emergency decompressive craniectomy from January 2014 to December 2017. Age, gender, laterality, aphasia, time interval between disease onset and treatment, and clinical and neurological outcomes using the Glasgow coma scale were assessed. The patients were stratified by age: a group of participants 60 years old or younger, and a group of participants older than 60 years old for assessment of survival and mortality by the Kaplan-Meier test and log-rank comparison. The intensity of the association between demographic and clinical variables was evaluated by multivariate Cox regression.

Results Ischemic stroke was prevalent in patients with hypertension (63.29%). Seventy-seven (84%) patients had some type of postoperative complication, mostly pneumonia (42.8%). The risk of death was 2.71 ($p = 0.0041$) and 1.93 ($p = 0.0411$) times higher in patients older than 60 and with less than 8 points on the Glasgow coma scale, respectively.

Conclusion Malignant iS has a significant mortality rate. Age above 60 years and Glasgow coma scale values below 8 were statistically correlated with unfavorable prognosis.

Keywords
- ischemic stroke
- cerebrovascular stroke
- middle cerebral artery
- decompressive craniectomy

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Resumo

Contexto A craniectomia descompressiva é um método consolidado para o tratamento do acidente vascular cerebral isquêmico (AVCI) maligno no território da artéria cerebral média. No entanto, os fatores envolvidos na mortalidade constituem objeto de investigação.

Objetivo Avaliar o perfil clínico epidemiológico e os preditores de mortalidade em uma população unicêntrica de pacientes submetidos à craniectomia descompressiva para tratamento de acidente vascular isquêmico maligno.

Métodos Um estudo retrospectivo unicêntrico foi realizado com 87 pacientes com AVCI maligno submetidos à craniectomia descompressiva de emergência de janeiro de 2014 a dezembro de 2017. Idade, gênero, lateralidade, afasia, intervalo de tempo entre o início da doença e o tratamento, e escala de coma de Glasgow foram avaliados. Os pacientes foram estratificados por idade: um grupo com participantes com 60 anos de idade ou menos, e outro com participantes com mais de 60 anos para avaliação de sobrevida e mortalidade pelo teste de Kaplan-Meier e comparação log-rank. A intensidade da associação entre variáveis demográficas e clínicas foi avaliada por regressão multivariada de Cox.

Resultados Houve prevalência de hipertensos (63,29%). Setenta e sete (84%) dos pacientes tiveram algum tipo de complicação pós-operatória, com predomínio de pneumonia (42,8%). O risco de morte foi 2,71 e 1,93 maior em pacientes com mais de 60 anos e com menos de 8 pontos na escala de coma de Glasgow, respectivamente.

Conclusão O AVCI maligno ainda tem uma taxa de mortalidade significativa. Idade acima de 60 anos e valores da escala de coma de Glasgow abaixo de 8 foram estatisticamente correlacionados com um prognóstico desfavorável.

Palavras-chave

- acidente vascular cerebral isquêmico
- AVC maligno
- artéria cerebral média
- craniectomia descompressiva

Introduction

Malignant Stroke

Ischemic stroke (iS), the most common and serious form of ischemic brain injury is a loss of neural function resulting from a critical reduction in cerebral blood flow.[1] Up to 10% of iSs are associated with massive space-occupying swelling (e.g., malignant middle cerebral artery [MCA] infarct). Typically, these patients deteriorate over 48 to 96 hours, with a progressive decline in the level of consciousness, ultimately succumbing to cerebral herniation, often despite medical treatment.[2]

The term "malignant hemispheric cerebral infarction" was introduced in 1996 and was described as a high morbidity and mortality clinical entity. It is an infarction that involves an area that covers at least two thirds of the MCA.[3,4]

The mortality of malignant infarction can be as high as 80% without neurosurgical intervention.[4] Infarctions in MCA territory are clinically well described.[5,6] The work of Foix and Levy, in the early 20th century, alludes to these infarctions.[7,8]

Currently, the description of malignant iS is a cerebrovascular stroke affecting more than 50% of the MCA territory seen on computed tomography and/or cranial magnetic resonance imaging, consonant with clinical presentation.[9–11]

The rationale for decompressive surgery is to reduce intracranial pressure (ICP) and the vicious circle of extensive edema and further infarction.[11] The best available evidence from recent randomized, controlled trials indicates that decompressive craniectomy is certainly a lifesaving operation in the setting of malignant stroke.[12]

The analysis of 3 published randomized studies (DECIMAL,[13] DESTINY[14] AND HAMLET[15]) showed that the survival rate of the group subjected to decompressive surgery (78%) more than doubled compared with that of the group treated conservatively (29%).[16,17] This staggering absolute risk reduction of 49% was highly significant.[18]

Despite the unquestionable efficacy of decompressive surgery, patient selection for this procedure is, to this date, a matter of discussion. Many studies were published trying to identify mortality predictors, helping the decision making about whom to operate. However, their results varied significantly.[19–22]

The present study took place in one of the many low- and middle-income countries where resources and scientific data are much scarcer. Highlighting this reality brings uniqueness to this article, making it meaningful in the literature.

Materials and Methods

This study involved a retrospective analysis of medical records of patients subjected to decompressive craniectomy for the treatment of malignant iS in a tertiary hospital in Distrito Federal, from January 2014 to December 2017. This research was approved by the research ethics committee of the Faculty of Medicine of Universidade de Brasília (CEP

–FM/UNB), having been approved on the Brazil Platform under the CAAE registration protocol 13501018.7.0000.555.

The inclusion criteria were as follows: individuals older than 18 years of age were included in the study, and the following variables were considered: a) age, b) gender, C) time between ictus and decompressive craniectomy, D) laterality of the iS, E) presence of preoperative aphasia, F) postsurgical complications, G) comorbidities, H) Glasgow coma scale (GCS) score on admission, I) Glasgow coma scale score in the preoperative period, J) preoperative pupillary diameter and L) prior chemical thrombolysis.

The exclusion criteria were as follows: A) patients younger than 18 years old, B) iS without involvement of the MCA, C) medical records with incomplete data, and D) traumatic iS.

Multivariate Cox regression models were used, and hazard ratios with 95% confidence intervals were calculated to analyze the intensity of the association between demographic and clinical variables and mortality. In this model, after the initial crude analysis, the variables associated with mortality, that is, $p < 0.25$, were included in the multivariate model.[23]

Kaplan-Meier estimators were used, and survival curves were constructed comparing age and postoperative complications (one group with pneumonia and other groups with pneumonia associated with other complications). Analyses were performed using the SAS 9.4 software (SAS Institute, Cary, NC, USA).

Results

The total sample had 87 patients, of whom 79 (90.8%) of the medical records met the inclusion criteria. Eight (9.2%) medical records were excluded (7 had incomplete data, and iS was of traumatic origin in 1 case). Of the 79 cases, there was a predominance of females, which corresponded to 60.76% (48/79) of the sample, compared with 39.24% (31/79) males; the mean age was 50.48 ± 11.75 years old.

In the percentage distribution of patients per age, the sample was 40% (32/79) in the group under 50 years; 35.44% (28/79) between 50 and 59 years; 21.25% (17/79) between 60 and 69 years old; and 2.5% (2/79) were between 70 and 79 years old.

Regarding laterality, 51.95% (41/79) were located in the left cerebral hemisphere, 46.75% (37/79) in the right cerebral hemisphere, and 1.3% (1/79) in both brain hemispheres. Of these, 49.37% (39/79) patients presented aphasia, and 8.86% (7/79) patients presented with anisocoria on admission. As for the cerebral dominance of 39 aphasic patients, 77% of the patients had left dominance (30/39), while 23% of the patients (9/39) had right dominance.

Fifty patients (63.29%) had hypertension, and 18 (22.78%) patients had diabetes mellitus. A minimal number of patients underwent previous chemical thrombolysis for the treatment of malignant stroke (9/79; 11.39%).

In the study, 39/77 patients (51%) were admitted to intensive care units. There were two losses due to the discontinuation of evolution in the medical record without confirmation of intensive care unit (ICU) admission. The mortality rate was 55.84% (43 cases). The interval between ictus and surgery was 2.21 ± 2.70 days.

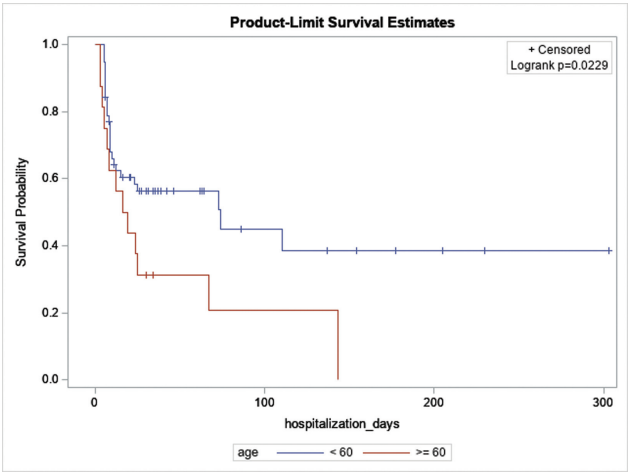

Fig. 1 Survival curve by age.

Of the patients who were admitted to the ICU, 26% (10/39) were under 40 years old; 26% (10/39) were between 40 and 49 years old; 28% (11/39) were between 50 and 59 years old; and 20% of patients (8/39) were over 60 years old;

Sixty-seven (84%) patients experienced postoperative complications. Thirty-three patients (42.86%) had pneumonia, and 19 (24.68%) had sepsis. Fifteen patients had other complications (10 patients progressed to surgical wound infection, and 5 presented brain death).

Regarding the level of consciousness, a mean score of 12 ± 3 was observed on admission, and, at the time of surgery, the score was 10 ± 3 points on the GCS. Survival over 300 days was significantly lower in patients aged 60 years or older ($p = 0.0229$) (►**Fig. 1**); these patients had a risk of death 2.71 times higher than that of patients younger than 60 years old ($p = 0.0041$) (►**Table 1**).

The log-rank test results showed that the survival probability of patients who only had pneumonia as a postoperative complication did not differ significantly from the survival probability of those who had other types of complications during the follow-up period ($p = 0.9987$).

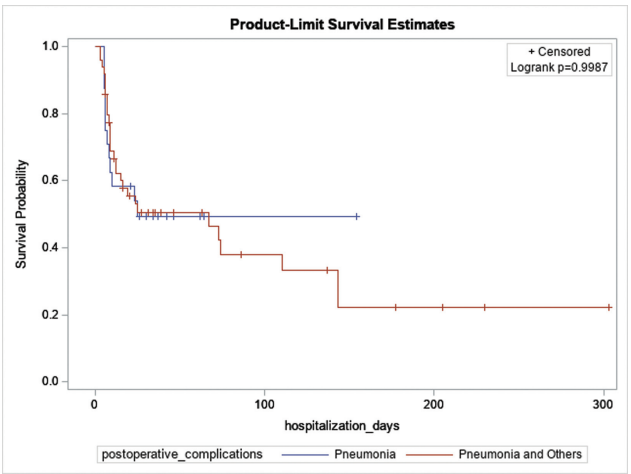

Fig. 2 Survival curve by postoperative complications.

Table 1 Crude hazard ratio and adjusted hazard ratio for mortality by selected demographic and clinical variables ($N = 73$) - Cox regression

	Hazard ratio - HR (95% CI)			
	Crude	*P*-value	Adjusted	*P*-value
Age		0.0294		0.0041
< 60	1	–	1	–
≥ 60	2.05 (1.07–3.92)	0.0294	2.43 (1.37–5.34)	0.0041
Gender		0.1020	–	–
Female	1	–	–	–
Male	1.67 (0.90–3.10)	0.1020	–	–
From ictus to surgery		0.1172		0.0526
≤ 2	1.93 (0.85–4.41)	0.1172	2.35 (0.99–5.57)	0.0526
> 2	1	–	1	–
Glasgow at surgery		0.0995		0.0411
≤ 8	1.68 (0.91–3.11)	0.0995	1.93 (1.03–3.65)	0.0411
> 8	1	–	1	–
Alteplase		0.0022		0.0012
No	1	–	1	–
Yes	3.83 (1.62–9.07)	0.0022	4.45 (1.81–10.97)	0.0012
Postoperative complication		0.9987		–
Pneumonia	1	–	–	–
Others complications	1.00 (0.50–1.98)	0.9987	–	–
ICU admission		0.6406	–	–
No	1.16 (0.63–2.14)	0.6406	–	–
Yes	1	–	–	–
Systemic arterial hypertension		0.6668	–	–
No	1	–	–	–
Yes	1.16 (0.60–2.24)	0.6668	–	–
Diabetes mellitus		0.2455	–	–
No	1	–	–	–
Yes	1.47 (0.77–2.82)	0.2455	–	–

Abbreviations: CI, confidence interval; ICU, intensive care unit.
A - age-adjusted, adjusted ictus until surgery, Glasgow at surgery and alteplase.

The use of alteplase showed a risk of death 4.45 times higher than when it was not used ($p = 0.0012$), and GCS score ≤ 8 was associated with a risk of death 1.93 times higher than when the GCS score was > 8 ($p = 0.0411$) (►**Table 1**). Patients older than 60 years of age had a risk of death 2.71 times higher than that of patients younger than 60 years old ($p = 0.0042$). In turn, patients with ictus ≤ 2 presented a risk of death 2.35 times greater than that of patients with ictus > 2, but this increase was not statistically significant ($p = 0.0526$).

Discussion

The present study evaluated the clinical-epidemiological variables associated with morbidity and mortality in patients undergoing decompressive craniectomy. These variables were age, gender, hypertension, diabetes, time from ictus to surgery, GCS score at surgery, previous infusion of alteplase, postoperative complications, and hospitalization or not in the ICU.

Vahedi, in a meta-analysis conducted in 2007, reported that patients who underwent surgery within 48 hours from ictus benefited from surgery and that the same benefit could not be proven after this period. The study also showed there was no additional benefit for the group operated on within 24 hours compared with the group operated on within 48 hours.[16] In our study, patients who underwent surgery within 48 hours after the event had a 2.35-fold higher mortality rate than those who underwent surgery after 48 hours of the the event; this result was not statistically significant ($p = 0.0526$). Most likely, those who underwent surgery within 48 hours after the event were considered more severe cases in the present study.

Regarding the mortality related to patient gender, our study showed a hazard ratio of 1.67 for males; however, $p = 0.10$, and the result was considered not significant. This result is consistent with a study of Campos et al (2011), in which they stated that gender does not have statistically significant predictive value to determine the course of cerebral stroke.[24]

There are reports in the literature indicating that clinical deterioration, evaluated by the decrease in GCS score from admission to surgery,[25] and age are relevant factors for worse outcomes.[26]

Koh et al. showed that outcomes were better when clinical deterioration of the preoperative GCS score remained at 9 or higher (66% favorable, 33% unfavorable) compared with when the GCS deteriorated to 8 or less (28% favorable, 72% unfavorable). The outcome was based on the Glasgow outcome score (GOS); a favorable outcome was a GOS between 4 and 5 (moderate or mild disability), and poor outcome was a GOS between 1 and 3 (death, vegetative state, or severe disability).[27]

Kilincer et al. showed that a presurgical GCS score lower than 8 is an important determinant of an unfavorable outcome, and that modified rank between 0 and 3 was associated with favorable outcomes, and modified rank between 4 and 6 was associated with unfavorable outcomes.[28]

In our study, patients with GCS scores equal to or lower than 8 had a risk of death 1.93 times higher than that of patients with GCS scores above 8 ($p = 0.0411$). These data have been important for not delaying the surgical approach until neurological deterioration occurs. No functional evaluation of the patients was performed; only a mortality variable was considered as a poor outcome.

In the present study, patients 60 years old or older presented a risk of death 2.71 times higher than that of patients younger than 60 years old ($p = 0.0041$). According to the log-rank test, the survival probability of patients 60 years old or older over the follow-up period of 300 days was significantly lower ($p = 0.0229$), which is in line with results reported by Arac et al. in 2009. In the review by Arac et al., the mortality rate was significantly higher in the group older than 60 years old (37 of 72 patients, 51.3%) than in the group 60 years old or younger (41 of 197 patients, 20.8%) ($p < 0.0001$).[29]

This fact can be explained by the following factors: advanced age, that is, patients older than 50 years old, may have an effect on the brain's ability to compensate for the effects of a stroke; however, these individuals tend to have additional comorbidities that increase the risk of poor prognosis and death. In turn, young patients can expect better outcomes and receive aggressive care, and they are more resilient to medical comorbidities that directly affect long-term outcomes.[30] However, the lack of atrophy may cause intolerance to extensive edema.[26,31,32]

Age is the most important risk factor for the development of a stroke. While the risk of stroke in the general population is $\sim$ 0.25% per year, this number doubles every decade for individuals older than 50 years old. At the age of 85 years old, the stroke incidence rate reaches 3.5%/year.[33] Regardless of other factors, age is an independent predictor of poor outcomes. The upper age limit for performing decompressive craniectomy has also been discussed considering the risk-benefit of the procedure.[26]

In a prospective, randomized, controlled study, Zhao et al. compared patients with malignant iS aged 18 to 80 years old who underwent decompressive craniectomy with those in the same age group who did not. Their results showed that there was benefit of undergoing craniectomy within 48 hours, even for patients in more advanced age groups.[34] However, approximately two thirds (18/29) of patients older than 60 years old were between 61 and 70 years old. Only 11 patients (4 randomized for surgery) were in the oldest subcohort, whose ages ranged between 71 and 80 years old. Although there are several studies indicating less beneficial effects for elderly patients, there has been a paucity of controlled prospective randomized studies.[35]

Eighteen patients (22.78%) had diabetes mellitus, and 50 (63.29%) had systemic arterial hypertension (SAH). These data are important because systolic and diastolic pressure levels are exponentially associated with the development of cerebrovascular disease. [36] However, the results of the multivariate analysis were not statistically significant in relation to the mortality of patients with hypertension and diabetes.

Providing life-saving treatment for major infarcts in the dominant hemisphere is a controversial topic in the literature. The main concern has been that heroic interventions can leave patients with an unacceptably low quality of life because of aphasia.[26] Data from the literature review, Gupta el al., however, do not restrict the surgical approach to the nondominant hemisphere. The functional outcomes among the 27 patients who underwent decompression of the dominant hemisphere was no worse than among the 111 patients who underwent decompression on the nondominant side.[26]

Among patients who suffer stroke, aphasia is the most prevalent language disorder among the total number of patients treated in the hospital environment.[37] The frequency of aphasia among patients who have suffered stroke is 21 to 38%.[38] There was a high prevalence of patients with aphasia in the present study, that is, 40 patients, corresponding to 50.63% of the patients, which is the largest result found in the literature.

Patients who used alteplase exhibited a 4.45 times higher risk of death than those who did not use the thrombolytic agent ($p = 0.0012$). The risk of death was related to increased bleeding and surgical morbidity. Nine patients underwent thrombolysis prior to surgery, corresponding to 11.39% of the total population studied. This percentage of patients with thrombolysis was probably higher than expected, given that extensive iSs are contraindicated for venous thrombolysis. This can be explained by the unavailability of magnetic resonance imaging (MRI) in the emergency department, which is a more sensitive imaging test for the early diagnosis of iS than computed tomography. [39] It is not possible to determine from this study or from the existing literature whether the increase in mortality caused by the previous use of alteplase would lead this group of patients to be ineligible for decompressive craniectomy.

Conclusion

Decompressive craniectomy for the treatment of malignant iS is a consolidated and effective surgical intervention; however, this clinical entity still has a significant mortality rate, despite this procedure increasing patient survival.

Age can be a tool to help guide surgical decisions because elderly patients have a significantly higher mortality rate. However, the treatment must be individualized, as a GCS score lower than 8 is also associated with higher mortality. Age over 60 years and GCS values below 8 were statistically correlated with an unfavorable prognosis.

Conflict of Interests

The authors have no conflict of interests to declare.

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Analysis of Myelomalacia and Posterior Longitudinal Ligament Ossification as Prognostic Factors in Patients with Cervical Spondylotic Myelopathy Submitted to Laminoplasty

Análise de mielomalácia e ossificação do ligamento longitudinal posterior como fatores prognósticos em pacientes com mielopatia espondilótica cervical submetidos a laminoplastia

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Abstract

Background Cervical spondylotic myelopathy is a degenerative disease of the intervertebral disc and the vertebral body of the spine that causes cervical spinal cord injury due to central vertebral canal stenosis. Its prevalence is higher in the elderly. Treatment is usually surgical when the spinal cord is affected either clinically with pyramidal release or radiologically with the altered spinal cord.

Objective The goal of the present study is to analyze the myelomalacia and the ossification of the posterior longitudinal ligament as prognostic factors in the postoperative evolution of patients with cervical canal compression who underwent laminoplasty with the open- or French-door techniques.

Methods We performed a retrospective analysis of 18 surgical cases of spondylotic cervical myelopathy of the same senior neurosurgeon, using the chi-squared test to analyze prognostic factors for patients' postoperative evolution in the Nurick scale, after open-door or French-door laminoplasty.

Findings The comparison between the pre and postoperative showed an improvement of 71.43% in cases that did not have ligament ossification compared with 45.45% of cases that presented posterior longitudinal ligament ossification. Also, there was a

Keywords
- cervical spondylotic myelopathy
- myelomalacia
- ossification of posterior longitudinal ligament
- laminoplasty
- prognostic factors

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better prognosis in patients without myelomalacia, as 71.43% of them improved their condition against only 45.45% of improvement in those with myelomalacia.

Conclusion There is a need for further studies with larger samples to expressively prove that the presence of longitudinal ligament ossification and the previous presence of myelomalacia are factors that can lead to worse prognosis in the postoperative evolution of patients with cervical spondylotic myelopathy submitted to laminoplasty.

Resumo

Introdução A mielopatia espondilótica cervical é uma doença degenerativa do disco intervertebral e do corpo da coluna vertebral que causa lesão da medula espinhal cervical devido à estenose do canal vertebral central. Sua prevalência é maior em idosos. O tratamento geralmente é cirúrgico quando a medula espinhal é afetada clinicamente com a liberação piramidal ou radiologicamente com a medula espinhal alterada.

Objetivo Este estudo tem como objetivo analisar a mielomalácia e a ossificação do ligamento longitudinal posterior como fatores prognósticos na evolução pós-operatória de pacientes com compressão do canal cervical submetidos à laminoplastia pelas técnicas de porta aberta ou porta francesa.

Métodos Foi realizada uma análise retrospectiva de 18 casos cirúrgicos de mielopatia espondilótica cervical do mesmo neurocirurgião sênior, utilizando o teste do qui-quadrado para analisar os fatores prognósticos da evolução pós-operatória dos pacientes na escala de Nurick, após laminoplastia aberta ou francesa.

Resultados A comparação entre o pré e pós-operatório mostrou uma melhora de 71,43% nos casos que não apresentavam ossificação ligamentar em comparação com 45,45% nos casos que apresentavam ossificação do ligamento longitudinal posterior. Além disso, houve um melhor prognóstico em pacientes sem mielomalácia, pois 71,43% deles melhoraram sua condição contra apenas 45,45% de melhora naqueles com mielomalácia.

Conclusão Há necessidade de mais estudos com amostras maiores para comprovar expressivamente que a presença de ossificação ligamentar longitudinal e a presença prévia de mielomalácia são fatores de pior prognóstico na evolução pós-operatória de pacientes com mielopatia espondilótica cervical submetidos à laminoplastia.

Palavras-chave
- mielopatia espondilótica cervical
- mielomalácia
- ossificação do ligamento longitudinal posterior
- laminoplastia
- fatores prognósticos

Introduction

Cervical spondylotic myelopathy is a degenerative disease of the intervertebral disc and the vertebral body of the spine that causes cervical spinal cord injury due to central vertebral canal stenosis, being the most common cause of cervical spinal involvement in adults.[1] Its clinical picture can be presented with a change in gait, difficulty in performing fine movements and in controlling the sphincter; besides, the neurological examination reveals hyperreflexia in the limbs and changes in proprioceptive sensitivity. Genetic, environmental, and biochemical factors have been implicated in the development of this disease, which is of high prevalence in the Asian population.[2–4] The prognosis is related to factors such as time of disease progression—the longer, the greater the impairment—and the age of the patients—with worse prognosis in the elderly.[1]

The evolution of cervical myelopathy may be unpredictable; 75% of patients discontinuously get worse after several years of stability, 20% progressively develop the disease over a short amount of time, and 5% have a catastrophic evolution with severe acute decompensation after minor trauma or even without any apparent cause. Thus, different surgical techniques have been suggested to address cervical spondylotic myelopathy: anteriorly, anterolaterally, and posteriorly.[1] It should be noted that some factors impact the patients' evolution after surgery, among them, myelomalacia and ossification of the posterior longitudinal ligament (OPLL), the factors under analysis in this study.

In cases of multilevel cervical stenosis with preservation of the lordotic curvature, laminoplasty is indicated, as well as in situations of posterior longitudinal ligament thickening or ossification, posterior comprehension of the spine cord by the flavum ligament, limiting factors of the anterior route such as the short neck and multiple levels (above 3). When laminectomy is contraindicated due to the risk of lordosis accentuation or risk of C5 paralysis syndrome, laminoplasty is considered a better option. This intervention aims to provide spine cord decompression, prevent instability, beneficially decrease movement rate by up to 50%, prevent kyphosis, a complication of laminectomy, and

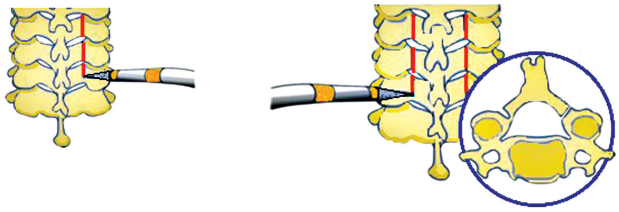

Fig. 1 Drawing showing the groove and the bone cut, to be able to rotate in a block and to place ceramic bone or bone graft between the blade and lateral mass

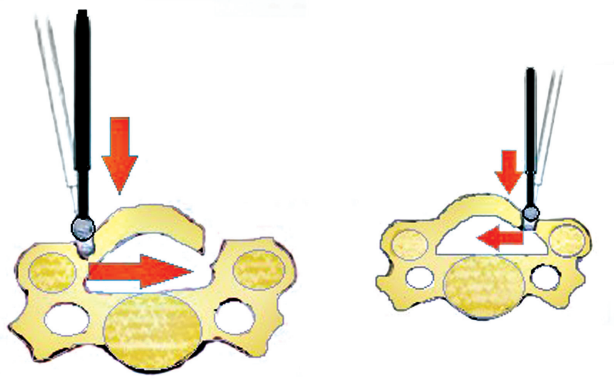

Fig. 2 Channel opening and green branch fracture

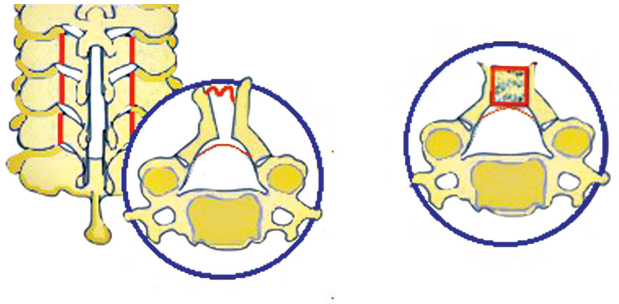

Fig. 3 The median opening of the spiny apophysis showing the opening in French-door

prevent perimedullary fibrosis and the risks of the lateral mass screw.

The vast majority of neurosurgeons use the posterior approach of laminoplasty if the patient has the involvement of several levels—3 or more.[5] For this approach, there is the open-door laminoplasty technique (images 1 and 2), described by Hirabayashi in 1981[6] and modified over the years, and there is the French-door laminoplasty technique (image 3), published by Hukuda et al. (1985)[7] and Hase et al. (1991)[8] and modified over decades by other authors.

The objective of this study is to analyze the myelomalacia and the OPLL as prognostic factors in the postoperative evolution of patients with cervical canal compression who underwent laminoplasty by open-door or French-door techniques (►**Figs. 1** to **3**).

Table 1 Nurick myelopathy scale

Nurick scale	Patient's situation
0	Patient has signs and symptoms of root involvement but no spinal cord disease
1	Patient has signs of spinal cord disease with difficulty
2	Patient has slight difficulty walking that does not prevent full-time employment
3	Patient has difficulty walking that prevents full-time employment or completion of daily tasks, but does not require assistance with walking
4	Patient is able to walk only with a walker or human assistance
5	Patient is chairbound or bedridden

*Based on Nurick, 1972.

Methods

Cases of 18 patients operated by the same senior neurosurgeon between 1998 and 2019 were reviewed. The study is composed of 14 male and 4 female participants, with a minimum age of 45 and a maximum age of 82 years (average age 66.5); 2 patients were characterized as brown, 11 as Caucasian, and 5 as Asian. They were analyzed according to the presence or absence of posterior longitudinal ligament calcification from pre and postmagnetic resonance image scans used to identify myelomalacia. The individuals were classified and divided according to the Nurick myelopathy scale (►**Table 1**).

To compare the individuals before and after surgery, their clinical aspects were listed (►**Table 2**), taking into consideration their basic information, as well as the pre and postoperative status that was listed according to the MRI evaluation. The baseline characteristics of our subjects were also organized (►**Table 3**). Then, we used the chi-squared test to examine the association of myelomalacia's or posterior longitudinal ligament ossification's presence in the patients' postoperative evolution in the Nurick classification.

Results

First, examining the interaction between the presence or absence of myelomalacia and the subjects' postoperative evolution in the Nurick scale, after laminoplasty (►**Table 4**), it was possible to note that, regarding patients who previously had myelomalacia, 45.45% of them improved their condition, while 27.27% had no change, and another 27.27% got worse.

Regarding the participants who did not have myelomalacia, 71.43% evolved to better Nurick classification and 28.57% remained unchanged, but no patient got worse.

When analyzing the evolution of patients with previous OPLL, after laminoplasty (►**Table 5**), it was possible to note an improvement in 45.45%, worsening in 18.18% of cases, and

Table 2 Clinical features

Patient	Ethnicity	Sex	Age	Ligament Calcification	Preoperative Nurick	Technique	Postoperative Nurick	Preoperative MRI	Postoperative MRI	Additional surgery	Follow up
EO	Asian	M	45	Existent	I	Open-door	III	With myelomalacia	Unchanged	Laminectomy	48 months
OER	Caucasian	M	73	Absent	III	Open-door	I	With myelomalacia	Unchanged	–	26 months
CMK	Asian	M	63	Existent	III	Open-door	I	Without myelomalacia	Unchanged	Anterior way	84 months
CAS	Caucasian	M	74	Existent	II	Open-door	I	Without myelomalacia	Unchanged	Anterior way	168 months
VM	Caucasian	M	61	Existent	III	Open-door	II	With myelomalacia	Unchanged	Anterior way + lateral mass	24 months
CBM	Caucasian	W	74	Absent	II	Open-door	III	With myelomalacia	Unchanged	Arcochristectomy	180 months
HER	Brown	M	55	Absent	III	Open-door	II	With myelomalacia	Unchanged	–	84 months
VK	Asian	W	55	Existent	I	Open-door	I	With myelomalacia	Unchanged	–	216 months
CAC	Caucasian	M	53	Existent	III	French-door	I	Without myelomalacia	Unchanged	–	72 months
ATS	Asian	M	56	Existent	II	French-door	I	With myelomalacia	Unchanged	Anterior way	132 months
LAP	Caucasian	M	56	Existent	I	French-door	I	Without myelomalacia	Unchanged	–	Lost follow up
ET	Caucasian	M	60	Absent	I	French-door	I	Without myelomalacia	Unchanged	Anterior way	120 months
FS	Caucasian	M	50	Existent	III	French-door	III	With myelomalacia	Unchanged	Anterior way	120 months
HH	Asiatic	W	55	Existent	III	French-door	III	With myelomalacia	Unchanged	–	Death 2019
CFG	Brown	M	76	Existent	IV	French-door	V	With myelomalacia	Unchanged	Anterior way	Death 2005
AT	Caucasian	W	75	Absent	II	French-door	I	Without myelomalacia	Unchanged	Later Tie	Alzheimer 10 years ago
CB	Caucasian	M	82	Absent	III	French-door	I	With myelomalacia	Unchanged	–	36 months
MRG	Caucasian	M	67	Absent	II	French-door	I	With myelomalacia	Unchanged	Anterior way	60 months

Table 3 Baseline characteristics

VARIABLES	n	%
GENDER		
Male	14	77.78
Female	4	22.22
ETHNICITY		
Asiatic	5	27.78
Caucasian	11	61.11
Brown	2	11.11
LIGAMENT CALCIFICATION		
Existent	11	61.11
Absent	7	38.89
MYELOMALACIA (MRI)		
Existent	11	61.11
Absent	7	38.89
TECHNIQUE		
Open-door	8	44.44
French-door	10	55.56
PREOPERATIVE NURICK		
I	4	22.22
II	5	27.78
III	8	44.44
IV	1	5.56
POSTOPERATIVE NURICK		
I	11	61.11
II	2	11.11
III	4	22.22
IV	0	0.00
V	1	5.56
AGE	**MEAN (sd)**	**min–max**
	62.78 (10.64)	45–82

Abbreviations: MRI, magnetic resonance imaging; sd, standard deviation.

Table 4 Patient's evolution/presence of myelomalacia

MYELOMALACIA	PATIENT'S EVOLUTION			*p*
	Better n (%)	No change n (%)	Worse n (%)	
Existent	5 (45.45)	3 (27.27)	3 (27.27)	0.297
Absent	5 (71.43)	2 (28.57)	0 (0.00)	

36.36% did not show any change in the Nurick scale. Moreover, for those who did not previously present OPLL, the evolution in the postoperative period was 71.43% for a better prognosis, 14.14% showed worsening after surgery, and 14.29% did not show a significant change in evolution.

Regarding the techniques used (►**Table 6**), 62.50% of individuals who underwent laminoplasty with the open-door technique had an evolution in their condition, reducing their Nurick classification; on the other hand, 25% worsened the condition, and 12.5% had no changes. For those who underwent laminoplasty with the French-door technique, there was an evolution in 50% of cases, no change in 40%, and worsening in 10%.

Table 5 Patient's evolution/presence of posterior longitudinal ligament ossification

LIGAMENT OSSIFICATION	PATIENT'S EVOLUTION			*p*
	Better n (%)	No change n (%)	Worse n (%)	
Existent	5 (45.45)	4 (36.36)	2 (18.18)	0.520
Absent	5 (71.43)	1 (14.23)	1 (14.29)	

Table 6 Patient's evolution/surgical techniques

TECHNIQUE	PATIENT'S EVOLUTION			*p*
	Better n (%)	No change n (%)	Worse n (%)	
Open-door	5 (62.50)	1 (12.50)	2 (25.00)	0.380
French-door	5 (50.00)	4 (40.00)	1 (10.00)	

Discussion

Success in the surgical treatment of the patient with spondylotic cervical myelopathy is highly dependent on the previous factors presented by the patient. Some studies analyzed and demonstrated the postoperative evolution taking into account the patient's age, smoking history, compromised levels, and cervical spine instability.[9]

Our study, on the other hand, sought to analyze the operative evolution of patients with myelopathy, taking into account the previous condition of OPLL or its absence, as well as the existence of myelomalacia, classifying them through the Nurick scale (1972) in the pre and postoperative periods.

Ossification of the posterior longitudinal ligament is a hyperostotic condition of the spine, in which the posterior longitudinal ligament becomes progressively calcified, usually leading to symptomatic stenosis of the spinal canal.[2,10,11]

Our study tried to identify the presence of calcification in the ligament as a factor of worse prognosis. This can be explained by the greater spinal cord injury caused during surgery, since the presence of the calcified content may promote more spinal cord injury when removed as it is commonly densely adherent to the underlying dura. Miyakoshi et al.,[12] for example, described dural adhesions as a deleterious factor for preoperative and short-term postoperative neurological evolution.

Myelomalacia, on the other hand, is characterized by the condition of softening of the spinal cord, which occurs due to ischemia in the spinal cord caused by an episode of hemorrhage or poor local circulation.

It was possible to identify, in our results, that there was a significant evolution according to the Nurick scale in patients who previously had myelomalacia, as they were classified between classes II and III in the preoperatory, and then reclassified as class I after surgery. However, there was a worse prognosis of evolution for cases whose initial Nurick classification was already high, presenting worsening in the classification after laminoplasty (evolving from IV to V postoperatively).

This can be explained by the different presentation of the spinal cord resulting from advanced myelomalacia, which leads to greater difficulty in the surgical procedure. Besides, myelomalacia is responsible for neurological injuries, which in addition to altering the structure of the spinal cord may result in a worse prognosis for patients undergoing laminoplasty.

Regarding the laminoplasty techniques, anterior decompression is a procedure of greater technical difficulty and with potential risk of complications.[13] There is a possibility of damage to the dura mater and possible postoperative cerebrospinal fluid fistula in the anterior access. Epstein NE (1994)[14] reviewed 112 patients with OPLL who underwent surgical treatment and found better results in those undergoing posterior decompression; for this reason, the posterior access was the route used in the patients in the present study. However, it was possible to note in our results that the use of open- or French-door technique did not interfere in the subjects' postoperative evolution.

Laminoplasty is still the technique of choice when the patient has OPLL and/or myelomalacia. And although it is possible to observe a certain evolution in patients submitted to laminoplasty based on the Nurick classification, as presented in the analysis of the cases, the patient's previous condition needs to be carefully evaluated, concerning the mentioned factors, for better surgical preparation.

It is worth highlighting that our study was limited by the difficulty in gathering a large sample of patients with the conditions that we sought to analyze, which is something that can also be noticed as a limiting factor in other studies described in the literature.

Conclusion

Concluding, it was possible to identify, statistically, that there was no significant discrepancy in the postoperative prognosis for those patients who previously had longitudinal ligament ossification or/and myelomalacia. However, if the study had a larger number of cases, the tendency could be to reveal a worse prognosis for individuals who preoperatively had both characteristics analyzed.

Therefore, besides the necessity of further studies, with larger sample sizes, to confirm this issue, the presence of OPLL as well as the previous presence of myelomalacia may be considered worse prognostic factors, individually or when both are present, in patients with spondylotic cervical myelopathy submitted to laminoplasty, especially when the patient's preoperative Nurick classification is already high.

Conflict of Interests

The authors have no conflict of interets to declare.

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Prognosis in Traumatic Brain Injury

Indicadores prognósticos no trauma cranioencefálico

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Abstract

Objective To characterize the profile of TBI victims who required neurosurgical approach in two reference hospitals in the metropolitan area of Florianópolis, state of Santa Catarina, Brazil, and to identify the prognostic increase in the Pupil Reactivity Score when subtracted from the Glasgow Coma Score, found in the Glasgow-P. Additionally, to present demographic, etiological, clinical, and tomographic data, and associate them with the outcome of death.

Methods Medical record data and computed tomography (CT) scans of patients with TBI undergoing neurosurgical procedures from January 2014 to April 2019, at 2 reference hospitals in the metropolitan area of Florianópolis, state of Santa Catarina, Brazil – Hospital Regional de São José Dr. Homero de Miranda Gomes (HRSJ-HMG, in the Portuguese acronym) and Hospital Governador Celso Ramos (HGCR, in the Portuguese acronym).

Results The results of the 318 cases studied indicated that the male gender predominated (87.7%). The most affected age group was between 35 and 65 years old (47.5%). The main cause was motorcycle accidents (26.1%), followed by a fall from a height (16.4%). Most patients required admission to the intensive care unit (ICU) (85.8%), with an average duration of 13 days. The average total hospital stay was 28 days. Most cases needed external ventricular drain (EVD) (64.8%). The predominant tomographic classification was Marshall II (43.4%), followed by Marshall IV (26.1%). Most patients presented with extra-axial hematoma (64.2%), with subdural hematoma (SDH) being the most frequent (45%). Most patients presented with sequelae at hospital discharge (43.4%).

Conclusion There was no clinically relevant increase between the Glasgow and Glasgow-P scores for the tested outcomes (need for decompressive craniectomy, midline shift, presence of basal cisterns obliteration, need for ICU admission, and death).

Keywords
- traumatic brain injury
- neurosurgery
- prognosis
- prevention and control
- epidemiology

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Resumo

Objetivos Caracterizar o perfil das vítimas de trauma cranioencefálico (TCE) que necessitaram de abordagem neurocirúrgica em dois hospitais de referência na Grande Florianópolis, SC, Brasil, e identificar o incremento prognóstico do Escore de Reatividade Pupilar quando subtraído do Escore de Coma de Glasgow, resultando no Glasgow-P. Ademais, apresentar dados demográficos, etiológicos, clínicos e tomográficos, e associá-los ao desfecho óbito.

Métodos Foram analisados dados de prontuários e exames tomográficos de pacientes com TCE submetidos a procedimentos neurocirúrgicos no período de janeiro de 2014 a abril de 2019, em 2 hospitais de referência na Grande Florianópolis – Hospital Regional de São José Dr. Homero de Miranda Gomes (HRSJ-HMG) e Hospital Governador Celso Ramos (HGCR).

Resultados Para os 318 casos analisados, os resultados mostraram que o sexo masculino predominou (87,7%). A faixa etária mais acometida foi de 35 a 65 anos (47,5%). A principal causa foi acidente motociclístico (26,1%), seguido por queda de nível (16,4%). A maioria dos pacientes necessitou de internação na unidade de tratamento intensive (UTI) (85,8%), com duração média de 13 dias. O tempo médio total de internação hospitalar foi de 28 dias. Houve necessidade de derivação ventricular externa (DVE) na maior parte dos casos (64,8%). A classificação tomográfica predominante foi Marshall II (43,4%), seguida pelo Marshall IV (26,1%). A maioria dos pacientes apresentou hematoma extra-axial (64,2%), sendo o hematoma subdural (HSD) o mais frequente (45%). A maoria dos pacientes apresentou sequelas na alta hospitalar (43,4%).

Conclusão Não houve um incremento clinicamente relevante entre os escores Glasgow e Glasgow-P para os desfechos testados (necessidade craniectomia descompressiva, desvio da linha média (DLM), presença de obliteração de cisternas basais, necessidade de internação em UTI e óbito).

Palavras-chave

- traumatismos craniocerebrais
- neurocirurgia
- prognóstico
- prevenção
- epidemiologia

Introduction

The Center for Disease Control and Prevention (CDC) defines traumatic brain injury (TBI) as a change in normal brain function caused by external forces or penetrating head injury.[1] Considered a "silent epidemic," TBI is the leading cause of death and disability in children and young adults worldwide, being involved in almost half of all deaths from trauma.[2] Many years of productive life are lost and many people suffer years with disability after brain injury, with a predicted burden that exceeds that of conditions such as cerebrovascular disease and dementia.[3]

Traumatic brain injury is a disorder that affects 50 million people each year and more than half of the population of the world throughout their lifetimes, with enormous economic consequences for individuals, families, and the society. Costs relating to the TBI in Europe in 2010 were estimated at € 33 billion,[4] and in the US, estimates reported costs ∼ USD 60.4 billion.[5]

The incidence and mortality rates of traumatic brain injury vary widely across countries and regions. In low-income countries, the highest incidence is related to traffic accidents; however, in high-income countries, TBI increasingly affects elderly people, mainly due to falls.[6]

According to data from the Hospital Information System of the Informatics Department of the Unified Health System (SIH/DATASUS, in the Portuguese acronym),[7] during the study period – from January 2014 to April 2019–there were 16,639 admissions due to external causes at the Hospital Regional de São José Doutor Homero Miranda Gomes (HRSJ-HMG, in the Portuguese acronym) and, among these, 385 evolved to death. In the Hospital Governador Celso Ramos (HGCR, in the Portuguese acronym), 12,490 admissions due to external causes were registered, with 207 deaths. In the period from 2014 to 2018, there was an increase of ∼ 17.8% in the number of admissions due to external causes in the study hospitals, with a reduction of ∼ 20.9% between 2018 and 2019, and when considering the total period, from 2014 to 2019, the reduction was of 6.8%. The increase was the most significant between 2015 and 2016, totaling an increase of ∼ 10% in the number of hospitalizations. The total cost related to external causes in both hospitals during the study period was BRL 45,621,725, with an average cost per hospitalization of BRL 1,566.20.[7]

Even knowing the limitations of databases, which result from underreporting, the relevance of this topic is evident, both for health and for the economy, mainly because TBI is largely avoidable. In this sense, the benefits of reducing its occurrence are comprehensive, so prevention measures should be instituted. In this context, robust epidemiological data are essential to quantify the public health burden caused by TBI, aiming to inform prevention policies and the understanding of healthcare needs, in addition to the appropriate allocation of health funds.

Objectives

To characterize the profile of TBI victims who required neurosurgical approach in two reference hospitals in the metropolitan area of Florianópolis, state of Santa Catarina, Brazil, and to identify the prognostic increase in the Pupil Reactivity Score (PRS) when subtracted from the Glasgow Coma Score (GCS), found in Glasgow-P (GCS-P). Additionaly, to present demographic, etiological, clinical, and tomographic data, identifying its overall distribution and profile regarding the gender, age group, and severity of the TBI, in addition to associating them with the outcome of death during the in-hospital stay.

Methods

All procedures performed in the present work complied with the norms established by Resolution 466/12 of the National Health Council of Brazil (CNS, in the Portuguese acronym), whose function is to regulate research involving human beings. After the research was approved by the Plataforma Brasil database and was authorized by the Committee on Ethics in Research of the HGCR and of the HRSJ-HMG – with the Certificates of Presentation of Ethical Appreciation, respectively, 18212819.4.3001.5360 and 18212819.4.3002.0113–, data were collected from electronic medical records and a spreadsheet elaborated for the present study was completed.

This is a retrospective, analytical, longitudinal, and multicenter cohort study based on the analysis of data from electronic medical records and computed tomography (CT) of patients with TBI undergoing neurosurgical procedures from January 2014 to April 2019 in 2 reference hospitals in the metropolitan area of Florianópolis (HRSJ-HMG and HGCR).

The Micromed system (Joinville, SC, Brazil) was used to collect data in both hospitals and, to obtain the skull CTs, the Integrated System of Telemedicine and Telehealth (Sistema de Telemedicina Catarinense [Florianópolis, SC, Brazil]) was used, and measurements were performed using the Weasis Medical Viewer (University Hospital of Geneva, Switzerland), version 3.6.2.

The initial sample includes all of the following codes of neurosurgical procedures among patients with TBI from January 2014 to April 2019:

1. Surgical treatment of extradural hematoma (0403010276)
2. Surgical treatment of intracerebral hematoma (0403010284)
3. Surgical treatment of intracerebral hematoma with complementary technique (0403010292)
4. Surgical treatment of acute subdural hematoma (0403010306)
5. Surgical treatment of chronic subdural hematoma (0403010314)
6. Surgical treatment of depressed skull fracture (0403010268)
7. Cranial trepanation for neurosurgical propaedeutics / intracranial pressure (ICP) monitoring (0403010349)
8. Decompressive craniectomy (0403010020)
9. External ventricular drainage (0403010098)

The ►**Fig. 1** and ►**Fig. 2** shows the sampling flow.

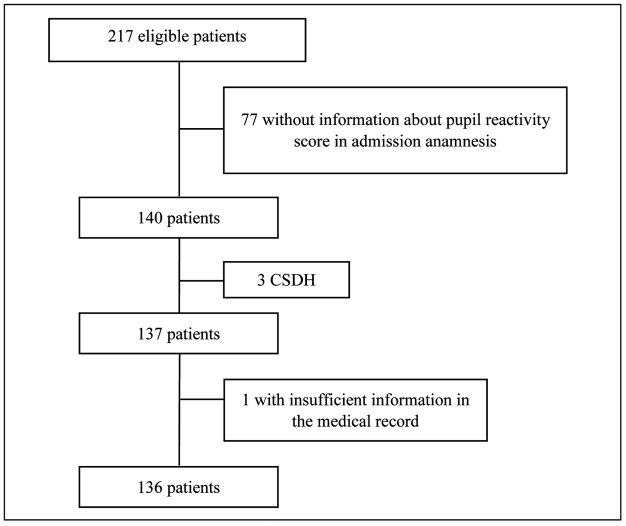


Fig. 1 HRSJ-HMG exclusion flowchart.

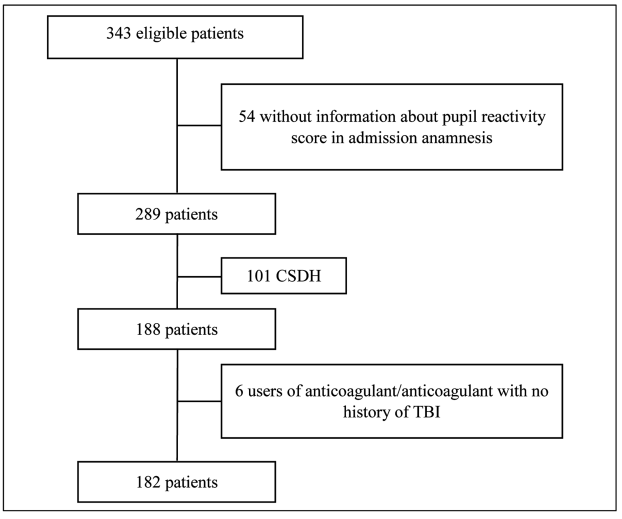


Fig. 2 HGCR exclusion flowchart.
Abbreviation: CSDH, chronic subdural hematoma.

Statistical Analysis

The final database contained 318 patients and, to carry out the descriptive analysis of the categorical variables of interest, the absolute and relative frequencies were used, while in the description of the numerical variables, position measures, central trend and dispersion were used.

Different tests were performed via univariate analysis to verify the association between the variables of interest and the Glasgow Coma Scale (GCS) and Glasgow Coma Scale - Pupils score (GCS-P), as well as in relation to the death outcome. Thus, for categorical variables, the Fisher exact test and the chi-squared test were used; numerical variables, the Mann-Whitney test and the Kruskal-Wallis test were used.

To correlate the GCS and the GCS-P with numeric and ordinal variables, Spearman correlation and a simple linear regression were used.

A logistic regression was also adjusted for the study of varying outcome with dichotomous behaviors and the construction of receiver operating characteristic (ROC) curves, and the Backward method was used for the selection of variables (procedure to remove, at a time, the highest value variable, repeating the procedure until there are only significant variables in the model). Additionally, significance was set at 5% and Pseudo R^2, Maximum variance inflation factor (VIF), and Hosmer-Lemeshow test statistics have been used to check the model adjustment quality.

To verify whether the adjusted models were adequate and had good predictive ability, some fit quality measures were calculated, as follows: area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC).

The software used in statistical analyzes was R Studio, version 3.6.0 (R Foundation, Vienna, Austria).

Results

The descriptive analysis of the categorical variables demonstrated that males predominated among patients (87.7%). The most affected age group was between 35 and 65 years old (47.5%), with a mean age of $\sim$ 41 years old, and half of the patients were $\leq$ 36 years old. The day with the highest number of cases was Sunday (20.1%), the month was May (11.6%), and the quarter was the 2nd of the year (29.9%). The causes of TBI were motorcycle accidents (26.1%), ground level fall (16.4%), falls from one's own height (14.2%), running over (12.3%), aggression (11%), automobile accident (9.4%), gunshot (2.8%), and others (7.9%). Most patients had severe TBI (53.1%) at hospital admission. Most of them did not have associated traumatic injuries (48.4%); however, when there was an associated injury, in general, they were multiple injuries (27.4%). When there was an isolated injury, besides TBI, orthopedic trauma was predominant (8.2%).

Most patients needed hospitalization at the ICU (85.8%), with a duration from 8 to 14 days of hospitalization (21.4%), with a mean duration of 13 days (6 patients were not recorded in this calculation because they had been transferred to other hospitals). Regarding the total time of hospital stay, most patients (23.8%) stayed up to 7 days, with an average time of $\sim$ 28 days (although it is important to point out that 3 patients were not considered in this statistic because they had been transferred). Most patients survived (65.7%); however, 43.4% of them had sequelae at hospital discharge, most of which were multiple sequelae (23.3%). Regarding isolated sequelae at hospital discharge, the most frequent was physical sequela (6.6%), followed by cognitive ones (4.7%), and by the absence of interaction with the environment (4.7%). Intracranial pressure monitoring was necessary in most cases (64.8%). The predominant Marshall CT classification was Marshall II (43.4%), followed by Marshall IV (26.1%). Most patients presented with extra-axial hematoma (64.2%), and acute subdural hematoma (ASDH) was the most frequent (45%). The midline shift (MLS) was 4.14 mm, and the greatest was 26 mm; however, in 15 patients it was not possible to measure the MLS as it was possible to retrieve the skull CT images (►**Tables 1**, **2**, and **3**).

Aiming to study how lethality was characterized within the two hospitals studied, its behavior was observed according to the periods presented in the database. Thus, it can be observed that the total lethality was 31.76%. The year with the highest lethality during the study period was 2018, with a lethality of 45.45%, and the quarter with the highest lethality was the 4th quarter, with a lethality of 36.36%.

In the univariate analysis, the chi-squared test and the Fisher exact test were used to compare the variables with deaths and, to calculate the 95% confidence interval (CI) for the odds ratio (OR), a logistic regression was used for each of the variables, considering death as the outcome variable.

The analysis showed that individuals with moderate TBI had a 74% increase in the chance of death (OR = 1.74; 95%CI: 1.17–2.59; $p = 0.013$) when compared with mild TBI. There was a significant association ($p = 0.038$) between the GCS-P and death, and most patients (87.8%) with a GCS-P of 15 did not die. In addition, the OR showed that each one-unit increase in the GCS-P was associated with an average 7% decrease in the risk of death.

There was a significant association ($p = 0.048$) between the presence of subarachnoid hemorrhage (SAH) and death, and most individuals (73.7%) who did not have SAH did not die either. Patients who required external ventricular drain (EVD) had a 175% increase in the chance of death (OR = 2.75; 95%CI; 1.59–4.77; $p < 0.001$). Patients underwent decompressive craniectomy showed a 105% increase in the chance of death (OR = 2.05; 95%CI: 1.23–3.41; $p = 0.008$). There was a significant association ($p < 0.001$) between length of stay in the ICU and death, and most (88.6%) patients who did not need to be admitted to the ICU did not die. Likewise, there was a significant association ($p = 0.020$) between ASDH and death, in which most individuals (74.1%) who did not have ASDH did not die either (►**Table 4**).

Table 1 Descriptive analysis of variables

Variables		N	%
Gender	Female	39	12,3%
	Male	279	87,7%
Age (years old)	15–34	138	43,4%
	35–65	151	47.5%
	> 65	29	9.1%
Origin	Florianópolis	46	14.5%
	São José	45	14.2%
	Palhoça	36	11.3%
	Others – metropolitan area of Florianópolis	45	14.2%
	Outside the metropolitan area of Florianópolis	146	45.9%
Level of schooling	Basic education	144	45.3%
	High school	86	27.0%
	Higher education	21	6.6%
	Others	67	21.1%
Year of the attendance	2014	60	18.9%
	2015	65	20.4%
	2016	76	23.9%
	2017	67	21.1%
	2018	33	10.4%
	2019 (until April)	17	5.3%
Days of the week	Sunday	64	20.1%
	Monday	52	16.4%
	Tuesday	31	9.7%
	Wednesday	35	11.0%
	Thursday	31	9.7%
	Friday	48	15.1%
	Saturday	57	17.9%
Days of the Week 2	Monday to Friday	197	61.9%
	Weekend	121	38.1%
Month	January	27	8.5%
	February	31	9.7%
	March	26	8.2%
	April	34	10.7%
	May	37	11.6%
	June	24	7.5%
	July	27	8.5%
	August	36	11.3%
	September	20	6.3%
	Octuber	20	6.3%
	November	19	6.0%
	December	16	5.0%
	Indeterminate	1	0.3%

Table 1 (*Continued*)

Variables		N	%
Quarter	1st Quarter	84	26.4%
	2nd Quarter	95	29.9%
	3rd Quarter	83	26.1%
	4th Quarter	55	17.3%
	Indeterminate	1	0.3%
TBI classification	Mild TBI	105	33.0%
	Moderate TBI	44	13.8%
	Severe TBI	169	53.1%
Pupils on admission	Isocorics no abnormalities	203	63.8%
	Anisocorics	33	10.4%
	Midriatics	20	6.3%
	Miotics	59	18.6%
	No information	3	0.9%
Cause of TBI	Motorcycle accident	83	26.1%
	Fall (level)	52	16.4%
	Fall (own height)	45	14.2%
	Trampling	39	12.3%
	Aggression	35	11.0%
	Automobile accident	30	9.4%
	Gunshot	9	2.8%
	Others	25	7.9%
Associated trauma	No associated injuries	154	48.4%
	Multiple injuries	87	27.4%
	Orthopedic	26	8.2%
	Face	24	7.5%
	Thorax	20	6.3%
	Spinal cord injury (SCI)	5	1.6%
	Abdominal	2	0.6%
Need for ICU	No	45	14.2%
	Yes	273	85.8%
ICU time (days)	Zero	44	13.8%
	1–3	26	8.2%
	4–7	52	16.4%
	8–14	68	21.4%
	15–21	67	21.1%
	> 21	55	17.3%
	Transferred	6	1.9%
Hospitalization time (days)	≤ 7	75	23.8%
	8–14	61	19.4%
	15–30	67	21.3%
	31–60	74	23.5%
	> 60	38	12.1%

(*Continued*)

Table 1 (*Continued*)

Variables		N	%
Death	No	209	65.7%
	Yes	101	31.8%
	Transferred	8	2.5%
Sequelae	No	69	21.7%
	Yes	138	43.4%
	Death	101	31.8%
	No information / transferred	10	3.1%
Which sequelae at hospital discharge	Death	101	31.8%
	No sequela /not informed /transferred	79	24.8%
	Multiple	74	23.3%
	Physical	21	6.6%
	Vegetative state	15	4.7%
	Cognitive	15	4.7%
	Present and uninformed sequela	8	2.5%
	Swallowing disorders/speech-language	4	1.3%
	Phychological	1	0.3%
Glasgow outcome scale (GOS)	Transferred	9	2.9%
	1 (Death)	100	31.4%
	2 (Vegetative state)	22	6.9%
	3 (Severe disability)	65	20.4%
	4 (Moderate disability)	38	11.9%
	5 (Mild disability/or good recovery)	84	26.4%
External ventricular drain (EVD)	No	112	35.2%
	Yes	206	64.8%
Descompressive craniectomy	No	228	71.7%
	Yes	90	28.3%
Neurosurgery	EVD (isolated)	106	33.3%
	Evacuation of extra-axial hematoma (with or without EVD)	79	24.8%
	Descompressive craniectomy + evacuation of intracranial hematoma (with or without EVD)	77	24.2%
	Surgical treatment of skull fracture/depressed skull fracture (isolated or associated)	29	9.1%
	Descompressive craniectomy (with or without EVD)	14	4.4%
	Evacuation of intracranial hematoma (with or without EVD)	13	4.1%

Table 1 (*Continued*)

Variables		N	%
Marshall CT classification	Marshall I	4	1.3%
	Marshall II	138	43.4%
	Marshall III	45	14.2%
	Marshall IV	83	26.1%
	Marshall V	27	8.5%
	Marshall VI	10	3.1%
	Unclassified	11	3.5%
Subarachnoid hemorrhage (SAH)	No	175	55.0%
	Yes	142	44.7%
	No information	1	0.3%
Obliteration of basal cisterns	No	181	56.9%
	Yes	125	39.3%
	No information	12	3.8%
MLS (mm)	Zero	155	48.7%
	> 0 and < 5	34	10.7%
	≥ 5 and < 12	85	26.7%
	≥ 12 and < 15	13	4.1%
	≥ 15	16	5.0%
	Not measured	15	4.7%
Cerebral herniation	No	223	70.1%
	Yes	92	28.9%
	No information	3	0.9%
Extra-axial hematoma	No	113	35.5%
	Yes	204	64.2%
	No information	1	0.3%
Acute subdural hematoma (ASDH)	No	174	54.7%
	Yes	143	45.0%
	No information	1	0.3%
Acute epidural hematoma (AEDH)	No	236	74.2%
	Yes	81	25.5%
	No information	1	0.3%
Maximun hematoma thickness (mm) – AEDH	≤ 10	245	77.0%
	> 10 and < 30	36	11.3%
	≥ 30	17	5.3%
	Not measured	20	6.3%
Maximun hematoma thickness (mm) – ASDH	≤ 10	233	73.3%
	> 10 and < 30	42	13.2%
	≥ 30	1	0.3%
	Not measured	42	13.2%
Intraparenchymal hemorrhage/cerebral contusion	No	113	35.5%
	Yes	204	64.2%
	No information	1	0.3%
Intraventricular hemorrhage (IVH)	No	289	90.9%

(*Continued*)

Table 1 (*Continued*)

Variables		N	%
	Yes	28	8.8%
	No information	1	0.3%
Skull base fracture	No	177	55.7%
	Yes (without depressed skull fracture)	138	43.4%
	Yes (depressed skull fracture)	1	0.3%
	No information	2	0.6%
Convexity fracture	No	186	58.5%
	Yes (without depressed skull fracture)	107	33.6%
	Yes (depressed skull fracture)	23	7.2%
	No information	2	0.6%

Abbreviation: TBI, traumatic brain injury.

Table 2 Descriptive analysis of numeric variables

Variable	Valid *n*	Mean	S.D.	Min.	Median	Max.
Age (years old)	318	40.58	17.11	15	38	93
ICU time (days)	312	12.62	11.17	0	10	79
Total hospital stay (days)	315	27.88	28.13	0	18	207
MLS (mm)	303	4.14	5.45	0	0	26

Abbreviations: ICU, intensive care unit; MLS, midline shift, S.D., standard deviation.

To assess the impact of the variables of interest together on patient death, a logistic regression was adjusted using the following variables: gender, age, GCS-P, pupils on admission, associated injuries, ICU time, EVD; need for decompressive craniectomy, Marshall CT classification, SAH, obliteration of basal cisterns, MLS, ASDH, AEDH, and intraventricular hemorrhage

Table 3 Lethality distribution

Period		Lethality (%)
Total		31.76%
Year	2014	35.00%
	2015	27.69%
	2016	34.21%
	2017	25.37%
	2018	45.45%
	2019 (until April)	23.53%
Quarter	1st quarter	27.38%
	2nd quarter	33.68%
	3rd quarter	31.33%
	4th quarter	36.36%

According to the final model, it may be concluded that patients with orthopedic trauma showed a 466% increase in the chance of death (OR = 5.66; 95%CI: 1.08–29.52; $p = 0.040$), and that individuals with thoracic trauma showed a 276% increase in the chance of death (OR = 3.76; 95%CI: 1.27–11.11; $p = 0.017$) compared with patients without associated injuries. There was a significant influence of the time of hospitalization in the ICU in the case of death, wherein additional day of hospitalization in the ICU is associated with an average decrease of 7% in the chance of death (OR = 0.93; 95%CI: 0.9–0.96; $p < 0.001$).

Patients submitted to EVD had an increase of ~ 561% in the chance of death (OR = 6.61; 95%CI: 3.26–13.4; $p < 0.001$). There was a significant influence of decompressive craniectomy in case of deaths, that is, patients who needed decompressive craniectomy, when compared with patients who did not need the procedure, showed a 265% increase in their chance of death (OR = 3.65; 95%CI: 1.88–7.1; $p < 0.001$).

There was a significant influence of the MLS on the outcome death. Patients who had an MLS between zero and 5 mm had a 172% increase in the chance of death

Table 4 Univariate analysis with death outcome

Variables		N	%	Survivors		Death		95%CI (OR)*	p*p-value*
				N	%	N	%		
Gender	Female	39	12,3%	24	61,5%	15	38,5%	1	00,438†
	Male	279	87,7%	193	69,2%	86	30,8%	0,71 [0.3–1.43]	
Age (years old)	15–34	138	43.4%	92	66.7%	46	33.3%	1	00.171†
	35–65	151	47.5%	109	72.2%	42	27.8%	0.77 [0.47–1.27]	
	> 65	29	90.1%	16	55.2%	13	44.8%	1.62 [0.72–3.66]	
Cause of TBI	Automobile accident	30	90.4%	21	70.0%	9	30.0%	1	00.554†
	Motorcycle accident	83	26.1%	58	69.9%	25	30.1%	1.04 [0.44–2.46]	
	Trampling	39	12.3%	24	61.5%	15	38.5%	1.19 [0.57–2.50]	
	Fall (own height)	45	14.2%	27	60.0%	18	40.0%	1.91 [0.85–4.32]	
	Fall (level)	52	16.4%	38	73.1%	14	26.9%	1.18 [0.48–2.89]	
	Aggression	35	11.0%	28	80.0%	7	20.0%	0.59 [0.24–1.41]	
	Gunshot	9	20.8%	6	66.7%	3	33.3%	0.82 [0.37–1.79]	
	Others	25	70.9%	15	60.0%	10	40.0%	1.02 [0.53–1.96]	
Associated trauma	No associated injuries	154	48.4%	103	66.9%	51	33.1%	1	00.158‡
	Multiple injuries	87	27.4%	58	66.7%	29	33.3%	0.90 [0.25–3.21]	
	Orthopedic	26	80.2%	16	61.5%	10	38.5%	4.62 [1.01–21.11]	
	Face	24	70.5%	21	87.5%	3	12.5%	0.92 [0.16–5.17]	
	Thorax	20	60.3%	16	80.0%	4	20.0%	2.94 [1.12–7.69]	
	SCI	5	10.6%	2	40.0%	3	60.0%	1.15 [0.24–5.57]	
	Abdominal	2	00.6%	1	50.0%	1	50.0%	1.64 [0.39–6.90]	
Classification of TBI	Mild TBI	105	33.0%	83	79.0%	22	21.0%	1	**00.013**†
	Moderate TBI	44	13.8%	27	61.4%	17	38.6%	1.74 [1.17–2.59]	
	Severe TBI	169	53.1%	107	63.3%	62	36.7%	0.68 [0.39–1.17]	
GCS-P	1	40	12.6%	20	50.0%	20	50.0%	0.93 [0.89–0.98]	**00.038**†
	2	12	30.8%	6	50.0%	6	50.0%		
	3	78	24.5%	56	71.8%	22	28.2%		
	4	6	10.9%	3	50.0%	3	50.0%		
	5	8	20.5%	5	62.5%	3	37.5%		

(*Continued*)

Table 4 (*Continued*)

Variables		N	%	Survivors		Death		95%CI (OR)*	p*p-value*
				N	%	N	%		
	6	11	30.5%	9	81.8%	2	18.2%		
	7	7	20.2%	3	42.9%	4	57.1%		
	8	8	20.5%	5	62.5%	3	37.5%		
	9	12	30.8%	7	58.3%	5	41.7%		
	10	15	40.7%	11	73.3%	4	26.7%		
	11	9	20.8%	4	44.4%	5	55.6%		
	12	8	20.5%	5	62.5%	3	37.5%		
	13	22	60.9%	16	72.7%	6	27.3%		
	14	41	12.9%	31	75.6%	10	24.4%		
	15	41	12.9%	36	87.8%	5	12.2%		
Pupils on admission	Isocorics no abnormalities	203	63.8%	145	71.4%	58	28.6%	1	00.291‡
	Anisocorics	33	10.4%	19	57.6%	14	42.4%	2.47 [0.52–11.69]	
	Midriatics	20	60.3%	13	65.0%	7	35.0%	1.60 [0.39–6.52]	
	Miotics	59	18.6%	39	66.1%	20	33.9%	2.09 [0.81–5.38]	
	No information	3	00.9%	1	33.3%	2	66.7%	0.99 [0.43–2.29]	
Marshall CT classification	Marshall I	4	10.3%	3	75.0%	1	25.0%	1	**00.030**†
	Marshall II	138	43.4%	107	77.5%	31	22.5%	0.87 [0.09–8.65]	
	Marshall III	45	14.2%	31	68.9%	14	31.1%	1.35 [0.13–14.20]	
	Marshall IV	83	26.1%	50	60.2%	33	39.8%	1.98 [0.20–19.86]	
	Marshall V	27	80.5%	15	55.6%	12	44.4%	2.40 [0.22–26.12]	
	Marshall VI	10	30.1%	4	40.0%	6	60.0%	4.50 [0.34–60.15]	
	Unclassified	11	30.5%	7	63.6%	4	36.4%	1.71 [0.13–22.51]	
EVD	No	112	35.2%	91	81.3%	21	18.8%	1	<**0.001**†
	Yes	206	64.8%	126	61.2%	80	38.8%	2.75 [1.59–4.77]	
Descompressive craniectomy	No	228	71.7%	166	72.8%	62	27.2%	1	**00.008**†
	Yes	90	28.3%	51	56.7%	39	43.3%	2.05 [1.23–3.41]	
ICU time (days)	Zero	44	13.8%	39	88.6%	5	11.4%	1	<**0.001**†
	1–3	26	80.2%	12	46.2%	14	53.8%	***	

Table 4 (*Continued*)

Variables		N	%	Survivors		Death		95%CI (OR)*	p*p-value*
				N	%	N	%		
	4–7	52	16.4%	21	40.4%	31	59.6%		
	8–14	68	21.4%	44	64.7%	24	35.3%		
	15–21	67	21.1%	51	76.1%	16	23.9%		
	> 21	55	17.3%	44	80.0%	11	20.0%		
	Transferred	6	1.9%	6	100%	0	0.0%		
Reference trauma center	HGCR	182	57.2%	123	67.6%	59	32.4%	1	00.866†
	HRSJ-HMG	136	42.8%	94	69.1%	42	30.9%	0.93 [0.58–1.50]	
SAH	No	175	55.0%	129	73.7%	46	26.3%	1	**00.048**†
	Yes	142	44.7%	87	61.3%	55	38.7%	***	
	No information	1	00.3%	1	100%	0	0.0%		
ASDH	No	174	54.7%	129	74.1%	45	25.9%	1	**00.020**‡
	Yes	143	45.0%	87	60.8%	56	39.2%	***	
	No information	1	00.3%	1	100%	0	00.0%		
AEDH	No	236	74.2%	156	66.1%	80	33.9%	1	00.330‡
	Yes	81	25.5%	60	74.1%	21	25.9%	***	
	No information	1	00.3%	1	100%	0	000%		

Abbreviations: ASDH. acute subdural hematoma; CI, confidence interval; CT, computed tomography; GCS, Glasgow coma scale; HGCR, Hospital Governador Celso Ramos; HRSJ-HMG, Hospital Regional de São José Dr. Homero de Miranda Gomes; ICU, intensive care unit; OR, odds ratio; SAH, subarachnoid hemorrhage; SCI, spinal cord injury; AEDH, acute epidural hematoma.

*95% confidence interval (CI) for odds ratio (OR).

†Chi-squared test.

‡Fisher exact test.

***Variables that have three asterisks in their 95% confidence interval for the odds ratio exhibited very large values for their intervals, as their statistics were overestimated due to the fact that there are empty groups at some levels of their respective variables, which compromised the estimation of their ranges.

Table 5 Final model logistic regression multivariate analysis with the outcome of death

Variables	N	%	Survivors		Death		95%CI (OR)	*p-value*[*]
			N	%	*n*	%		
Gender								
Female	39	12.3%	24	61.5%	15	38.5%	1	
Male	279	87.7%	193	69.2%	86	30.8%	0.74 [0.3–1.84]	0.521
Age (years old)								
15–34	138	43.4%	92	66.7%	46	33.3%	1	
35–65	151	47.5%	109	72.2%	42	27.8%	0.88 [0.47–1.66]	0.690
> 65	29	9.1%	16	55.2%	13	44.8%	1.80 [0.6–5.41]	0.292
Pupils on admission[†]								
Isocorics no abnormalities	203	63.8%	145	71.4%	58	28.6%	1	
Anisocorics	33	10.4%	19	57.6%	14	42.4%	0.89 [0.46–1.73]	0.728
Midriatics	20	6.3%	13	65.0%	7	35.0%	1.61 [0.66–3.93]	0.298
Miotics	59	18.6%	39	66.1%	20	33.9%	1.48 [0.55–3.97]	0.434
Associated trauma								
No associated injuries	154	48.4%	103	66.9%	51	33.1%	1	
Multiple injuries	87	27.4%	58	66.7%	29	33.3%	1.92 [0.44–8.49]	0.388
Orthopedic	26	8.2%	16	61.5%	10	38.5%	5.66 [1.08–29.52]	**0.040**
Thorax	20	6.3%	16	80.0%	4	20.0%	3.76 [1.27–11.11]	**0.017**
Face	24	7.5%	21	87.5%	3	12.5%	1.38 [0.23–8.29]	0.723
SCI	5	1.6%	2	40.0%	3	60.0%	1.01 [0.2–5.13]	0.992
Abdominal	2	0.6%	1	50.0%	1	50.0%	2.98 [0.6–14.82]	0.182
EVD								
No	112	35.2%	91	81.3%	21	18.8%	1	
Yes	206	64.8%	126	61.2%	80	38.8%	6.61 [3.26–13.4]	< **0.001**
Descompressive craniectomy								
No	228	71.7%	166	72.8%	62	27.2%	1	
Yes	90	28.3%	51	56.7%	39	43.3%	3.65 [1.88–7.1]	< **0.001**
SAH[‡]								
No	175	55%	129	73.7%	46	26.3%	1	
Yes	142	44.7%	87	61.3%	55	38.7%	1.50 [0.69–3.28]	0.305
ASDH[‡]								
No	174	54.7%	129	74.1%	45	25.9%	1	
Yes	143	45%	87	60.8%	56	39.2%	1.70 [0.84–3.42]	0.138
AEDH[‡]								
No	236	74.2%	156	66.1%	80	33.9%	1	
Yes	81	25.5%	60	74.1%	21	25.9%	1.49 [0.68–3.27]	0.319
Intraventricular hemorrhage[‡]								
No	289	90.9%	198	68.5%	91	31.5%	1	
Yes	28	8.8%	18	64.3%	10	35.7%	1.75 [0.63–4.85]	0.279
Obliteration of basal cisterns								
No	181	56.9%	135	74.6%	46	25.4%	1	
Yes	125	39.3%	74	59.2%	51	40.8%	0.89 [0.22–3.69]	0.877
No information	12	3.8%	8	66.7%	4	33.3%	0.53 [0.21–1.31]	0.166

Table 5 (*Continued*)

Variables	N	%	Survivors		Death		95%CI (OR)	*p-value*[*]
			N	%	*n*	%		
MLS (mm)								
Zero	155	48.7%	115	74.2%	40	25.8%	1	
>0 and <5 mm	34	10.7%	25	73.5%	9	26.5%	2.72 [1.07–6.93]	**0.036**
≥ 5 mm and <12 mm	85	26.7%	55	64.7%	30	35.3%	0.75 [0.3–1.87]	0.532
≥ 12 mm and <15 mm	13	4.1%	8	61.5%	5	38.5%	0.37 [0.14–0.97]	**0.043**
≥ 15 mm	16	5%	5	31.3%	11	68.8%	0.67 [0.25–1.78]	0.416
Not measured	15	4.7%	9	60.0%	6	40.0%	0.54 [0.21–1.38]	0.198
Marshall CT classification								
Marshall I	4	1.3%	3	75.0%	1	25.0%	1	
Marshall II	138	43.4%	107	77.5%	31	22.5%	1.54 [0.06–37.34]	0.791
Marshall III	45	14.2%	31	68.9%	14	31.1%	1.07 [0.04–31.32]	0.971
Marshall IV	83	26.1%	50	60.2%	33	39.8%	1.42 [0.04–45.26]	0.842
Marshall V	27	8.5%	15	55.6%	12	44.4%	3.33 [0.11–98.13]	0.485
Marshall VI	10	3.1%	4	40.0%	6	60.0%	4.61 [0.13–162.45]	0.400
Unclassified	11	3.5%	7	63.6%	4	36.4%	2.65 [0.04–163.73]	0.643
ICU time (days)							0.93 [0.9–0.96]	$<$ **0.001**
GCS-P							0.94 [0.87–1.01]	0.108
VIF Maximum	43.40				6.00			
Hosmer – Lemeshow test	0.170				0.575			
R[†]	28.0%				23.0%			

Abbreviations: ASDH. acute subdural hematoma; CI, confidence interval; CT, computed tomography; GCS-P, Glasgow P; ICU, intensive care unit; MLS, midline shift; OR, odds ratio; SAH, subarachnoid hemorrhage.

[*]Regarding the variables that were not significant, the p-value refers to the initial model. And for significant variables, the p-value refers to the final model.

[†]Three patients had no information about their pupils on admission.

[‡]The presence of SAH, ASDH, AEDH and intraventricular hemorrhage were not determined in one patient.

(OR = 2.72; 95%CI: 1.07–6.93; $p = 0.036$). However, patients with an MLS $\geq$12 and <15 mm, when compared with a patient with an MLS equal to zero, showed a 63% decrease in the chance of death (OR = 0.37; 95%CI: 0.14–0.97; $p = 0.043$).

The maximum VIF of the final model was 6. Therefore, it can be concluded that this model does not have multicollinearity problems, since no VIF was >10. By the Hosmer–Lemeshow test, the model presented a suitable adjustment ($p = 0.575$), not rejecting the null hypothesis of the adjustment of the regression model used. The R^2 of the final model showed that significant variables to the model were able to explain 23.0% of the variability of the outcome variable (death) of individuals (►**Table 5**).

To evaluate the predictive measures of the GCS-P and the GCS, logistical regressions were adjusted to study their relationship with the following variables: need for decompressive craniectomy, MLS, presence of basal cistern obliteration, need for hospitalization in the ICU, and death.

►**Fig. 3** presents graphically the ROC curves for the outcomes "decompressive craniectomy" and "MLS." In this way, it can be concluded that, in the case of need for decompressive craniectomy, the GCS curve had a better behavior when compared with that of the curve related to the GCS-P, since it had a larger area below the curve (AUC = 0.574). However, it is important to point out that the difference between the curves was <0.05, indicating that there was no clinically relevant increment between the scores. Similarly, in the case of MLS, the curve related to the GCS behaved better in relation to the representative curve of the GCS-P, since it presented a larger area below the curve (AUC = 0.538). However, the difference between the curves was <0.05, without a clinically relevant increment between the scores.

►**Fig. 4** shows graphically the ROC curves for the outcomes "obliteration of basal cisterns" and "needed for ICU hospitalization." Thus, it can be concluded, for the case of obliteration of basal cisterns, that the GCS-P curve had a better behavior when compared with that of the GCS-

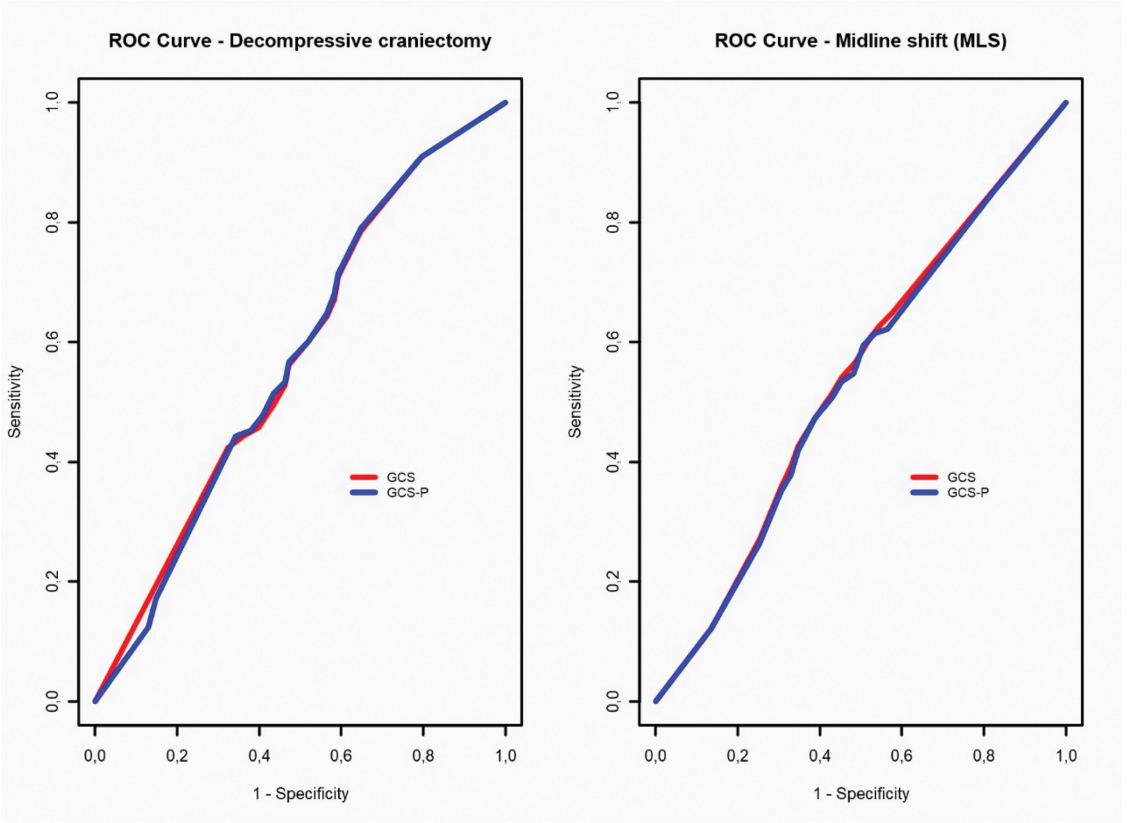


Fig. 3 ROC curve for Decompressive Craniectomy and Midline Shift (MLS).

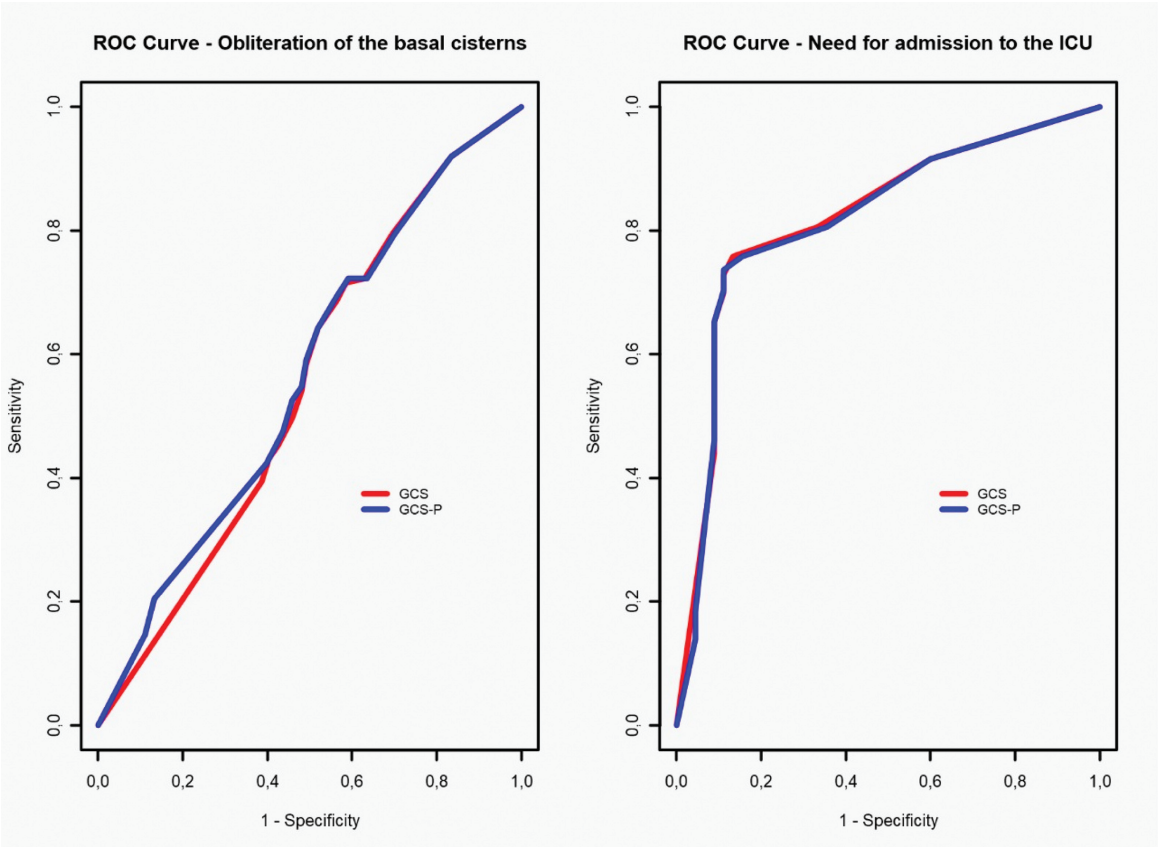


Fig. 4 ROC curve for obliteration of basal cisterns and need for admission to the ICU.

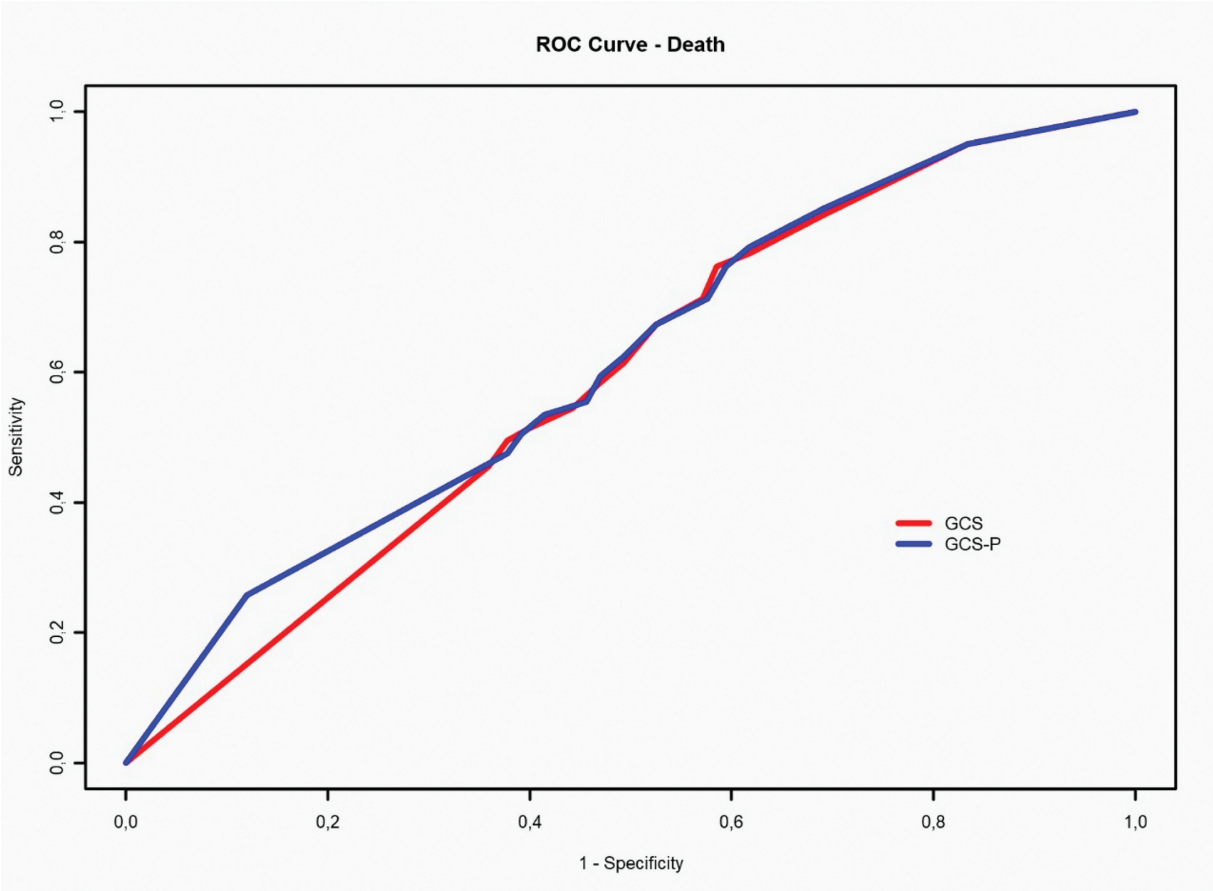


Fig. 5 ROC curve for death.

related curve, since it has had a larger area under the curve (AUC = 0.563). However, the difference between the curves was < 0.05, indicating that there was no clinically relevant increase between the scores. In case of need for ICU hospitalization, the GCS-related curve behaved superiorly to the GCS-P curve, since it had a larger area under the curve (AUC = 0.820). However, similarly, the difference between the curves was < 0.05, indicating that there was no clinically relevant increase between the scores.

►**Fig. 5** presents graphically the ROC curve for the outcome "death." From it, we can verify that the curve related to the GCS-P behaved in a better way compared with the curve related to the GCS, since it has had a higher value of the area below the curve (AUC = 0.612). Nonetheless, the difference between the curves was < 0.05, indicating that there was no clinically relevant increment between the scores.

Discussion

The present study reinforced some variables as prognostic predictors, according to previous studies and models already established. Variables such as patient age, GCS, pupillary reactivity, and tomographic aspects have already been widely validated in previous studies as the most important prognostic characteristics in patients with TBI.[8–10]

In univariate analysis, it was identified that the following variables were strongly associated with the outcome death: TBI classification based on admission GCS, GCS-P, Marshall CT classification, EVD, decompression craniectomy, hospitalization time in the ICU, SAH, ASDH, obliteration of basal cisterns, and MLS. In the multivariate model, it was demonstrated that orthopedic trauma, thoracic trauma, hospitalization time in the ICU, EVD, decompressive craniectomy, and MLS between zero and 5 mm are predictors independent of the occurrence of death at time of discharge.

As the junction of variables for the creation of prognostic predictor models is a useful tool in clinical decision-making, there are several studies proposing prognostic markers for neurotrauma. Among the pioneers with well-delineated models, one can cite The International Mission for Prognosis and Analysis of Clinical Trials[11,12] (IMPACT) and The Corticosteroid Randomization After Significant Head Injury.[8] The IMPACT aims to estimate the prognosis for the next 6 months after TBI and points to 3 variables as being the most important: GCS, pupillary response, and tomographic features. The second study, CRASH, aims to calculate the probability of death

within 14 days after TBI and the probability of neurological sequelae arising 6 months after the trauma, using for the calculation the following variables: age, motor response, pupils, tomographic features, and biochemical markers. More recently, a study[13] used the IMPACT and CRASH databases combined with the Pupillary Reactivity Score (PRS) and the GCS, culminating in the creation of a new score with both pieces of information: GCS-P, which is the GCS by arithmetically subtracting the PRS. In it, 2, 1, and 0 are the numbers assigned to the PRS for unresponsive pupils, unilateral reagent, and bilateral reagents, respectively.

Thus, although the outcome of traumatic events in an individual is not certain, research in recent decades has provided greater clarity in terms of prognostic probabilities. Therefore, the present study compared the GCS and the new scale with the subtraction of the PRS, through the accuracy of the numerical models, based on the results of the AUC. The results obtained when comparing both scores with the outcome variables "need for decompressive craniectomy," "MLS," "presence of basal cistern obliteration", "need for ICU admission", and "death" showed that there was no clinically relevant increase between them.

The National Traumatic Coma Data Bank (TCDB) classification,[14,15] described by Marshall, is one of the most widely used tomographic criteria. Thus, Marshall I classifies the CT as normal (mortality of 9.6%); Marshall II, when there are small hemorrhagic lesions, with the cisterns present and without deviation of the midline structures (mortality of 13.5%); Marshall III, when cisterns are erased or absent, without MLS (mortality 34%); and Marshall IV, when a MLS >5 mm occurs, usually accompanied by erased or absent cisterns and no lesion $>25\,cm^3$ (mortality 56.2%). Additionally, there are 2 categories used for lesions $>25\,cm^3$, classified in surgically addressed lesions (Marshall V) and nonsurgically addressed lesions (Marshall VI). In the present study, there was a significant association between the tomographic findings present in the Marshall CT classification and the number of deaths; however, Marshall II cases had a decrease in the chance of death in relation to Marshall I cases in the univariate analysis.

In relation to MLS, corroborating the results of the present work, Zumkeller et al.[16] reported that deviations <12 mm are possibly tolerated, that with deviations >12 mm the survival rate decreases considerably, and that deviations >28 mm were incompatible with life. Similarly, Eisenberg et al. observed 70% of deaths in patients with an MLS >15 mm.[17] Given that the presence of MLS is an indication of increased ICP, it is expected that the greater the deviation, the worse the prognosis; however, there are other factors that may interfere with this reasoning, such as the location of intracranial lesions and the presence of bilateral abnormalities. Then, the absolute value of the deviation is less relevant than other tomographic parameters.

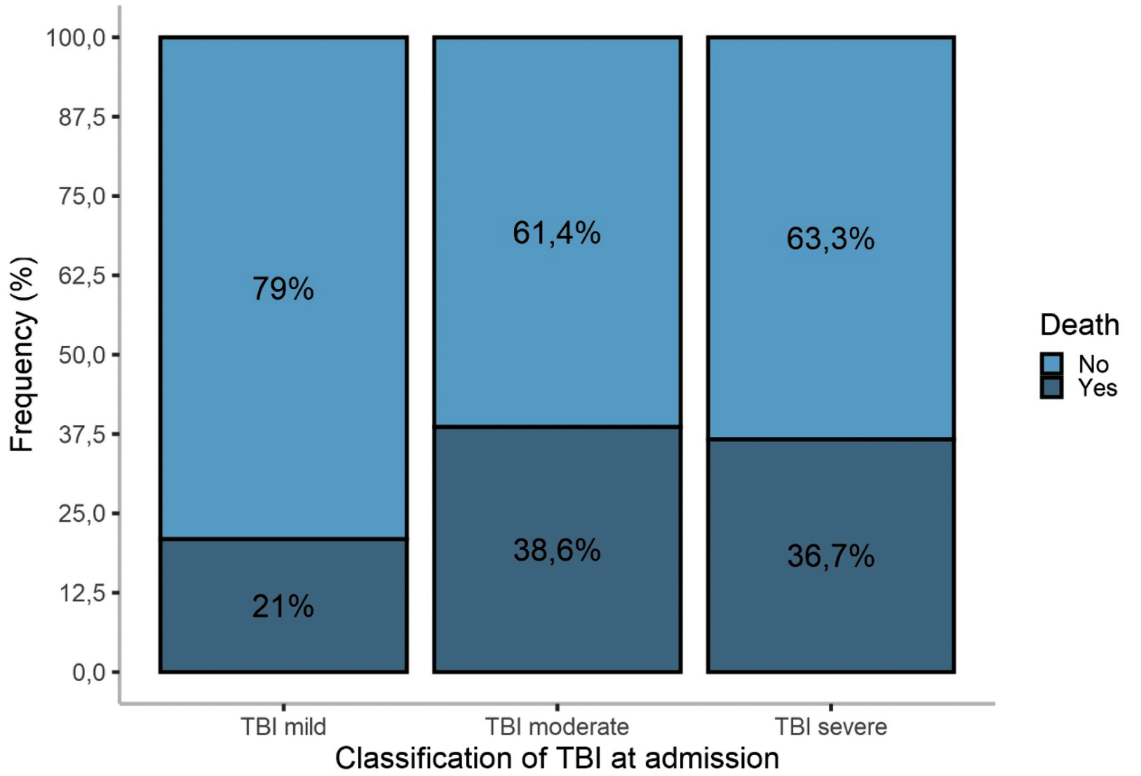
The AEDH showed better prognoses when compared with the ASDH, which had already been evidenced in other studies.[14,18] A controversial fact was the higher number of deaths for AEDH $\leq$ 10 mm when compared with AEDH between 10 and 30 mm; however, this result may have as a confounding factor the association with other primary or secondary lesions, both encephalic and in other locations. This bias is also a hypothesis to justify the higher number of deaths in cases of moderate TBI (38.6%) when compared with cases of severe TBI (36.7%). Although many studies show a direct relationship between the GCS at admission and the increase in the number of deaths, ►**Graphic 1** shows this contradiction in the distribution of deaths in relation to moderate and severe TBI.

Obliteration of the basal cisterns is considered an indicator of high intracranial pressure and is related to worse prognosis.[19] Therefore, management of cerebral swelling and of high ICP is an essential component of the acute treatment of TBI.[20] Thereby, the objective of decompressive craniectomy is to increase the compartment to reduce the increase of ICP caused by cerebral edema.[21,22] In this way, patients who need such an approach, in general, are more seriously affected, thus contributing to a larger number of deaths, as observed in this subgroup.

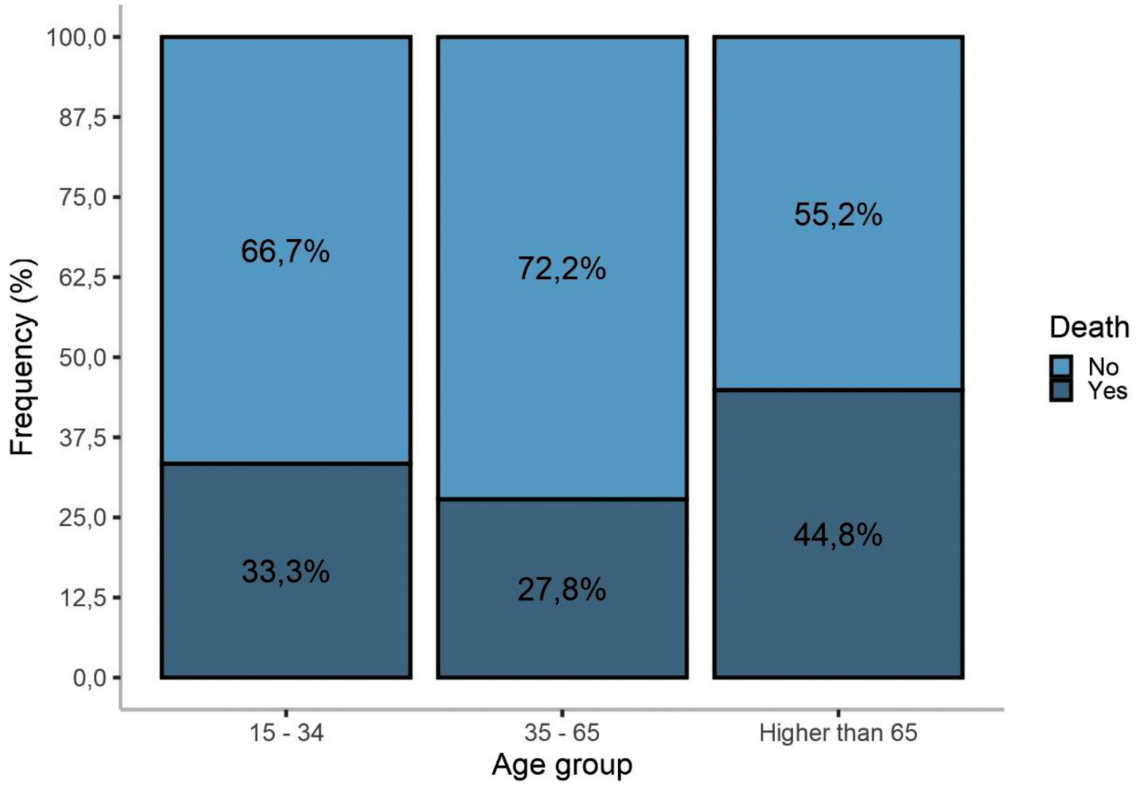
In the multivariate model, among the associated lesions, patients with thoracic and orthopedic trauma had a greater chance of death, which may be due to the impairment of the pulmonary function and to the decrease in volume, contributing to the worsening of secondary brain lesions because of hypoxia and hypotension, mainly.[23–25]

Throughout the world, TBI standards are changing,[30] with increase in traffic acidentes mainly in low-income countries and the growing problem of falls among the elderly mainly in high-income countries. Accordingly, the age in which the trauma occurs correlates with the prognosis, since the causes of the accidents depend on the age group, and that the chances of systemic complications are larger among the elderly. The present research showed the prevalence of falling from a height among the elderly over 65, which is the age group that presented the largest number of deaths (►**Graphic 2**). However, ground-level falls occur more frequently in the age group between 35 to 65 years and motorcycling and automotive accidents predominated among adults under 34 years (►**Graphic 3**). Regardless of the cause, TBI results in high morbidity and mortality, in addition to representing a risk factor for dementia.[27] Therefore, an in-depth knowledge of its epidemiology is essential for a more effective guidance on TBI prevention strategies in different populations.

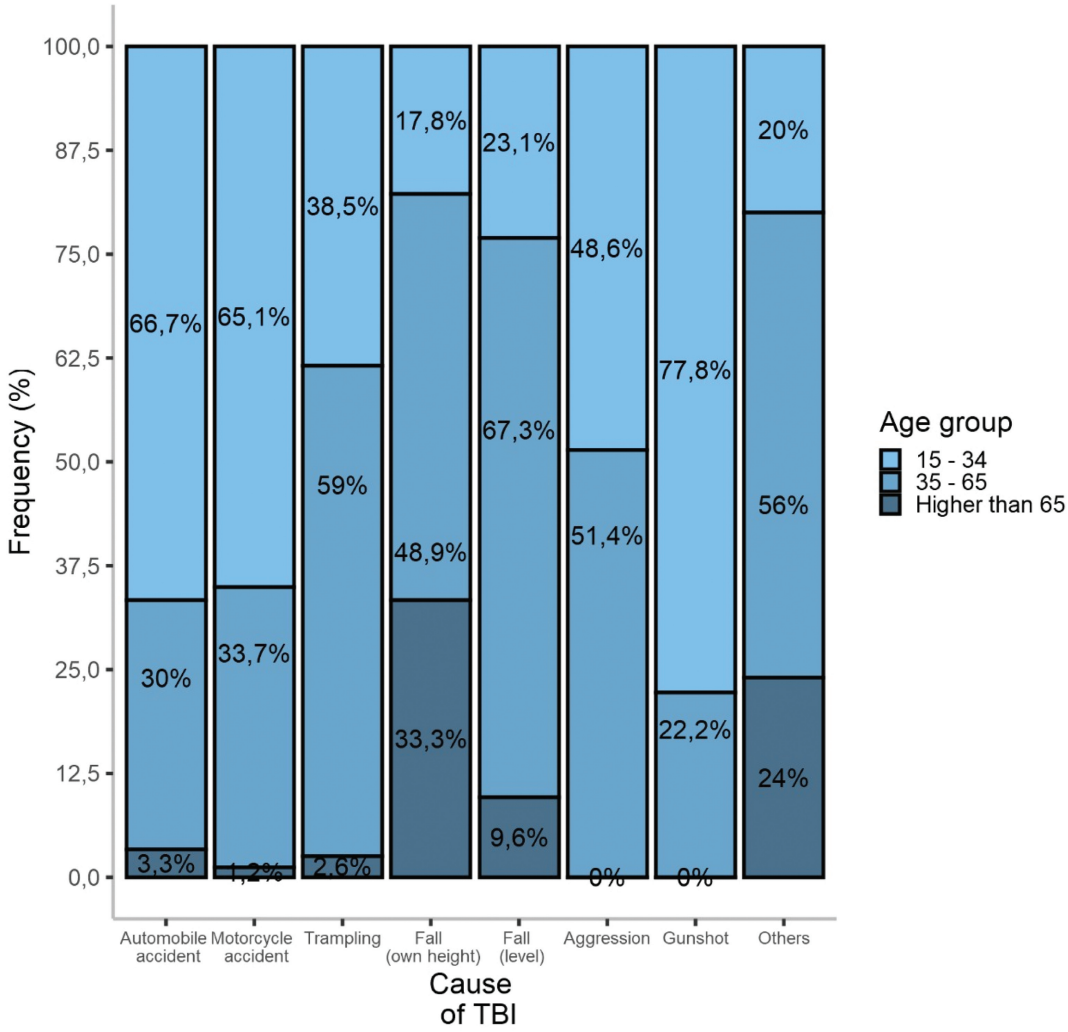
Considering that the literature on the subject is large and of variable quality,[28] various prognostic models in neurotrauma have already been proposed;[11,29,30] however, their application in practice runs into some obstacles, such as the additional time involved in data collection, coupled with the uncertainty of applicability. A Canadian study with intensivists, neurosurgeons, and neurologists involved in the care of patients with severe TBI evidenced a variability of approaches,[31] reinforcing the importance of more consistent models to predict the neurological outcome. In this context, their use is associated with support in decision-making and



Graphic 1 Death by TBI classification.



Graphic 2 Death by age group.



Graphic 3 Causes by age group.

better communication about risks among health professionals, patients, and their families.[31]

The retrospective identification of the profile of TBI victims from two reference hospitals in the metropolitan area of Florianopolis allowed a critical analysis to be performed, focusing both on public policies and on the care flows of the institutions. However, because this is a documental-based study, with the use of medical records as a source of data, it has been observed that much information is not properly recorded or is lost. Therefore, investment is needed in systems for efficient data collection and sharing, aiming at the formation of more robust and reliable databases, as well as at the standardization of methods for epidemiological monitoring.

Limitations

The main limitation of the present study was the difficulty in having good historical data with the possible occurrence of bias due to errors in medical records. When considering the use of the initial GCS for prognosis, the two most important problems are the reliability of the initial measurement and its lack of accuracy when factors such as prehospital medications or intubation are present.

Another obstacle encountered during the present study was the difficulty in gaining access to all tomographic images, especially to the older ones. To minimize losses, all possible information was collected from CT scan reports; however, Marshall measurements and classifications were missing for some cases.

Conclusion

1. There was no clinically relevant increment between the GCS and the GCS-P for the outcomes tested.
2. Male gender predominated among the patients. The most affected age range was between 35 and 65 years old, with a mean age of $\sim$ 41 years old, and half of the patients were $\leq$

36 years old. The day with the highest number of cases was Sunday, the month was May, and the quarter was the 2nd quarter of the year. The leading cause was motorcycle accidents, followed by falls. Most patients presented with severe TBI at hospital admission. The main associated injury was orthopedic trauma. Most patients required admission to the ICU for an average of 13 days. Regarding the total length of hospital stay, the mean time was ~ 28 days. Most patients presented with sequelae at hospital discharge, with a predominance of multiple sequelae. Most cases needed EVD. The predominant Marshall CT classification was Marshall II, followed by Marshall IV. Most patients presented with extra-axial hematoma, and ASDH was the most frequent.

3. In the univariate analysis with death as the outcome, there was a significant association with the variables TBI classification, GCS-P, Marshall CT classification, EVD, decompressive craniectomy; length of stay at the ICU, SAH, ASDH, obliteration of basal cisterns, and MLS.
4. The final logistic regression model for the multivariate analysis showed that:
   - Patients who had orthopedic trauma or thoracic trauma presented, respectively, increases of 466 and 276% in the chance of death when compared with patients without associated injuries.
   - Each additional day of ICU stay is associated with a 7% decrease in the chance of death.
   - Patients with EVD showed a 561% increase in the chance of death when compared with patients without EVD.
   - The need for decompressive craniectomy meant a 265% increase in the chance of death when compared with a patient who did not need it.
   - Patients who had an MLS between zero and 5 mm had a 172% increase in the chance of death. However, patients with an MLS between 12 and 15 mm, when compared with patients with an MLS equal to zero, presented a 63% decrease in the chance of death.

Institutions in Which the Present Work was Performed
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Hospital Governador Celso Ramos (HGCR).

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Appendix

The following tables provide a descriptive analysis, respectively, of the following variable levels: GCS, sequelae at discharge, days of hospitalization, days of ICU stay, death, Marshall CT classification, and decompressive craniectomy, regarding the values of the variable GCS-P (►**Tables 6** to **12**).

Table 6 Descriptive analysis: GCS-P x GCS

GCS/ GCS-P	3		4		5		6		7		8		9		10		11		12		13		14		15	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1	40	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
2	8	66.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	4	33.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
3	76	97.4%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	2.6%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
4	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	4	66.7%	0	0.0%	2	33.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
5	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	5	62.5%	1	12.5%	2	25.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
6	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	9	81.8%	2	18.2%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
7	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	6	85.7%	0	0.0%	1	14.3%	0	0.0%	0	0.0%
8	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	8	100.0%	0	0.0%	0	0.0%	0	0.0%
9	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	12	100.0%	0	0.0%	0	0.0%
10	0	0.0%	1	6.7%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	14	93.3%	0	0.0%
11	0	0.0%	1	11.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	8	88.9%
12	0	0.0%	7	87.5%	0	0.0%	1	12.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
13	0	0.0%	0	0.0%	22	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
14	0	0.0%	0	0.0%	0	0.0%	41	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
15	0	0.0%	0	0.0%	0	0.0%	0	0.0%	41	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%

Abbreviations: GCS, Glasgow coma scale; GCS-P, Glasgow P.

Table 7 Descriptive analysis: GCS-P x Sequelae

GCS-P x Sequelae	Cognitive		Swallowing disorders/ Speech-language		Psychological		Physical		Multiple		Death		Vegetative state		No sequela/ Not informed/ Transferred		Present and uninformed sequela	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1	1	2.5%	0	0.0%	0	0.0%	1	2.5%	9	22.5%	20	50.0%	4	10.0%	3	7.5%	2	5.0%
2	1	8.3%	1	8.3%	0	0.0%	0	0.0%	3	25.0%	6	50.0%	1	8.3%	0	0.0%	0	0.0%
3	5	6.4%	1	1.3%	0	0.0%	6	7.7%	22	28.2%	22	28.2%	5	6.4%	16	20.5%	1	1.3%
4	0	0.0%	0	0.0%	0	0.0%	1	16.7%	0	0.0%	3	50.0%	1	16.7%	1	16.7%	0	0.0%
5	0	0.0%	0	0.0%	0	0.0%	2	25.0%	3	37.5%	3	37.5%	0	0.0%	0	0.0%	0	0.0%
6	1	9.1%	0	0.0%	0	0.0%	0	0.0%	5	45.5%	2	18.2%	1	9.1%	2	18.2%	0	0.0%
7	1	14.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	4	57.1%	1	14.3%	1	14.3%	0	0.0%
8	1	12.5%	0	0.0%	0	0.0%	0	0.0%	2	25.0%	3	37.5%	0	0.0%	2	25.0%	0	0.0%
9	0	0.0%	0	0.0%	0	0.0%	1	8.3%	5	41.7%	5	41.7%	0	0.0%	1	8.3%	0	0.0%
10	3	20.0%	1	6.7%	0	0.0%	3	20.0%	2	13.3%	4	26.7%	0	0.0%	1	6.7%	1	6.7%
11	0	0.0%	0	0.0%	0	0.0%	2	22.2%	2	22.2%	5	55.6%	0	0.0%	0	0.0%	0	0.0%
12	0	0.0%	0	0.0%	0	0.0%	0	0.0%	3	37.5%	3	37.5%	0	0.0%	2	25.0%	0	0.0%
13	1	4.5%	1	4.5%	0	0.0%	2	9.1%	1	4.5%	6	27.3%	1	4.5%	10	45.5%	0	0.0%
14	1	2.4%	0	0.0%	0	0.0%	3	7.3%	11	26.8%	10	24.4%	0	0.0%	15	36.6%	1	2.4%
15	0	0.0%	0	0.0%	1	2.4%	0	0.0%	6	14.6%	5	12.2%	1	2.4%	25	61.0%	3	7.3%

Abbreviations: GCS-P, Glasgow P.

Table 8 Descriptive analysis: GCS-P x Hospitalization time (days)

GCS-P/Hospitalization time (days)	≤ 7 days		8–14 days		15–30 days		31–60 days		> 60 days	
	N	%	N	%	N	%	N	%	N	%
1	9	22.5%	6	15.0%	7	17.5%	9	22.5%	9	22.5%
2	3	25.0%	1	8.3%	3	25.0%	5	41.7%	0	0.0%
3	10	13.3%	11	14.7%	21	28.0%	22	29.3%	11	14.7%
4	3	50.0%	0	0.0%	1	16.7%	1	16.7%	1	16.7%
5	1	12.5%	2	25.0%	1	12.5%	2	25.0%	2	25.0%
6	1	9.1%	1	9.1%	2	18.2%	5	45.5%	2	18.2%
7	1	14.3%	2	28.6%	1	14.3%	2	28.6%	1	14.3%
8	0	0.0%	3	37.5%	1	12.5%	3	37.5%	1	12.5%
9	3	25.0%	1	8.3%	4	33.3%	3	25.0%	1	8.3%
10	2	13.3%	6	40.0%	5	33.3%	2	13.3%	0	0.0%
11	1	11.1%	2	22.2%	2	22.2%	3	33.3%	1	11.1%
12	3	37.5%	1	12.5%	1	12.5%	2	25.0%	1	12.5%
13	9	40.9%	6	27.3%	2	9.1%	3	13.6%	2	9.1%
14	12	29.3%	11	26.8%	6	14.6%	8	19.5%	4	9.8%
15	17	41.5%	8	19.5%	10	24.4%	4	9.8%	2	4.9%

Abbreviation: GCS-P, Glasgow P.

Table 9 Descriptive analysis: GCS-P x ICU time (days)

GCS-P/ICU time (days)	Transferred		Zero		1–3 days		4–7 days		8–14 days		15–21 days		> 21 days	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1	0	0.0%	2	5.0%	3	7.5%	8	20.0%	6	15.0%	11	27.5%	10	25.0%
2	0	0.0%	0	0.0%	1	8.3%	3	25.0%	3	25.0%	3	25.0%	2	16.7%
3	5	6.4%	2	2.6%	1	1.3%	11	14.1%	22	28.2%	16	20.5%	21	26.9%
4	0	0.0%	0	0.0%	1	16.7%	1	16.7%	2	33.3%	1	16.7%	1	16.7%
5	0	0.0%	0	0.0%	0	0.0%	1	12.5%	3	37.5%	3	37.5%	1	12.5%
6	0	0.0%	0	0.0%	0	0.0%	1	9.1%	2	18.2%	5	45.5%	3	27.3%
7	0	0.0%	0	0.0%	0	0.0%	3	42.9%	2	28.6%	0	0.0%	2	28.6%
8	0	0.0%	0	0.0%	0	0.0%	1	12.5%	4	50.0%	2	25.0%	1	12.5%
9	0	0.0%	0	0.0%	2	16.7%	2	16.7%	4	33.3%	2	16.7%	2	16.7%
10	0	0.0%	1	6.7%	2	13.3%	2	13.3%	6	40.0%	3	20.0%	1	6.7%
11	0	0.0%	0	0.0%	1	11.1%	1	11.1%	4	44.4%	2	22.2%	1	11.1%
12	0	0.0%	2	25.0%	1	12.5%	1	12.5%	1	12.5%	2	25.0%	1	12.5%
13	1	4.5%	8	36.4%	2	9.1%	4	18.2%	1	4.5%	2	9.1%	4	18.2%
14	0	0.0%	11	26.8%	5	12.2%	6	14.6%	4	9.8%	11	26.8%	4	9.8%
15	0	0.0%	18	43.9%	7	17.1%	7	17.1%	4	9.8%	4	9.8%	1	2.4%

Abbreviations: GCS-P, Glasgow P; ICU, intensive care unit.

Table 10 Descriptive analysis: GCS-P x death

GCS-P/death	No		Yes		Transferred	
	n	%	*n*	%	*n*	%
1	20	50.0%	20	50.0%	0	0.0%
2	6	50.0%	6	50.0%	0	0.0%
3	51	65.4%	22	28.2%	5	6.4%
4	3	50.0%	3	50.0%	0	0.0%
5	5	62.5%	3	37.5%	0	0.0%
6	9	81.8%	2	18.2%	0	0.0%
7	3	42.9%	4	57.1%	0	0.0%
8	5	62.5%	3	37.5%	0	0.0%
9	7	58.3%	5	41.7%	0	0.0%
10	11	73.3%	4	26.7%	0	0.0%
11	4	44.4%	5	55.6%	0	0.0%
12	4	50.0%	3	37.5%	1	12.5%
13	15	68.2%	6	27.3%	1	4.5%
14	31	75.6%	10	24.4%	0	0.0%
15	35	85.4%	5	12.2%	1	2.4%

Abbreviation: GCS-P, Glasgow P.

Table 11 Descriptive analysis: GCS-P x Marshall CT classification

GCS-P/ Marshall	Marshall I		Marshall II		Marshall III		Marshall IV		Marshall V		Marshall VI		Unclassified	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
1	0	0.0%	17	42.5%	6	15.0%	12	30.0%	3	7.5%	2	5.0%	0	0.0%
2	1	8.3%	3	25.0%	1	8.3%	5	41.7%	0	0.0%	0	0.0%	2	16.7%
3	0	0.0%	40	51.3%	13	16.7%	18	23.1%	3	3.8%	1	1.3%	3	3.8%
4	0	0.0%	3	50.0%	1	16.7%	0	0.0%	0	0.0%	1	16.7%	1	16.7%
5	0	0.0%	4	50.0%	1	12.5%	3	37.5%	0	0.0%	0	0.0%	0	0.0%
6	0	0.0%	4	36.4%	1	9.1%	3	27.3%	1	9.1%	1	9.1%	1	9.1%
7	0	0.0%	3	42.9%	3	42.9%	0	0.0%	1	14.3%	0	0.0%	0	0.0%
8	0	0.0%	2	25.0%	2	25.0%	3	37.5%	1	12.5%	0	0.0%	0	0.0%
9	1	8.3%	3	25.0%	4	33.3%	2	16.7%	2	16.7%	0	0.0%	0	0.0%
10	0	0.0%	6	40.0%	0	0.0%	6	40.0%	2	13.3%	0	0.0%	1	6.7%
11	0	0.0%	3	33.3%	0	0.0%	3	33.3%	3	33.3%	0	0.0%	0	0.0%
12	0	0.0%	4	50.0%	0	0.0%	3	37.5%	1	12.5%	0	0.0%	0	0.0%
13	0	0.0%	5	22.7%	5	22.7%	6	27.3%	3	13.6%	1	4.5%	2	9.1%
14	0	0.0%	19	46.3%	5	12.2%	9	22.0%	4	9.8%	3	7.3%	1	2.4%
15	2	4.9%	22	53.7%	3	7.3%	10	24.4%	3	7.3%	1	2.4%	0	0.0%

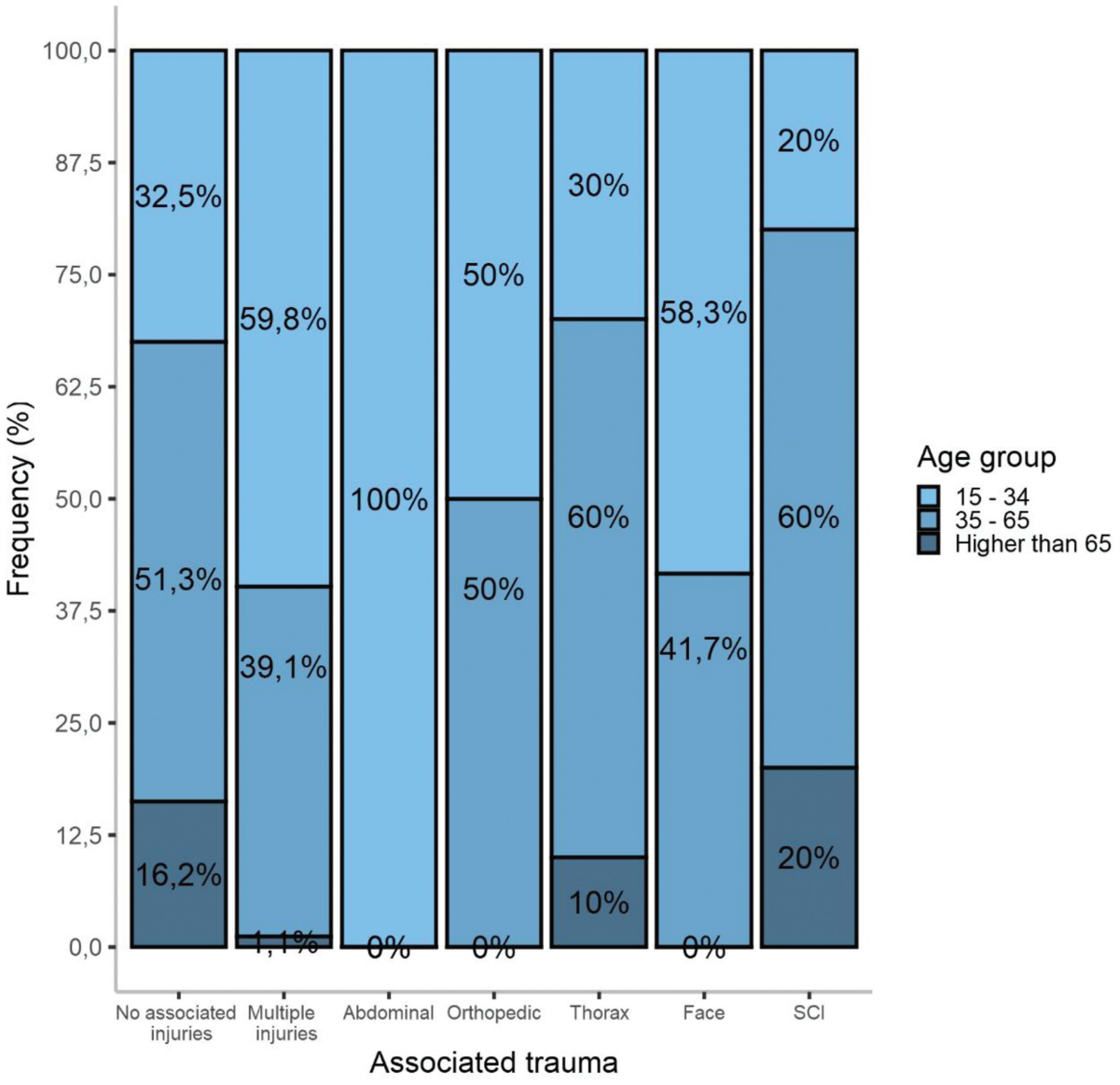
Abbreviations: CT, computed tomography; GCS-P, Glasgow P.

Table 12 Descriptive analysis: GCS-P x decompressive craniectomy

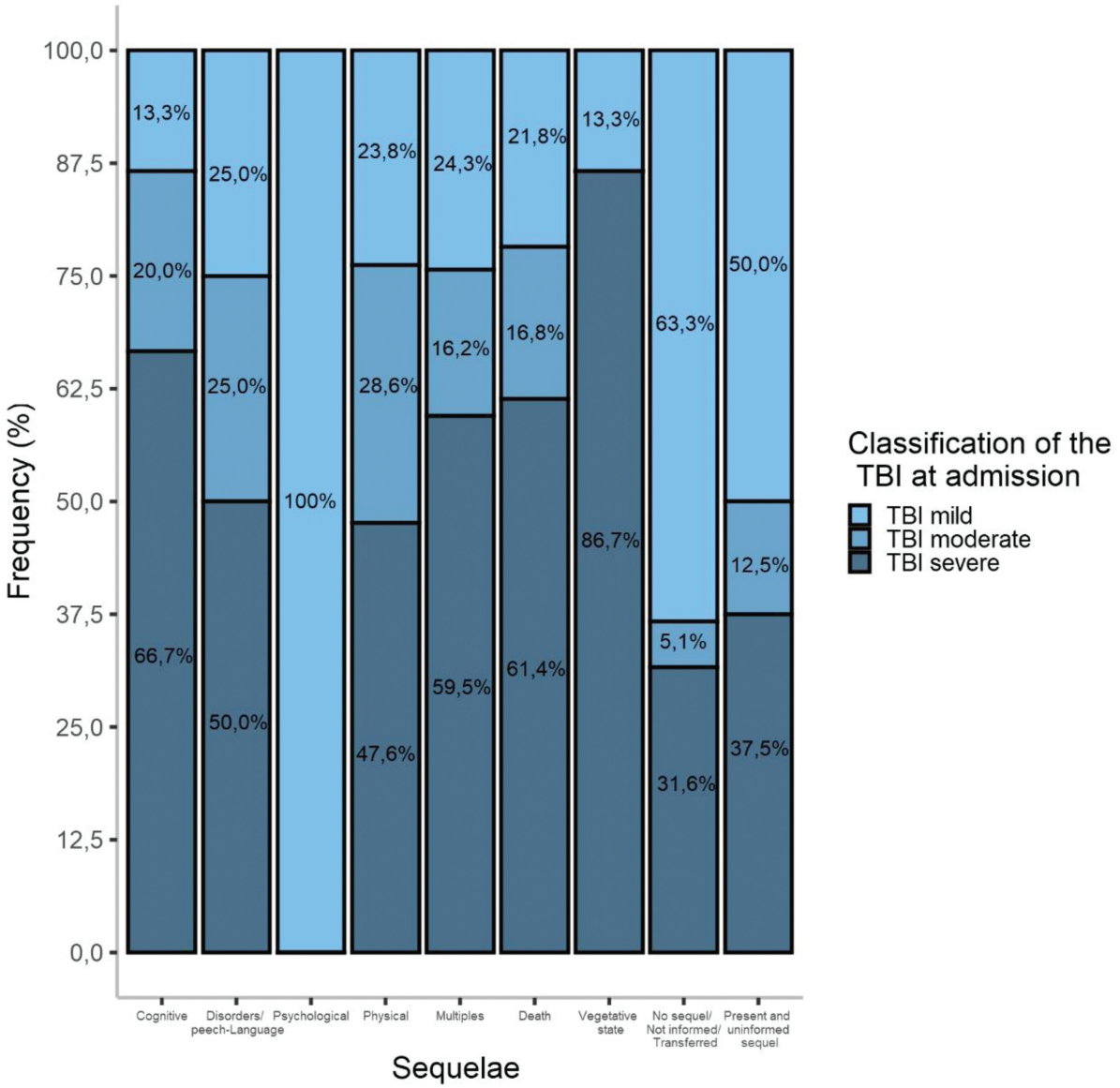
GCS-P/Decompressive craniectomy	No		Yes	
	N	%	N	%
1	27	67.5%	13	32.5%
2	8	66.7%	4	33.3%
3	57	73.1%	21	26.9%
4	4	66.7%	2	33.3%
5	7	87.5%	1	12.5%
6	6	54.5%	5	45.5%
7	5	71.4%	2	28.6%
8	5	62.5%	3	37.5%
9	7	58.3%	5	41.7%
10	12	80.0%	3	20.0%
11	6	66.7%	3	33.3%
12	7	87.5%	1	12.5%
13	15	68.2%	7	31.8%
14	25	61.0%	16	39.0%
15	37	90.2%	4	9.8%

Abbreviations: GCS-P, Glasgow P.

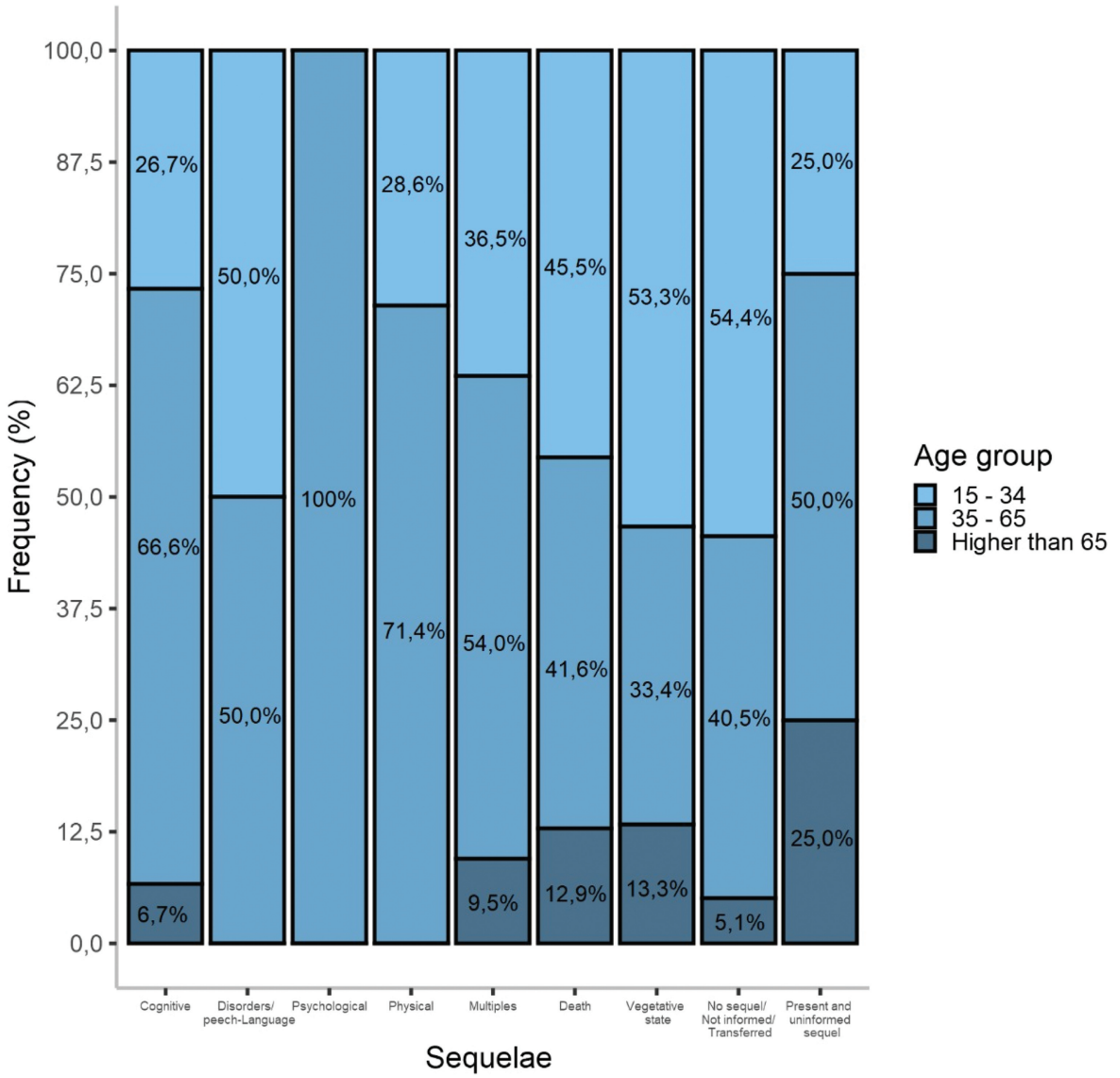
The following graphs show the relationship between, respectively: age group and associated trauma, TBI classification and sequelae at hospital discharge and age group and sequelae at hospital discharge (►**Graphs 4** to **6**).



Graphic 4 Age group and associated trauma.



Graphic 5 TBI classification and sequelae at hospital discharge.



Graphic 6 Age group and sequelae at hospital discharge.

Peculiarities of Atypical Meningiomas: Literature Review

Peculiaridades dos meningiomas atípicos: Revisão da literatura

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Abstract

Introduction Meningiomas are common tumors of the central nervous system that represent around 30% of primary tumors. However, the incidence of atypical meningiomas (AMs) is lower, of approximately 15% of all meningiomas, and they present high rates of relapse and mortality.

Aim To review peculiarities of AMs.

Methodology A literature review of articles published in English between 2009 and 2020 on the PubMed and Biblioteca Virtual em Saúde (BVS) databases using the terms *meningioma* and *atypical*.

Results Atypical meningiomas are rare and more prevalent in older males. The clinical condition depends on the site of the tumor, and a definitive diagnosis of AM is only possible via anatomical pathology. Moreover, prominent studies have indicated a relationship between the presence of the anti-Ki67 antibody/mindbomb (K_i-67/*MIB1*) marker as an aid in the definition of AM and one of the determinants of tumor aggressiveness. Imaging studies have also advanced in terms of seeking criteria using magnetic resonance that may suggest the malignancy of a lesion. As far as treatment is concerned, total resection remains the main therapeutic option, and it has a direct relationship with survival and time until disease progression. Lastly, there are many factors involved in the prognosis of AM.

Keywords
- meningioma
- malign meningioma
- immuno-histochemistry
- prognosis

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Conclusion Atypical meningiomas continue to be a challenge, requiring further and more specific studies to provide a better understanding of it.

Resumo

Introdução Os meningiomas são tumores comuns do sistema nervoso central, representando cerca de 30% dos tumores primários. Contudo, a incidência de meningiomas atípicos (MA) é menor, cerca de 15% do total dos meningiomas, e eles apresentam altas taxas de recidiva e mortalidade.

Metodologia Revisão da literatura, nas bases de dados PubMed e Biblioteca Virtual em Saúde (BVS), utilizando os termos "meningioma" e "atypical", publicados em língua inglesa entre 2009 e 2020.

Objetivo Revisar as particularidades dos MA.

Resultados MA são raros, mais prevalentes em homens de idade avançada. O quadro clínico depende da localização do tumor e o diagnóstico definitivo de MA só se dá por meio do anatomopatológico. Ademais, estudos importantes têm apontado para a relação da presença do marcador anticorpo monoclonal/mindbomb (Ki-67/MIB1) como auxiliador na definição de MA e um dos determinantes de agressividade tumoral. Os estudos de imagem também avançam no sentido de buscar critérios na ressonância magnética que possam sugerir a malignidade de uma lesão. Em relação ao tratamento, a cirurgia de ressecção total se mantém como principal terapêutica, com relação direta na sobrevida e no tempo livre de progressão de doença. Por fim, o prognóstico em MA é multifatorial.

Conclusão MA continuam como um desafio, necessitando de mais estudos específicos para compreendê-los melhor.

Palavras-chave
- meningioma
- meningioma maligno
- imuno-histoquímica
- prognóstico

Introduction

The original definition of meningioma was coined in 1922 by Harvey Cushing, who described it as a tumor originating in the meninges, in both the brain and the spinal cord.[1] According to the definition, these tumors originate from cells in the arachnoid meninge.[2]

Their incidence shows that they are common tumors of the central nervous system (CNS) originating in the meninge, in particular the arachnoid, and are usually benign and one-off.[3,4] This type of lesion equates to around 30% of all primary tumors of the CNS, and it typically occurs in older individuals, for whom the incidence is of approximately 6 per 100 thousand.[3,5]

According to the 2016 classification by the World Health Organization (WHO), there are three different grades of meningioma, namely: benign meningioma (grade I), atypical meningioma (AM, grade II), and anaplastic meningioma (grade III).[6] Grade I accounts for 80% to 92% of the cases, while grade II represents 4.2% to 15% of all meningiomas, and grade III, 1% to 3%.[5,7,8]

Grade-II meningiomas are characterized by high rates of mitosis, accompanied by cell necrosis, hypercellularity, structural changes to the cells, in addition to leading to invasion of the adjacent tissue.[2,7] They also present a 40% recurrence rate within 5 years of total resection, and a high rate of mortality when compared with grade-I meningiomas.[6,7]

In addition to a histological evaluation, immunohistochemistry is of paramout importance in the evaluation of AMs and anaplastic meningiomas, particularly the following markers: the epithelial membrane antigen, the MIB-1 antibody, and the cell proliferation marker anti-K_i67 antibody (K_i–67).[7] The present study intends to provide a broad, updated review of the literature concerning the peculiarities of AMs.

Methodology

Imaging

The present study used the imaging scans of a patient with an AM cared for in Clinic N3 and operated on at the neurosurgery services of Hospital Evangélico de Londrina, state of Paraná, Brazil by one of the authors (CAMZ). Permission for the use of the images was acquired through a Free and Informed Consent Agreement, which was understood and signed by the patient.

Literature Review

The literature review of articles published between 2009 and 2020 was conducted on the PubMed and Biblioteca Virtual em Saúde (BVS) databases.

The descriptors used were *meningioma* and *atypical*. The inclusion criteria were: the explicit mention of the words *atypical meningioma* or *WHO grade-II meningioma*, articles published in journals with an impact factor greater than 1, and studies in English. The following articles were excluded: those relating to pediatric meningiomas, those concerning

syndromes that mimic meningiomas, and case reports, editorials, ideas and opinions. Access to the articles was gained via the periodical platform of Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).[a]

Results

Epidemiology

Meningiomas are responsible for more than 30% of CNS tumors, with an incidence between 4.4 and 6 per 100 thousand inhabitants, and AMs consitute 4.2% to 15% of the cases.[9–11] In general, meningiomas are more common in women aged between 50 and 60 years; however, WHO grade-II meningiomas are more prevalent in older males, usually between 60 and 70 years of age.[8,9,12] This epidemiological difference seems to be explained by the influence of estrogen in the pathogenicity of WHO grade-I meningiomas, which does not occur with grade-II or grade-III meningiomas.[10] The average rate of incidence of meningiomas in the United States was higher than 25 thousand cases a year between 2008 and 2012, a consequence of the greater access to imaging examinations and the aging of the population, leading to an increase of 3.9 times since 1943.[13,14] The chance of developing this type of lesion, in the absence of risk factors, is of $\sim$ 1%.[13] Metastasis is extremely rare, occurring in 0.1% of cases, mainly affecting the lungs and liver, and as many as 3% of WHO grade-II meningiomas evolve into grade III.[12,15]

Clinical Condition and Site of the AM

The clinical presentation of meningiomas depends on the site affected, commonly associated with cephalea secondary to tumor growth, focal neurological deficit, convulsions directly or indirectly associated with the tumor, and changes in vision and behavior.[12,13] The case studies presented by Gyawali et al.[16] demonstrate that one of the more common sites for the development of meningiomas, in general, is the frontal lobe, and patients may develop psychiatric symptoms such as severe depression and, in more serious cases, Godot syndrome, which is characterized by the association of accentuated symptoms of anxiety and dementia. Obsessive symptoms are more frequently linked to lesions situated in the left frontal lobe, while the involvement of the right frontal lobe is more commonly related to bipolar disorders, alcohol abuse, and visual and auditory hallucinations.[16] A short while after, another study[13] demonstrated that the most common site of intracranial and juxtacrine meningiomas is the convexity (lateral area of the hemispheres), corresponding to 20% to 34% of cases, while the frontobasal lesions are ranked in fourth position, accounting for around 10% of the cases; therefore, the clinical presentation depends on the site of the lesion.

AMs present with a slightly different behavior. The most common location is also in the convexity, it corresponds to around 57% of the cases, followed by the cerebral sickle (12%), the posterior fossa (10%), frontobasal (6%), the sphenoid wing (4%), the parasagittal (4%), the tentorial (4%), the cavernous sinus (2%), and other sites that correspond to around 1% of the cases (tuberculum sellae, orbital sphenoid, and orbit).[17] The lesions at the base of the skull is an independent risk factor for WHO grade-II and grade-III tumors.[18]

Anatomical Pathology

The diagnosis of meningiomas is still established through an anatomo-pathological analysis of the resected tumor.[8,10] According to the 2016 WHO classification, atypical meningiomas are characterized by the presence of at least three of the following histological changes: 1) spontaneous necrosis; 2) loss of architectural structure; 3) prominent nucleus; 4) hypercellularity; and 5) small cells or the presence of cerebral invasion with 4 or more mitosis per field. Accordingly, the rate of mitosis per field may be used to differentiate between an atypical lesion and an anaplastic lesion, and this is because meningiomas with more than 20 mitoses per 10 high-power fields are classified as WHO grade-III, while rates between 4 and 19 mitoses remain in the WHO grade-II spectrum.[13] Goés et al.,[20] in a case study involving 106 patients, evaluated spontaneous necrosis present in WHO grade-I and grade-II tumors, and concluded that those patients suffering from AM with evidence of spontaneous necrosis present a 4.2-time higher risk of recurrence compared with patients without this histological characteristic. Moreover, a recent systematic review with meta-analysis[21] demonstrated that, for every increase of 1 mitosis per 10 high-power fields, the risk of recurrence of AM goes up 20%.

Besides the microscopic characteristics, the immunohistochemical analysis has great diagnostic and prognostic value regarding WHO grade-II meningiomas.[8,10] Several studies have indicated that, in addition to the presence of *epithelial membrane antigen* (EMA) and negativity for *protein S-100* (also present in grade-I meningiomas), the positivity of marker *K_i-67/MIB-1* may be useful for differentiating between AMs and other subtypes.[8] The presence of this marker is directly related to the more aggressive behavior of this subtype.[8,22] The systematic review with meta-analysis conducted by Liu et al.[22] (2020), demonstrated that the high expression of *K_i-67* ($>$ 4%) is linked to worse overall survival, greater disease progression, and higher rates of recurrence of the tumor.

The *K_i-67* marker may be positive in around 7.2% of patients with AMs; moreover, the male gender may be considered an independent risk factor for high rates of *K_i-67* positivity. Tumors at the base of the skull usually present a low *K_i-67* index.[16] Progesterone receptors are less prominent in grade-II meningiomas and may have an inverse relationship with *K_i-67* rates.[18]

Bromodeoxyuridine (*BrdU*) has a close relationship with the rates of tumor recurrence: when greater than 5%, a 100% probability of recurrence is denoted; moreover, the high

[a] A foundation within the Brazilian Ministry of Education whose central purpose is to coordinate efforts to improve the quality of Brazil's faculty and staff in higher education through grant programs.

expression of *fatty acid synthase* (FAS) and *brain fatty acid-binding protein* (BFABP) is associated with invasion of the adjacent tissue by the tumor and an increased chance of recurrence.[18]

Around 71.4% of WHO grade-II tumors present an overexpression of CD163, and this is associated with the accelerated growth of the tumor and, in other types of cancer, with a bad prognosis.[23]

Genetic, Epigenetic and Molecular Alterations

High-grade meningiomas, like AMs, have been shown to have high cytogenetic and molecular complexity, with activation of oncogenes, inactivation of tumor-suppressor genes, and alterations to other genes involved in various molecular pathways.[9] In this regard, these neoplasias present a higher expression of *patched 1* (*PTCH1*) *messenger ribonucleic acid* (*mRNA*, an important receptor protein), aberrant methylation of *tissue inhibitor of metalloproteinase 3* gene (*TIMP3*), aberrant methylation of *WNK lysine deficient protein kinase 2* (*WNK2*), high levels of *microRNA-21* (*miR-21*), as well as anomalous signaling through proteins of the *insulin-like growth factor* (IGF) family.[9] In general, these alterations are related to greater progression, increased tumorigenicity, and to a higher rate of recurrence of grade-II and -III meningiomas.[9] Moreover, AMs may be generated by mutations in particular genes, such as a loss of *6q*, *9p*, *10q* and *14q*, as well as expansion in *17q*. There are also rare cases in which grade-II meningiomas develop due to mutations in tumor-suppressor genes such as *TP53* and/or deletion of the *cyclin-dependent kinase inhibitor 2A* (*CDKN2A*) gene.[8,9]

The association of mutations in the *neurofibromin 2* (*NF2*) gene with meningioma is well documented; moreover, there is a predilection for this mutation when linked to losses in chromosomes *22q* and *1p* in WHO grade-I lesions, present in around 50% of cases.[24] This genetic pattern is associated with patients diagnosed with AM with an average age of 60 years, more common in men and less frequently afflicting the base of the skull.[24]

Imaging Examination

With regard to the radiology of AMs, recent studies point to certain characteristics in magnetic resonance imaging (MRI) that may indicate high-grade meningiomas.[10,25] In this regard, the case series by Tan et al.[25] (2015) demonstrated that the points that differentiate WHO grade-I meningiomas from grades II and III are: increased perfusion (mean cerebral blood volume), high-value tensor diffusion imaging (anisotropic fraction), spectroscopy with increased choline/creatine (-Cho/Cr), and the presence of lactate. Other characteristics that point to atypia of the meningioma are areas of hypodense tumor and margins indicative of cerebral invasion.[9]

Recently, studies have shown that there are semantic, radiomic values in MRI that may be able to predict AM recurrence. In this regard, Darius Kalasauskas et al.[26] (2020), in a cohort study comprising 76 patients with an average follow-up of 41.6 months, identified that the presence of a cystic component in AM was associated with a worse prognosis and shorter time until recurrence ($p < 0.001$).

Examples of AM can be seen in ►**Figs. 1** and **2**.

Surgery

Surgery is the main treatment for meningiomas, as it enables the histopathological classification and exerts an important influence on the time until recurrence.[8,10,12,21,26] The aims of surgery and Simpson resection grades are the same as those for WHO grade-I meningiomas and other meningioma subtypes.[10,21,27] Simpson grade-I surgical resection is the technique with the highest margin of safety, which involves complete resection of the tumor, with a healthy margin of dura mater and of the affected bone.[10] The use of this technique is linked to greater patient survival and a longer recurrence-free time.[27] Nevertheless, there are situations in

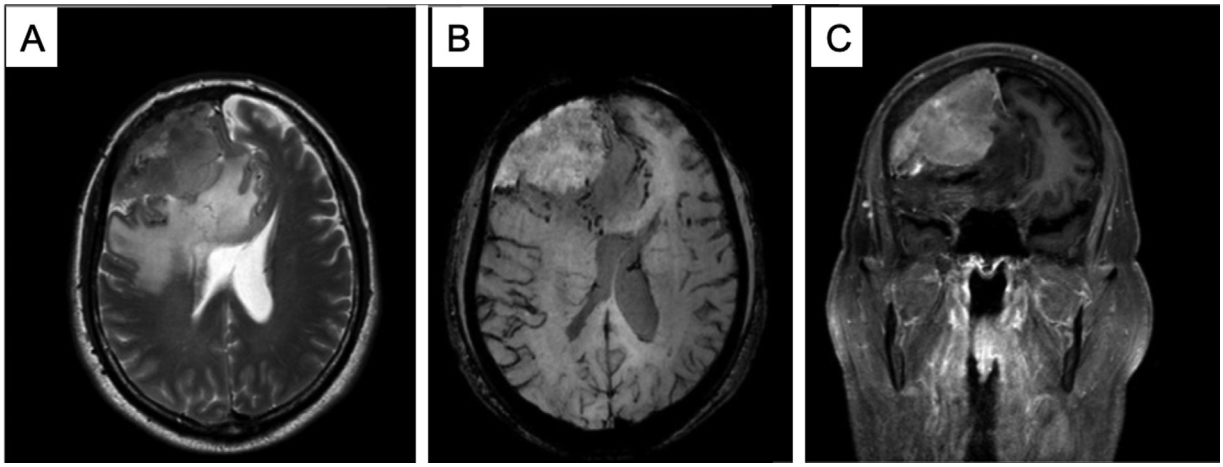

Fig. 1 Axial section of a T2-weigthed magnetic resonance imaging (MRI) scan (**A**) and fluid-attenuated inversion recovery (FLAIR) (**B**), and coronal section (**C**) demonstrating an expansive lesion measuring 7.4 × 7.3 × 4.2 cm (latero-lateral (LL) x antero-posterior (AP) x craniocaudal (CC)), particularly extra-axial in the right frontal region, with signs of dural implantation in the inner table of the frontal right bone and contact with the interhemispheric falx and upper sagittal sinus (anterior region). The lesion presents an extensive area with hypersignal in T2/FLAIR in the adjacent parenchyma, suggesting edema. Mass effect is evidenced through the deviation of the midline to the left, as well as obliteration of grooves and descending transtentorial uncal herniation.

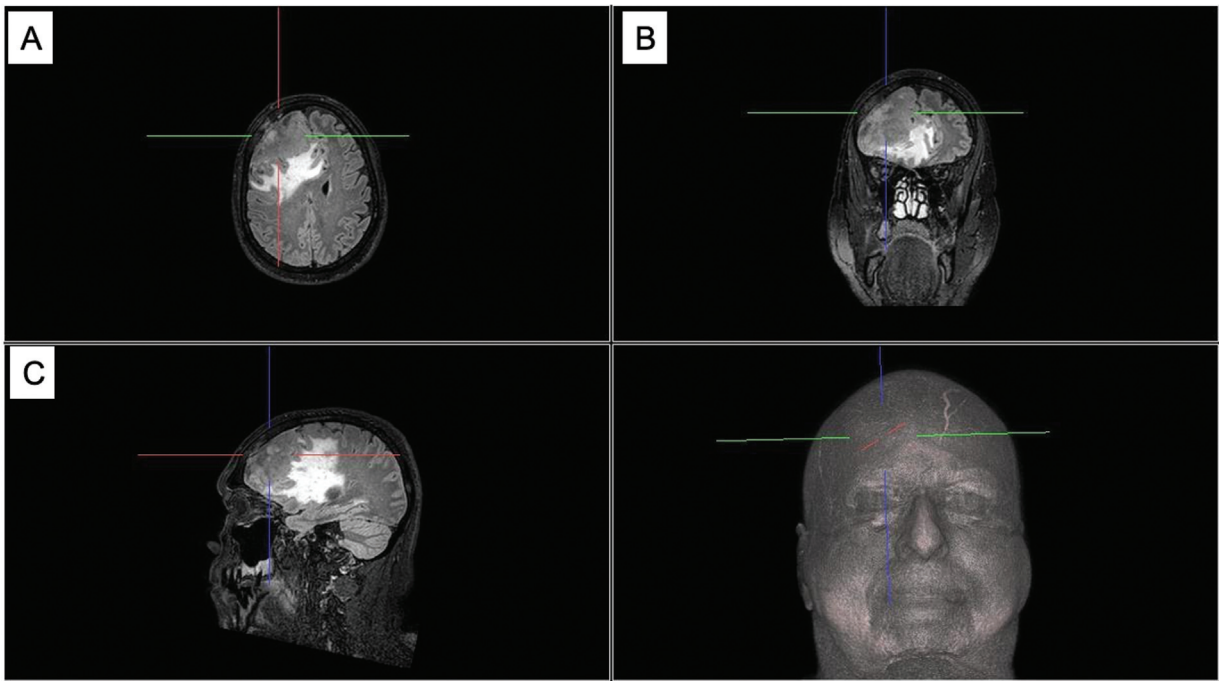

Fig. 2 Encephalon MRI. Axial (**A**), coronal (**B**) and sagittal (**C**) sections in FLAIR demonstrating an atypical meningioma with an emphasis on tumor infiltration.

which this technique cannot be used, depending on the site and the degree of invasion in the cerebral parenchyma.[10,27] In this regard, the other Simpson resection grades that may be used are: grade II (complete macroscopic resection with coagulation of the dural attachment); grade III (macroscopic resection of the tumor without resection of the affected dura mater or bone); grade IV (partial resection); and grade V (biopsy). It is important to stress that the extent of tumor resection is recognized as the main predictor of survival in patients with meningiomas.[8,10,12,21,26–28]

Meningiomas are generally vascularized and, in cases in which hypervascularization is identified, or when it is supposed that it will be possible to rapidly control the bleeding during the surgical procedure, this may be preceded by prior embolization of the tumor.[10] In these cases, an embolic liquid is normally used, such as ethylene vinyl-alcohol (EVOH) copolymer, with the aim of facilitating the surgical procedure.[10]

Surgical planning and postoperative control are as important as the surgical procedure itself (►**Figs. 3** and **4**).

Associated Treatment

There are differences of opinion about the benefits and the harm caused by adjunct radiotherapy (RT) after the partial and total resection of the AM.[3,10,29] Many studies[3,27,29] demonstrate that RT after total resection of the tumor is not relevant for the local control of recurrence and for the survival of the patient. Meanwhile, other articles indicate[3,10,30] an important benefit when said adjunct therapy is used. The types of RT that can be employed are stereotaxic radiosurgery and fractionated external beam RT.[3]

Due to the aggressive behavior of these meningiomas, the use of drug therapy may be necessary. In this regard, recent studies[10,31] have pointed to the efficacy of hydroxyurea in cases of incomplete AM resection in relation to the increase in progression-free survival when compared with the conservative treatment. Other studies[32] show success with the use of bevacizumab (Avastin, Genentech, South San Francisco, CA, United States), a monoclonal antibody that blocks the action of vascular endothelial growth factor (VEGF), precluding the growth of blood vessels that feed malignant tumors, for the treatment of refractory AMs. It should be stressed that, with meningiomas, there was no significant efficacy of the classic chemotherapy agents like temozolomide, irinotecan, doxorubicin and ifosfamide.[27]

Prognosis

As far as AM is concerned, after total resection, the rate of recurrence is of $\sim$ 40%, and survival is of $\sim$ 11.8 years.[11,19] Of the prognosis markers, K_i-*67* is related to the rate of survival, and patients who present K_i-*67* $< 10\%$ have a 60% higher rate of survival when compared with patients with K_i-*67* $> 10\%$.[33] Another factor related to the increase in AM patient survival is being under 60 years of age, and undergoing Simpson grade I resection ($p = 0.055$). Radiotherapy and adjuvant chemotherapy did not show statistical significance in terms of the increase in the survival of these patients.[33] In general, atypical lesions are associated with a longer time to disease progression (TDP), when compared with anaplastic lesions. In 2009, Durand et al.[33] suggested that patients submitted to postoperative RT presented a shorter TDP when compared with those who did not undergo RT. In cases in which a subtotal or partial resection is performed, there appears to be consensus as to the indication of postoperative RT, while in patients submitted to total resection of the lesion with tumor recurrence, reoperation is preferable due to high mortality rates of AMs, as recurrent AMs present an increased risk of mortality.[34]

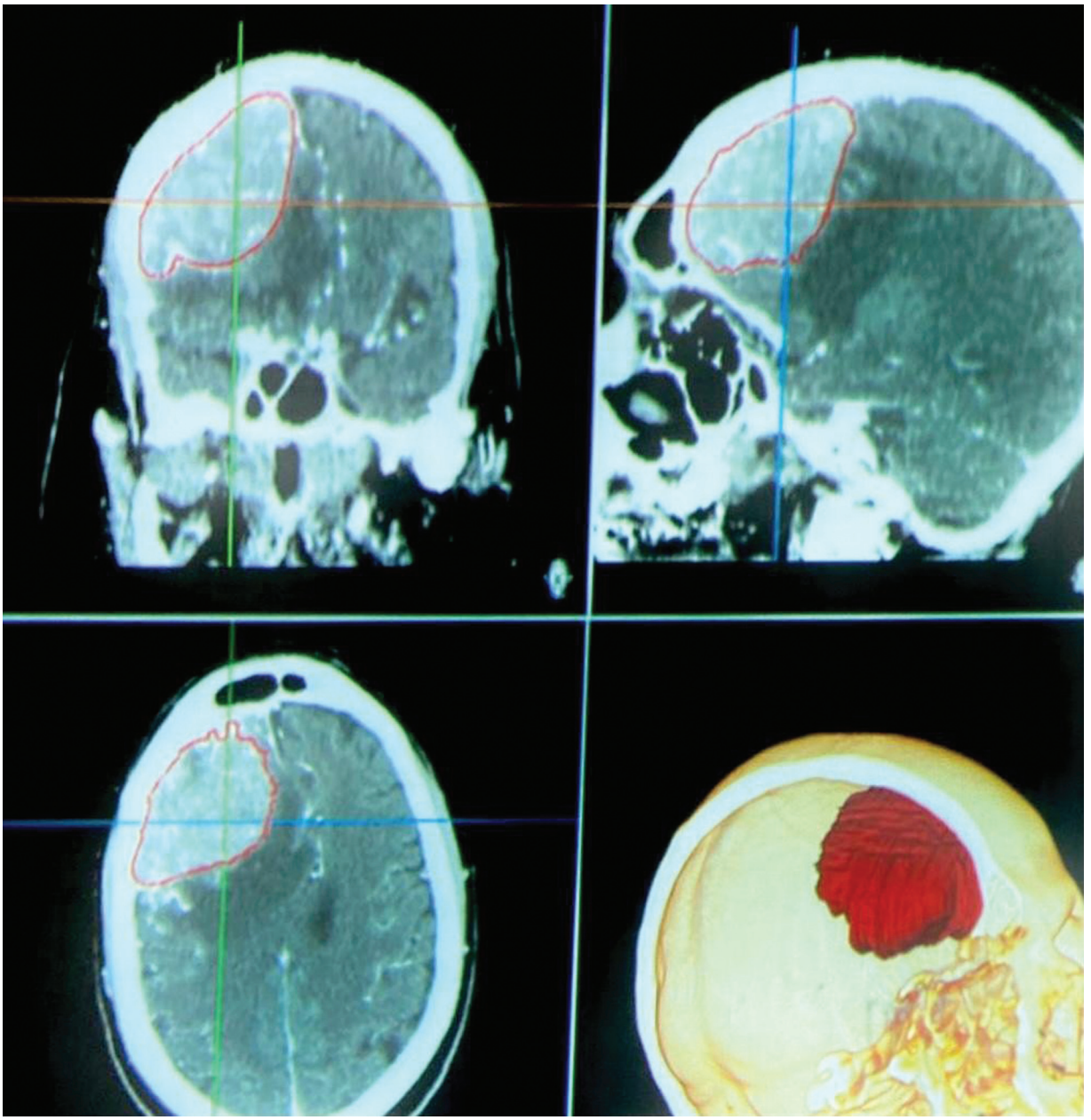

Fig. 3 Image of the neuronavigation for surgical planning.

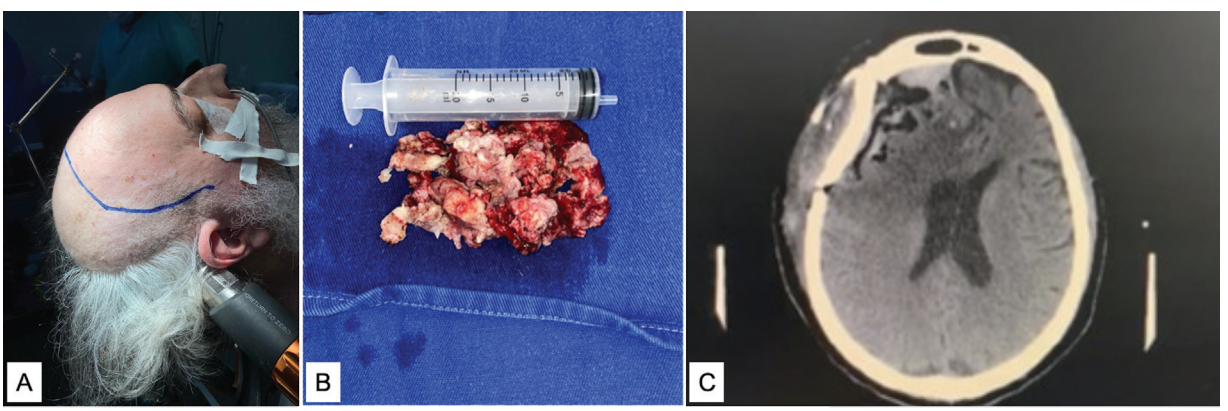

Fig. 4 Patient positioned with Mayfield skull clamp (**A**). Macroscopic view of the tumor (**B**). Postoperative computed tomography scan of sthe kull demonstrating total resection of the tumor (Simpson grade I) with cranial reconstruction with bone cement (**C**).

Metastasis is rare. The cohort study by Williams et al., who evaluated a group of meningioma patients of all grades, emphasized the recurrence of metastasis mainly in grade-II lesions (16/441), and it seems to be associated with genetic alterations related for the most part to *NF2*, in addition to cyclin-dependent kinase inhibitor 2A (CDKN2A), BRCA1 associated protein-1 (BAP1), telomerase reverse transcriptase promoter (TERTp).[24]

Lastly, Chen et al.[28] (2020) indicated, in a cohort study, that preoperative blood tests can help predict the prognosis of patients with AM, as they observed a significant association between the pre-operative score of the *fibrinogen and neutrophil–lymphocyte ratio* (F-NLR) biomarker and a recurrence of the tumor within three years. The group who presented with high levels of hyperfibrinogenemia and a high neutrophil–lymphocyte ratio had a recurrence earlier (median: 29.79 months), when compared with the groups who presented low levels of fibrinogen or a low neutrophil–lymphocyte ratio.[28]

Final Considerations

In this literature review, we sought to clarify the peculiarities of atypical meningiomas, in order to facilitate the diagnosis and follow-up of these patients.

In this context, AMs have peculiar characteristics in comparison with WHO grade-I meningiomas, such as the increased prevalence in men, the more aggressive treatment of the tumor, and the therapeutic limitation, with surgery being the only treatment offering well-established efficacy. Moreover, although several publications[10,19,25] have highlighted that imaging may present characteristics which help differentiate the grades of meningioma, the histopathological analysis is still the definitive way to classify them, in addition to supplying material for molecular, histochemical and immunohistochemical tests.

Despite these limitations, the present study summarizes the scientific advances in the field of AM, which are mainly related to the prognosis of the disease. In this regard, it is worth mentioning the importance of the K_i*-67/MIB1* marker, and genetic, molecular and histological developments, as well as the imaging findings that serve as adjunct tools to predict the chances of recurrence of the tumor and survival of the patient. Moreover, with regard to the adjunct therapy, consensus is also needed concerning the real benefits and harms of RT in atypical meningiomas, as well as the efficacy of hydroxyurea and bevacizumab. We would like to highlight the importance of presurgical embolization in selected cases. In any case, AM remains a challenge within neuro-oncology and neurosurgery, requiring further studies.

Conflict of Interests

The authors have no conflict of interests to declare.

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Surgical Treatment Compared to Conservative Treatment in Remission of Pain and Hyposthesia in Tarsal Tunnel Syndrome – Systematic Review

Tratamento cirúrgico comparado ao tratamento conservador na remissão da dor e hipoestesia na síndrome do túnel do tarso – Revisão sistemática

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Abstract

Introduction Tarsal tunnel syndrome (TTS) is caused by compression of the posterior tibial nerve.

Objective To evaluate the effectiveness of surgical treatments compared to conservative treatments in reducing the symptoms of the syndrome.

Methods The PubMed, Lilacs, Cochrane Library, and PEDro databases were used for this review.

Results Only 11 articles were selected.

Conclusion The most common causes of TTS identified were presence of ganglia, bone prominence causing a talocalcaneal collision, trauma, varicose and idiopathic veins. The main symptom was pain in the medial plantar region and paresthesia that can radiate to the fingers or to the calf. Most patients have a positive Tinel sign upon physical examination. Electrodiagnostic test usually shows the presence of latency in sensory nerve conduction. There is no consensus suggesting that a longer time between diagnosis and surgical treatment leads to worse prognosis. In the group of operated patients, the ones who benefited most from the procedure were those who had a structure such as ganglion, cysts, or varicosities causing compression. The most

Keywords
- tarsal tunnel syndrome
- posterior tibial nerve
- conservative treatment
- surgical treatment.

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cited surgical complications were postsurgical wound infection, wound dehiscence, and calcaneus hypoesthesia. Regarding surgical techniques, the release of the posterior tibial nerve via endoscopy had a favorable outcome in relation to the symptoms of pain and hypoesthesia, with no reports of infection of the operative site in the articles identified in this review. We observed a rate of good or excellent pain control of 68% (n = 204) for open surgery (n = 299), 100% (n = 8) for endoscopic surgery (n = 8), and 7% (n = 2) for conservative treatment (n = 28).

Resumo

Introdução A síndrome do túnel do tarso (STT) é causada pela compressão do nervo tibial posterior.

Objetivo Avaliar a eficácia dos tratamentos cirúrgicos em comparação aos conservadores na redução dos sintomas da síndrome.

Métodos Foram utilizados as bases de dados PubMed, Lilacs, Cochrane Library e PEDro.

Resultados Apenas 11 artigos foram selecionados.

Conclusão As causas mais comuns de STT identificadas foram presença de gânglios, proeminência óssea causando colisão talocalcânea, trauma, varizes e veias. O principal sintoma foi dor na região plantar medial e parestesia, que pode irradiar para os dedos ou panturrilha. A grande maioria dos pacientes apresenta um sinal de Tinel positivo no exame físico. O teste eletrodiagnóstico geralmente mostra a presença de latência na condução nervosa sensorial. Não há consenso de que o maior tempo entre o diagnóstico e o tratamento cirúrgico leva a um pior prognóstico. No grupo de pacientes operados, os que mais se beneficiaram com o procedimento foram aqueles que apresentavam estrutura como gânglio, cistos ou varicosidades causando compressão. As complicações cirúrgicas mais citadas foram infecção da ferida operatória, deiscência da ferida e hipoestesia do calcâneo. A cirurgia endoscópica teve evolução favorável em relação aos sintomas de dor e hipoestesia, não havendo relato de infecção do sítio operatório. Observou-se que a taxa de bom ou excelente controle da dor foi de 68% (n = 204) para cirurgia aberta (n = 299), 100% (n = 8) para cirurgia endoscópica (n = 8), e 7% (n = 2) para o tratamento conservador (n = 28).

Palavras-chave
- síndrome do túnel do tarso
- nervo tibial posterior
- tratamento conservador
- tratamento cirúrgico.

Introduction

The tarsal tunnel syndrome (TTS) was implemented in 1962 by Charles Keck, who published the first clinical cases on the topic and, in that same year, Lam published an article detailing the syndrome.[1–3] The compression of the tibial nerve and its branches has a close anatomical relationship with its adjacent structures: bone, muscle, and vascular structures (**Image 1**).

The flexor retinaculum extends between the medial malleolus and the medial side of the calcaneus supporting the tendons of the posterior tibial muscles, the long flexor of the fingers, the long flexor of the hallux, and the vascular structures—posterior tibial artery and vein. The bony floor and the deep fascia of the abductor hallucis muscle form the tunnel of the distal tarsus.[4]

Symptoms include pain and paresthesia in the posterior region of the foot that can radiate to the plantar region. Initially, pain complaints tend to occur after strenuous physical activity, prolonged standing periods, and use of certain types of shoes, but they tend to improve with rest.[3,5] The clinical diagnosis can be reinforced by the positivity of the Tinel signal and due to the presence of changes in nerve conduction at electroneuromyography (ENMG).[3–5]

Many causes can contribute to the onset of the disease: fractures or dislocations involving the talus, calcaneus or medial malleolus, ganglion cysts, tumors, hypothyroidism, and inflammatory causes, such as rheumatoid arthritis and diabetes mellitus.[3,5–10]

Tarsal tunnel syndrome is the fifth most discussed compressive disease in the literature; however, there are still controversies in relation to treatment since opinions are greater than the evidence when it comes to choosing surgical treatment or maintaining conservative measures and what to do in cases of recurrence. Therefore, the present review aims to evaluate the efficacy of surgical treatment, compared with conservative treatment, in reducing the symptoms of TTS.

Methods

Guiding question

Is surgical treatment more effective in remission of pain and hypoesthesia in TTS compared to conservative treatment? (►**Table 1**)

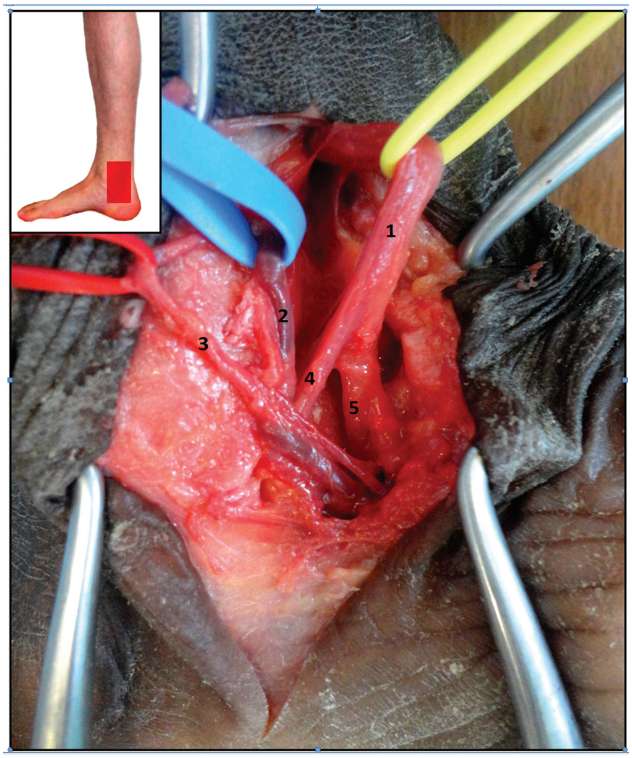

Image 1 Tibial nerve at the level of the medial malleolus in the right lower limb. Note that the flexor retinaculum was sectioned, exposing the division of the tibial nerve into the medial and lateral plantar nerve. The posterior tibial vein was isolated through the blue strip, and the posterior tibial artery through the red strip. Image kindly provided by Magalhães MJS. *Neuroanataomia dos nervos periféricos*. 1st edition. Brazil. Independently published. 2021. 1-Tibial nerve. 2-Posterior tibial vein. 3-Posterior tibial artery. 4-Medial plantar nerve. 5-Lateral plantar nerve.

Table 1 Construction of the guiding question

P	Population	Tarsal tunnel syndrome patients
I	Intervention	Surgical treatment
C	Control	Conservative treatment
O	Outcome	Remission of pain and hypoesthesia

Eligibility criteria and variables

Only clinical studies with and without randomization were selected for the construction of the systematic review. We also opted for studies with a minimum of 3 months of follow-up after intervention and that used the following diagnostic criteria: clinical symptoms, positive Tinel signal, and/or altered electrodiagnostic study. All surgical techniques were included, and all conservative treatments were considered. Two researchers independently searched the databases, and another was the tiebreaker.

The variables studied are the complementary exam used for diagnosis, treatment modality, number of patients enrolled, symptoms presented, outcome after treatment, and complications.

Studies that did not address the treatment of patients were not considered, neither were those that included patients with diabetic polyneuropathy, leprosy, tendinopathies, and painful syndromes involving other nerves of the foot. This strategy was used to reduce confusion bias.

Table 2 Keywords used in the researched databases with last access on July 21, 2020

Data base	Keywords	Number of articles found
PubMed	*syndrome, tarsal tunnel* OR *tibial neuropathy* OR *posterior tibial nerve neuralgia* AND *tarsal, tunnel syndrome* AND *surgical interventions* AND *surgical treatment* AND *conservative treatment*.	8
Lilacs	*tarsal tunnel syndrome* [Subject descriptor] or *síndrome do tunel do tarso* [Subject descriptor] or *síndrome del túnel tarsal* [Subject descriptor]	25
PEDro (Physiotherapy Evidence Database)		PEDro: 2
Cochrane Library	*Tarsal tunnel syndrome*	Cochrane: 17

Reasoning

After a literature search in the Cochrane Library, PubMed and SciElo databases, no previous published studies were found that definitively answered the question, which corroborates the relevance of the study in question.

Source of data and search

The databases used were PubMed, Lilacs, Cochrane Library, and Physiotherapy Evidence Database (PEDro), with the date of the last access being July 21, 2020. The bibliography of the articles found was also analyzed in search of other relevant articles, with the last search being on September 4, 2020. The date of publication and the language of the study were not considered as criteria for the selection of articles. (►**Table 2**)

Data collection process

After identifying the articles available in the databases, the title and abstract were initially read, thus resulting in a sample of 52 articles. Then, the Mendeley desktop reference manager was used to assist in the selection of studies. From the complete reading of the texts, 11 articles were chosen to compose the research. (►**Figure 1**)

Risk of bias

After analyzing the selected articles, some significant differences were found. Among them, we can mention the time interval between diagnosis and the beginning of treatment, the etiology of nerve compression and the evaluation of the therapeutic response. It is known that such situations can

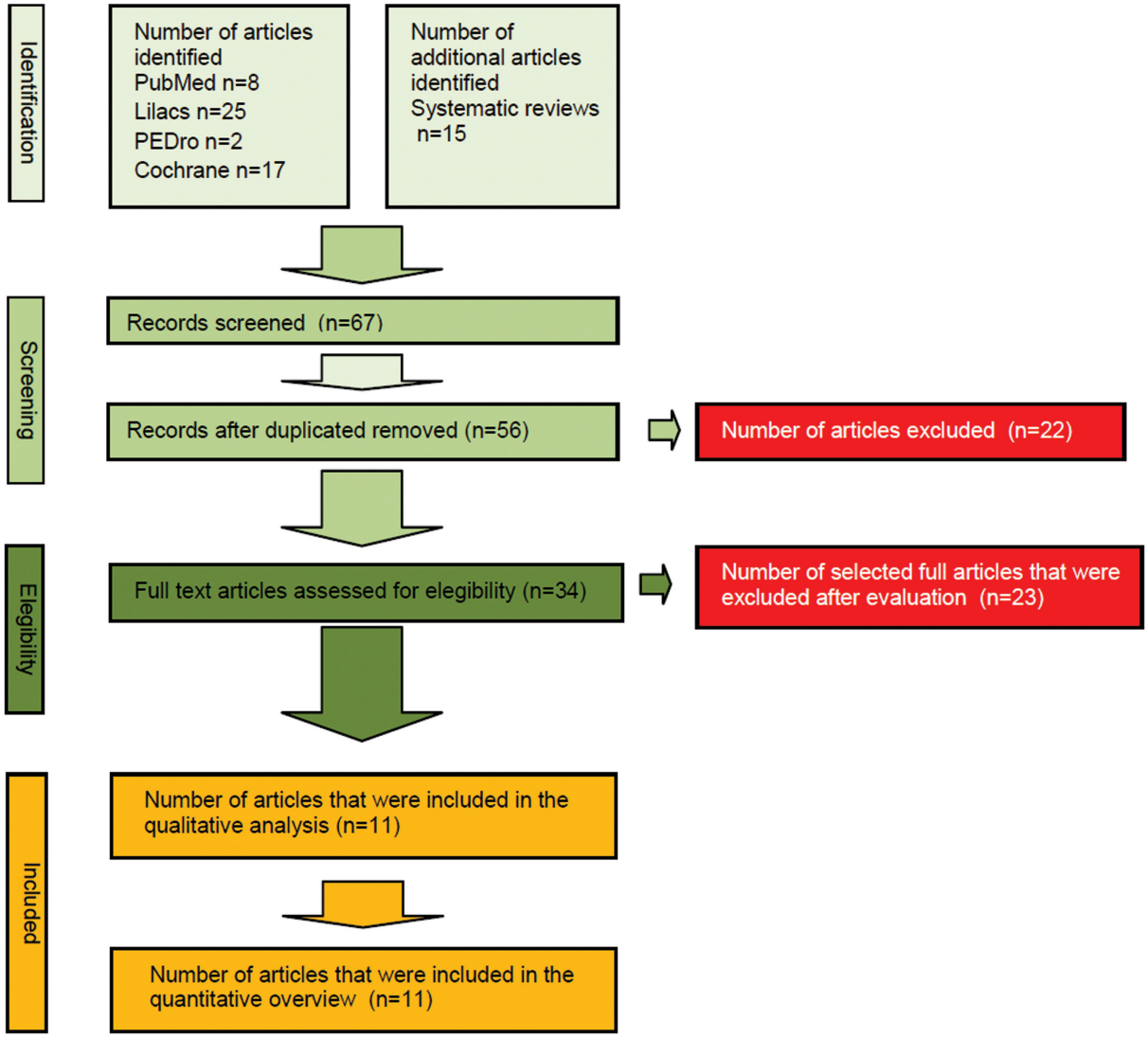

Fig. 1 Data collection

generate bias when comparing the effectiveness of the treatment.

There was a bias both in the choice of articles (different levels of evidence) as well as in the size and characteristics (gender, age, comorbidities) of the studied samples. In view of the management proposed in the different studies, there was no standardization between the types of conservative treatment and surgical techniques used, which may compromise the reliability of this systematic review.

Results

Description of the studies

Two case reports were found (SETTANNI, 1994; CHON, 2014). Settanni et al. (1994) evaluated 7 female patients, with clinical and ENMG evidence of TTS, who had previously undergone some type of conservative treatment. The seven patients underwent open surgery, two of which were bilateral. There was improvement in pain and hypoesthesia in three, improvement in pain and partial recovery of hypoesthesia in three, and one loss to follow-up. In the study by Chon et al. (1994), only 2 patients (one woman and one man) were evaluated, with the presence of a positive Tinel signal and an altered ENMG. Only one of them had a history of open surgery for decompression of the tibial nerve, with no improvement in pain. After the pulsed radiofrequency, the patients were followed for a period of 8 to 12 months, with good response (control of pain and reduction of hypoesthesia).[9,11]

In addition to these, 9 clinical trials were analyzed (TAKAKURA et al., 1991; PFEIFFER et al.,1994; BABA et al., 1997; KOHNO et al., 2000; SAMMARCO et al., 2003; FLORES, 2005; JEROSCH et al., 2006; KRISHAN et al., 2006; KAVALAK et al., 2011).[5–8,10,12–15]

In the study of Kavalak et al. (2011), 28 patients were randomly divided into 2 groups. In the control group, the patients underwent a 6-week physical therapy program at home, while in the other, patients received, in addition to the physical therapy program, nerve mobilization exercises. Before starting the treatment, the patients were evaluated

for muscle strength and range of motion. All of them had clinical manifestations compatible with TTS, and the Tinel signal was present in most of them. At the end of the 6 months, both groups were reevaluated, and an increase in muscle strength and reduced pain was found in both groups, but improvement in sensory parameters was reported only in the test group.[12]

Another study by Krishan et al. (2006) involved 20 patients, 11 with ulnar sulcus syndrome, 8 with TTS, and 1 with meralgia paresthesia. All patients underwent surgery with an integrated endoscopic technique. Of the eight patients with TTS, three were female and five were male. The presence of classic symptoms of nerve compression, failure of conservative treatment, altered ENMG, and non-violated anatomical region were used as selection criteria. The follow-up time varied between 3 and 28 months, and the results found were: absence of pain and paresthesia in five feet, and improvement of pain and reduction of paresthesia in three.[7]

The study conducted by Jerosch et al. (2006) addressed 77 surgical decompressions performed on 75 patients (54 women and 21 men), with the mandatory criterion of a minimum period of 6 months of conservative treatment. The results were evaluated according to pain at rest, pain during walking, and weakness, and, according to the modified American Orthopedic Foot and Ankle Society (AOFAS) score, there was a reduction in pain at rest in 53 patients, and improvement in subjective muscle weakness in 6. Only three feet had superficial infection of the postoperative wound.[5]

The study conducted by Flores (2005) consisted of a retrospective analysis of nine patients diagnosed with idiopathic TTS, in which open surgery was performed with the aid of a surgical magnifying glass. The nine feet showed improvement in pain and paresthesia; however, five had postoperative wound infection, and six had wound dehiscence.[8]

Kohno et al. (2000) published the surgical results of complete resection of the flexor retinaculum associated with the insertion of a fat graft between the dissected vessels and the nerve. This procedure was performed on 12 feet of 9 patients diagnosed with idiopathic TTS. Most patients had a good response in the first 3 months of postoperative follow-up.[6]

In another study by Sammarco et al. (2003), 72 feet underwent open surgery for decompression of the tibial nerve. The diagnosis was made in the presence of clinical signs and symptoms and altered ENMG; 31 patients had a history of foot trauma. Postsurgical follow-up lasted an average of 58 months. The Maryland Foot Score (MFS) was used before and after the operation, with the average score obtained before the procedure being 64/100, and after 80/100. The AOFAS score was used only in the postoperative period, and the average was also 80/100. Patients presenting with symptoms for less than 1 year had the highest score on both scores.[10]

Baba et al. (1997) described 34 patients with TTS, with the condition being bilateral in 3 cases. Of these, 9 were male, and 25 were female, with an average age of 41 years. Open surgery with excision of compressive structures was performed. There was no report of previous conservative treatment. The average follow-up period was 3.8 years, and the multivariate analysis showed that the results are influenced by the presence of fibrosis around the nerve, severity of the preoperative condition, history of ankle sprain and heavy work.[13]

Takakura et al. (1991) linked the causes of TTS to the response to treatment, with the best results in patients in whom some structure was causing compression, such as coalition and tumor.[14] These authors described 45 patients with TTS. Of these, 21 were male, and 24 were female. All patients underwent surgery with follow-up time varying between 1 and 13 years. Good pain control was obtained in patients with diagnosis of tarsal coalition, tumor, and ganglion. Fair pain control was observed in patients with idiopathic TTS and previous trauma.

Finally, the work of Pfeiffer et al. (1994) reviewed the clinical results of 30 patients (32 feet) who underwent surgical decompression of the posterior tibial nerve in the period between 1982 and 1990. The average duration of the segment was 31 months, and the results obtained were: 44% of the feet benefited from the surgery with good or excellent results; 38% had unsatisfactory results, with no long-term pain relief; pain reduced by 19%, but patients still complained about paresthesia; and 13% of the feet had complications in the surgical wound. Based on these results, the authors concluded that unless there is a known structure causing compression of the tibial nerve, surgery should be recommended with caution.[15]

We identified a rate of good or excellent pain control of 68% (n = 204) for open surgery (n = 299), 100% (n = 8) for endoscopic surgery (n = 8), and 7% (n = 2) for conservative treatment (n = 28).[5–10,12–15]

Discussion

The research considered 11 articles, 2 case reports and 9 clinical trials, with a total of 309 participants (337 feet evaluated). As for the etiology of the syndrome, it can be primary (idiopathic) or secondary to a series of diseases in the hindfoot region. The most common causes identified were presence of ganglia, bone prominence causing a talocalcaneal collision, trauma, varicose, and idiopathic veins.[16]

The clinical manifestations may differ according to the disease that causes the compression; however, most patients presented the classic picture of pain in the medial plantar region, and paresthesia that can radiate to the fingers or to the calf (Valleix phenomenon). Pain tends to worsen at night.[16,17]

The diagnosis was based on clinical history and physical examination, the vast majority of patients have a positive Tinel sign, some have a positive tibial nerve compression maneuver, and others report improvement in pain and paresthesia with posterior tibial nerve block with 3 ml of 1% lidocaine.[16]

As for complementary exams, the presence of latency in sensory nerve conduction is the most common finding in

electrodiagnostic tests, because, in the initial stages, the damage is mainly sensory, due to the greater susceptibility of the sensitive fibers to injury. Kohno et al. (2000) performed the measurement of the sensory nerve conduction VELOCITY (NCV) in 5 of his patients, and only 2 presented slow VCS, less than 35 m/s. No study has been able to correlate the results of electrodiagnostic tests with the results obtained after the surgical procedure, so these tests should only be used as an aid to diagnosis, and the presence of a normal test does not rule out the presence of TTS.[6,17]

Imaging exams play an important role for the identification of secondary etiologies of TTS. A simple foot X-ray can identify fractures and bony prominences in the vicinity of the tarsal tunnel. Magnetic resonance imaging is the most suitable for assessing the structures close to the flexor reticulum and to identify those that may be causing the compression of the posterior tibial nerve or one of its branches. In patients complaining of low back pain associated with pain in the foot radiating to the calf, a magnetic resonance imaging (MRI) of the lumbosacral spine should be requested to perform a differential diagnosis with S1 radiculopathy.[16]

The time of disease evolution was quite variable between the articles, some authors mentioned as an eligibility criterion that the patient must have undergone at least a few months of conservative treatment before being submitted to the surgical procedure.[5,6]

Regarding surgical techniques, the release of the posterior tibial nerve via endoscopy had a favorable outcome in relation to the symptoms of pain and hypoesthesia, with no reports of infection of the operative site.[7] ►**Table 3**

In open surgeries, there is no consensus on the use of tourniquets during the procedure. Although the tourniquet is effective in reducing intraoperative bleeding, some authors argue that it alters neurovascular conditions, making it impossible for the surgeon to identify possible arteries or veins that may be responsible for compression. As for sedation, some studies have recommended the use of local anesthesia associated with mild sedation, so that the patient is able to alert the professional about pain irradiation at the time of surgery, which can assist in the correct identification of the affected nervous branch. According to Kohno et al. (2000), if during the surgical procedure no structure is found that may be causing the compression, a fat graft should be placed between the nerve and the vessels to prevent them from sticking later.[6,8] ►**Table 3**

The follow-up period for patients varied between 3 months and 13 years. The tools used to assess patients' improvement after therapeutic intervention have not been standardized. One of the articles used more than one method,[7] while others did not report the method used.[2,9] ►**Table 3**

Among the strategies applied are validated scales (visual analogue scale, Maryland foot score, American Orthopedic Foot and Ankle Society - Ankle Kind foot score)[5,10–12]; own scales[13,14]; clinical evaluation (Tinel sign), and complementary exams (computed tomography [CT], MRI, ENMG).[6,15] Some studies have suggested a follow-up of at least 12 months, as the patient may experience an improvement in pain and paresthesia initially, with recurrence a few months later.[5,15]

In the group of operated patients, the ones who benefited most from the procedure were those who had a structure such as ganglion, cysts, or varicosities causing compression; in other patients, the results were poor even with the authors reporting careful decompression of the nerve. Patients who had previously undergone some previous foot surgery, mainly involving the tibial nerve had a poor result, possibly due to the presence of fibrosis around the nerve (►**Table 3**).

The most cited complications were postsurgical wound infection, wound dehiscence, and calcaneus hypoesthesia. ►**Table 3** Flores draws attention to the varied origin of the medial calcaneus branch, which may emerge from the tibial nerve or from one of its branches,. According to this author, during surgery, care must be taken to avoid injury to the calcaneus branch, which can result in hypoesthesia of the heel or formation of heel.[8]

The study of Chon et al. (1994) showed the effectiveness of ultrasound-guided pulsed radiofrequency, despite the small number of patients analyzed. It has shown promise, especially for patients who have not improved after surgical decompression, and also for those who the surgery has not been beneficial to (trauma, idiopathic origin, presence of plantar fasciitis, systemic inflammatory disease). However, more studies are needed.[11]

Conclusion

The most common causes of TTS identified were presence of ganglia, bone prominence causing a talocalcaneal collision, trauma, and varicose and idiopathic veins. The main symptoms were pain in the medial plantar region and paresthesia that can radiate to the fingers or to the calf. Most patients have a positive Tinel sign in their physical examination. The electrodiagnostic test usually shows the presence of latency in sensory nerve conduction. There is no consensus that a longer time between diagnosis and surgical treatment leads to worse prognosis. In the group of operated patients, the ones who benefited most from the procedure were those who had a structure such as ganglion, cysts, or varicosities causing compression. The tools used to assess patients' improvement after therapeutic intervention have not been standardized. The most cited surgical complications were: postsurgical wound infection, wound dehiscence, and calcaneus hypoesthesia. Regarding surgical techniques, the release of the posterior tibial nerve via endoscopy had a favorable outcome in relation to the symptoms of pain and hypoesthesia, with no reports of infection of the operative site. We identified a rate of good or excellent pain control of 68% (n = 204) for open surgery (n = 299), 100% (n = 8) for endoscopic surgery (n = 8) and 7% (n = 2) for conservative treatment (n = 28).

6.0 - Funding Acknowledgements
This work was supported by PROCIÊNCIA.

Table 3 Summary of studies about treatment of tarsal tunnel syndrome selected for systematic review

Authors	Article	Patients	Number of limbs	Age	Gender	Comorbidities	Treatment	Time of follow up	Outcome
Jerosch J et al.	Results of surgical treatment of tarsal tunnel syndrome	75	77	17–77	F: 54 M: 21	–	Open surgery	6–100 months and mean value = 39 months	- Good pain control (n = 53) -Improvement of paresia (n = 6) -Incision infection (n = 3)
Kohno M et al.	Neurovascular decompression for idiopathic tarsal tunnel syndrome: technical note	9	12	52–78	F: 6 M:3	–	Open surgery	9–61 months and mean value = 26.8 months	- No pain control (n = 2) - Good pain control (n = 10) - Incision infection (n = 0)
Krishnan GK et al.	A novel endoscopic technique in treating single nerve entrapment syndromes with special attention to ulnar nerve transposition and Tarsal Tunnel release: clinical application	8	8	35–64	F: 3 M: 5	Diabetes mellitus (n = 1)	Endoscopy surgery	3–28 months and mean value = 10.1 months.	- Excellent pain control (n = 5) - Good pain control (n = 3) - Partial pain control (n = 0) - No pain control (n = 0) - Incision infection (n = 0)
Settanni FA et al.	Management of tarsal tunnel syndrome. Report of seven cases	7	10	43–72	F: 7 M: 0	-Previous foot surgery (n = 12) -Previous Tarsal decompressive surgery (n = 6) -Rheumatoid arthritis (n = 3_ - Neuroma plantar medial (n = 1)	Open surgery	3 months–3 years	- Excellent pain control (n = 3) - Good pain control (n = 3) - No information (n = 1)
Pfeiffer WH, Crachiolo A	Clinical results after tarsal tunnel decompression	30	32	13–72	F: 24 M: 6	–	Open surgery	24–118 months and mean value = 31 months	-Excellent pain control (n = 5) - Good pain control (n = 9) - Partial pain control (n = 5) - No pain control (n = 10) - Incision infection (n = 1)
Flores LP	Outcome of surgical treatment of idiopathic posterior tarsal tunnel syndrome	9	9	33–52	F: 7 M: 2	–	Open surgery	4–24 months	- Good pain control (n = 9) - Incision infection (n = 5) -Incision dehiscence: (n = 6)
Chon JY et al.	Pulsed radiofrequency under ultrasound guidance for the tarsaltunnel syndrome: two case reports	2	2	56–67	F:1 M:1	-Foot trauma (n = 1)	Pulsed radiofrequency	8–12 months	- Good pain control (n = 2)
Kavlak Y et al.	Effects of nerve mobilization exercise as an adjunct to the conservative treatment for patients with Tarsal Tunnel syndrome	28	28	40–57	F: 4 M: 12	- Hypertension (n = 7) - Diabetes mellitus (n = 3) - Ateriosclerosis (n = 1) - Foot trauma (n = 14)	Mobilization exercise as an adjunct to the conservative treatment	3 months	- Good control pain (n = 2)
Baba H et al.	The tarsal tunnel syndrome: evaluation of surgical results using multivariate analysis	34	37	14–73	F: 25 M:9	-Ankle arthritis (n = 33) - Foot trauma (n = 31)	Open surgery	1-7 years. Mean	- Excellent pain control n = 26 *-Good pain control

(*Continued*)

Table 3 (*Continued*)

Authors	Article	Patients	Number of limbs	Age	Gender	Comorbidities	Treatment	Time of follow up	Outcome
						- Diabetes mellitus (n = 7) - Low back pain (n = 37)		value = 3.8 years	n = 6* -No pain control (n = 5) * * number of limbs
Sammarco GJ et al.	Outcome of surgical treatment of tarsal tunnel syndrome	62	72	17–80	F:44 M: 18	- Foot trauma (n = 5) - Tumor (n = 3)	Open surgery	12–185 months and mean value = 58 months	-Excellent pain control (n = 21)* -Good pain control (n = 17)* -Partial control (n = 19)* - No pain control (n = 16)* * number of limbs
Takakura Y et al.	Tarsal tunnel syndrome. Causes and results of operative treatment	45	50	10–71	F:24 M:21	- Ganglia (n = 18), - Bony prominence from talocalcaneal coalition (n = 15) - Tumor (n = 3) - Trauma (n = 5)	Open surgery	1-13 years and mean value= 4 years and 9 months	- Good pain control in tarsal coalition, tumor, and ganglion groups. Fair pain control in idiopathic and trauma group.

Conflict of Interests
The authors have no conflict of interests to declare.

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The Evolution of Neurosurgery Throughout the Ages: From Trepanations in Prehistory to The Robotic Era

A evolução da neurocirurgia ao longo das eras: Das trepanações pré-históricas à era robótica

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Abstract

Introduction Throughout the historical course, the emergence of neurosurgery invariably involved the narrative about different eras, marked by relevant discoveries in the field of medical science. From prehistoric mystical and therapeutic reports to the Robotic Era in the 21st century, there were changes that contributed to current neurosurgery. Thus, this study will analyze articles and studies that describe the history of neurosurgery and demonstrate the main advances in the field of science.

Materials and methods This is a narrative review of scientific literature, carried out by searching the following databases: Scientific Electronic Library Online (SCIELO), Online System for Searching and Analyzing Medical Literature (MEDLINE), Latin American Literature and Caribbean in Health Sciences (LILACS), and Public Medical Literature Analysis and Retrieval System Online (PubMed).The following descriptors were used: *History of neurosurgery* and *Neuroanatomy*, together with the Boolean operator "AND". In addition, the descriptors *History of Neurosurgery* and *Robotics* were used between the

Keywords
- neuroanatomy
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- neurosurgery
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Boolean operator "AND". In this sense, in order to establish a linearity of the narrative presented, the evolution of neurosurgery in five eras was didactically separated.
Conclusion Neurosurgery, throughout history, has undergone several transformations. There was a series of events that made neurosurgery one of the most evolutionary and progressive sciences. This is because technology combined with scientific knowledge was, in fact, what made it possible to get where we are. In this sense, the studied ages allow the comprehension of a history that needs to be understood and valued by all students of the neurological and neurosurgical sciences.

Resumo

Introdução Ao longo do percurso histórico, o surgimento da neurocirurgia envolveu invariavelmente a narrativa sobre diferentes épocas, marcadas por descobertas relevantes no campo da ciência médica. Desde relatos místicos e terapêuticos pré-históricos até a Era Robótica no século XXI, ocorreram mudanças que contribuíram para a neurocirurgia atual. Assim, este estudo analisará artigos e estudos que descrevem a história da neurocirurgia e demonstram os principais avanços no campo da ciência.
Materiais e métodos Trata-se de uma revisão narrativa da literatura científica, realizada por meio de busca nas seguintes bases de dados: Scientific Electronic Library Online (SCIELO), Online System for Searching and Analyzing Medical Literature (MEDLINE), Literatura Latino-Americana e Caribenha em Ciências da Saúde (LILACS) e Public Medical Literature Analysis and Retrieval System Online (PubMed). Foram utilizados os seguintes descritores: "History of neurosurgery" e "Neuroanatomy", juntamente com o operador booleano "AND". Além disso, foram utilizados os descritores "História da Neurocirurgia" e "Robótica" entre o operador booleano "AND". Nesse sentido, para estabelecer uma linearidade da narrativa apresentada, separou-se didaticamente a evolução da neurocirurgia em cinco eras.
Conslusão A neurocirurgia, ao longo da história, passou por diversas transformações. Houve uma série de acontecimentos que fizeram da neurocirurgia uma das ciências mais evolutivas e progressivas. Isso porque a tecnologia aliada ao conhecimento científico foi, de fato, o que possibilitou chegar onde estamos. Nesse sentido, as idades estudadas permitem a compreensão de uma história que precisa ser compreendida e valorizada por todos os estudantes das ciências neurológicas e neurocirúrgicas.

Palavras-chave
- neuroanatomia
- história da
- neurocirurgia
- robotização

Introduction

Throughout the historical course, the emergence of neurosurgery invariably involved the narrative about different eras, marked by relevant discoveries in the field of medical science. Prehistoric mystical and therapeutic reports document the first descriptions of primitive cranial surgical procedures, including cranial perforation, called trepanation, a procedure indicated for individuals with mental disorders, headaches and head injuries.

Harvey Cushing, a physician and neurosurgeon at Harvard University, marked the 20th century with his contributions that leveraged the history of medicine and made him one of the greatest references of all time.[1] Among his achievements are the use of radiography in the diagnosis of brain tumors, the encouragement of studies and research on electroencephalic stimulation, and the demonstration of the importance of knowledge and control of intracranial pressure, contributing to the historical decrease in mortality from brain tumors, being, therefore, the precursor of a new era, the Cushing Era.

Still in the 20th century, there was the advent of new imaging techniques, such as radiology and radiotherapy, allowing for better surgical outcomes and enabling the consolidation of neurosurgery as a well-defined specialty worldwide. In parallel to this, the development of new microsurgical techniques by M. Gazi Ysargil, a Turkish neurosurgeon, ushered in a new era in medicine. New surgical instruments were conceived, which transformed the scenario of surgical microanatomy and resolved technical limitations that, until then, made some patients inoperable. In 1980, there was a great advance in the history of medical science with the first use of robotics to perform neurosurgical biopsies, a fact of extreme importance that boosted the search for robotic systems that contributed to microsurgery.[2,3]

In view of this, among prehistoric trepanations, the use of robots that respond to commands from neurosurgeons and perform complex microsurgery, there is a time and a space that must be understood on several aspects. In this context, the present study seeks, through a narrative review of the

literature, to synthesize and discuss the main milestones in the evolution of neurosurgery throughout the ages, focusing on the current scenario of microsurgery and surgical robotization.

Materials and Methods

This is a narrative review of the scientific literature, carried out by searching the following databases: Scientific Electronic Library Online (SCIELO), Online System for Searching and Analyzing Medical Literature (MEDLINE), Latin American Literature and Caribbean in Health Sciences (LILACS), and Public Medical Literature Analysis and Retrieval System Online (PubMed). The searches were carried out in two stages in order to obtain better results in the literature. In the first analysis, the following descriptors were used: *History of neurosurgery* and *Neuroanatomy*, together with the Boolean operator "AND". In addition, the descriptors *History of Neurosurgery* and *Robotics* were used between the Boolean operator "AND". Thus, the searches aimed to identify studies of systematic reviews and narratives that describe the history of neurosurgery throughout the ages and its advancement in the modern era. In this sense, in order to establish a linearity of the presented narrative, the evolution of neurosurgery in five eras was didactically separated: (a) medicine in the Pre-Cushing Era, (b) medicine in the Cushing Era, (c) medicine in the Yasargil Era, (d) medicine from the Endoscopic Era and, finally, (e) medicine from the Robotic Era.

The inclusion criteria were: articles that addressed the neurosurgery narratives, studies, and essays on the evolution of neurosurgery throughout history and systematic reviews that described the development of medicine according to historical periods. The exclusion criteria were: articles that did not contemplate the theme about the history, evolution, and development of neurosurgery in the course of history. Duplicates were also excluded.

Results

Number of Studies

A total of 28 studies were included.

Discussion

Pre-Cushing Era

Since the beginning, classical philosophers like Aristotle and Descartes have attributed important functions to the brain in cognitive control. In mythology, Egyptian society documented the first record of a surgical intervention in the spinal cord, in which the god Osiris was resurrected with Isis and Thoth, which reveals previous knowledge of neuroanatomy.[1] In the real world, mysticism inspired neurosurgical and practical applications, such as cranial trepanations and craniectomies reported in the Neolithic period.[2,3] Both procedures allowed the simple perforation of the skull, indicated for high-intensity headaches, convulsions, and changes in the mental picture, and the wider opening of the skull, called craniectomy, allowed bone regeneration over time and contributed to the history of neurosurgery.[4]

Around 300 BC, in the Egyptian city of Alexandria, anatomists such as Hippocrates and Erasistratus began dissecting criminals, which allowed greater anatomical knowledge and further spreading of the teaching of these human structures in schools and museums.[5,6] Thus, it was possible to deepen the understanding of neuroanatomy, especially in the particularity of the grooves, gyres, and the description of the torula responsible for the union of venous sinuses.

In Greece, Plato and Democritus discussed the role of cognition with the human soul, framing the brain as part of the soul located in the head, while Galen, in Rome, disagreed with the correlation between gyrations and intellect, suggested by Erasistratus.[7,8] Therefore, the era called pre-Cushing was marked by a great advance in the knowledge of neuroanatomy through dissections, mythology and philosophy that marked the history of neurosurgery.[9,10]

Cushing Era

With the advent of the Middle Ages, little is known about the contribution to neurosurgical knowledge. Although science was abolished, especially by the Catholic Church, the first illustration of the human brain was obtained, in the 11th century, and the first human dissections were performed in Europe.[11,12] The scenario changed with the height of the Renaissance period, in which human dissection became legal and contributed to new surgical and anatomical foundations, such as the description of Sylvius groove by it. Thus, neuroanatomy has progressed in detailed descriptions throughout the 17th, 18th and 19th centuries,[13,14] beginning an era that bears the name of one of the most important names in the consolidation of neurosurgery as a medical specialty in the United States: Harvey Cushing.

At the beginning of the 20th century, the Cushing Era begins with great contributions from the neurosurgeon who gives the name to the era, primarily due to the description of the treatment of traumatic brain injuries and missile injuries, but finds its peak in the 1930s with cerebral tumor surgery.[15] Cushing was also responsible for mapping motor and sensory activities in different regions of the cerebral cortex, being one of the pioneers of cortical stimulation in epileptic patients.

Yasargil Era

The second half of the 20th century enabled the advent of microneurosurgery with the leading role of the Turkish neurosurgeon M. Gazi Yasargil, who initiated the Yasargil Era. At the University of Basel, he had his first contact with microsurgery performing transpalatinal exploration of the hypophysis in frogs for research. The neurosurgical microscope was used for the treatment of acoustic neuromata through translabyrinthine and through the middle fossa,[16,17] allowing the introduction of this equipment in the area of neurosurgery. In addition, Yasargil was responsible for developing techniques for vascular neurosurgery that started working on the middle cerebral arteries of dogs, transforming the prognosis of patients who until then were considered inoperable.[18] Microsurgical instruments, retractors, floating microscope, and aneurysm clips were conceived by her. The

technique for transplantation of the superficial temporal artery to the middle cerebral artery by end-to-side anastomosis was also developed by Yasargil.

Thus, the era of microsurgery enabled the detailed and meticulous study of brain areas, contributing to topographic reasoning and to the further development of more improved equipment in microsurgery. So, the neurosurgical procedures that are performed today has been affected by the work of this neurosurgeon.

Endoscopic Era

The advent of magnetic resonance imaging (MRI), from a surgical point of view, in addition to being an element of neuroimaging coupled to different stereotaxis systems, its digital image storage and manipulation base allowed and allows three-dimensional reconstructions to be easily created. With the different information obtained by the method, which can be observed from different points of view, thus lending itself and even simulations of accesses and surgical views.[19] The digital basis of storage and manipulation of the different modalities of neuroimaging exams, associated with the technology of transmission of light pulses, culminated in the development of the so-called surgical neuronavigator, as idealized initially by Watanabe et al., in 1987, and which is characterized as being a stereotactic neuronavigation system. Having images obtained before surgery and related to cranial repair points in a computer station, whose position will be constantly updated during the surgical procedure, the neuronavigation system is able to identify, in the stored images, structures properly pointed in the surgical field, by means of a triangulation process similar to that used by the well-known navigation instrument called global positioning system (GPS).

With the development of optical and camera systems in the last 30 years, the endoscope has been added to the arsenal of neurosurgery techniques. Neuroendoscopy can be classified into: 1) pure neuroendoscopy: when the entire procedure is done under the view of the endoscope and the instruments pass through working channels coupled to the shirt or trocar that also contains the optics; 2) microsurgery controlled by endoscopy: where the endoscope serves as an instrument of magnification and illumination replacing the microscope, but the surgical instruments are the same as those used in conventional microsurgery and penetrate the field parallel to the endoscope; 3) endoscopy-assisted microsurgery: where the entire procedure is performed as in conventional microsurgery and the endoscope serves as an aid to view portions of the operative field to which the microscope does not allow access (AMATO, 2016). Currently, there is already an endoscope model that allows the use of an ultrasonic aspirator inside, increasing the efficiency of resection.

Robotic Era

Kwoh et al. were the pioneers in using a robotic system in surgery. They adapted an industrial system produced by Unimation, the PUMA 200, whose function was to position and align the trajectory of a stereotaxic biopsy cannula.[20] The development of several systems for stereotaxic surgery followed, one of them a precursor to NeuroMate by Benabid et al. in 1987.[21] Later, due to the need for precision and the potential impact of the displacement of intracranial structures during the surgical procedure, systems compatible with the acquisition of intraoperative image emerged. Minerva (University of Lausanne, Switzerland) was created with the purpose of operating inside a computed tomography device, allowing the acquisition of intraoperative images in real time 1987.[22,23]

Subsequently, systems compatible with intraoperative MRI were created by the Universities of Harvard, Tokyo and Calgary 1987.[24] More recently, in addition to new stereotactic surgery systems such as NeuroMate and PathFinder, systems with other neurosurgical applications have also been developed, such as microsurgery (for example, NeuRobot and neuroArm), spinal surgery (SpineAssist) and radiosurgery (CyberKnife).[25]

Unlike stereotactic surgery, the systems used in microsurgery are passive. They are typically controlled remotely through a console, which can present an input mode similar to surgical instruments, which makes the task more intuitive for the surgeon.[26,27] This way, the surgeon will be away from the operative field during the procedure. The console includes a monitor that transmits visual information to the surgeon, coming from a video camera built into the system. Often, a system of visualization in three dimensions is used, which allows a better perception of depth.

The Era of Robotics included not only transformations (►**Figure 1**) in surgical procedures with greater precision, technology and effectiveness, but brought safety to the surgeon due to systems complementary to his practice that, in the past, were not available due to the gradual progress of a society that developed in the field of neurosurgery from trepanations to the use of robots in surgical interventions. In this sense, it is clear that the history of humanity over the historical eras also reflects the evolution of a scientific field increasingly marked by the robotization technique (►**Figure 2**).

Conclusion

Neurosurgery, throughout history, has undergone several transformations. From trepanations, skull perforations, to the use of robotics, there was a series of events that made neurosurgery one of the most evolutionary and progressive sciences. Mystical accounts during the Pre-Cushing Era boosted the execution of a historical narrative about the beginning of neurosurgery that started from anatomical descriptions about the peculiarity of the brain, but which is already consolidated in the Cushing Era when brain stimulation in epileptic patients becomes real. Furthermore, this is because technology combined with scientific knowledge was, in fact, what made it possible for us to get to where we are.

Era after era, passing through Yasargil, the microsurgery using microscopes also allowed, with cerebral mapping, to gain contours, definitions, names, and identifications more and more specific and significant. Vascular structures and

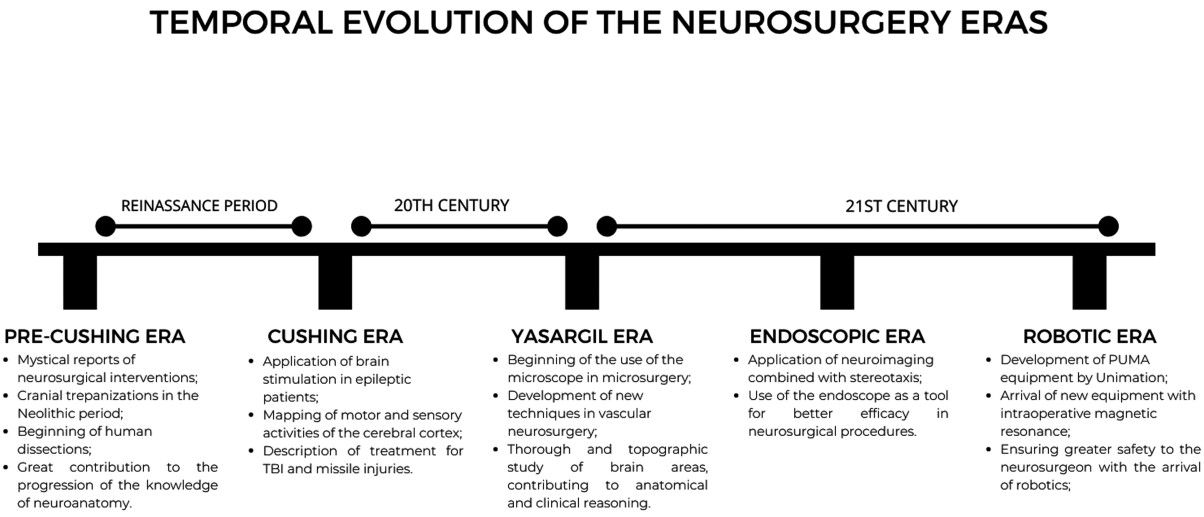

Fig. 1 Timeline with the main milestones of each era throughout the history of neurosurgery.

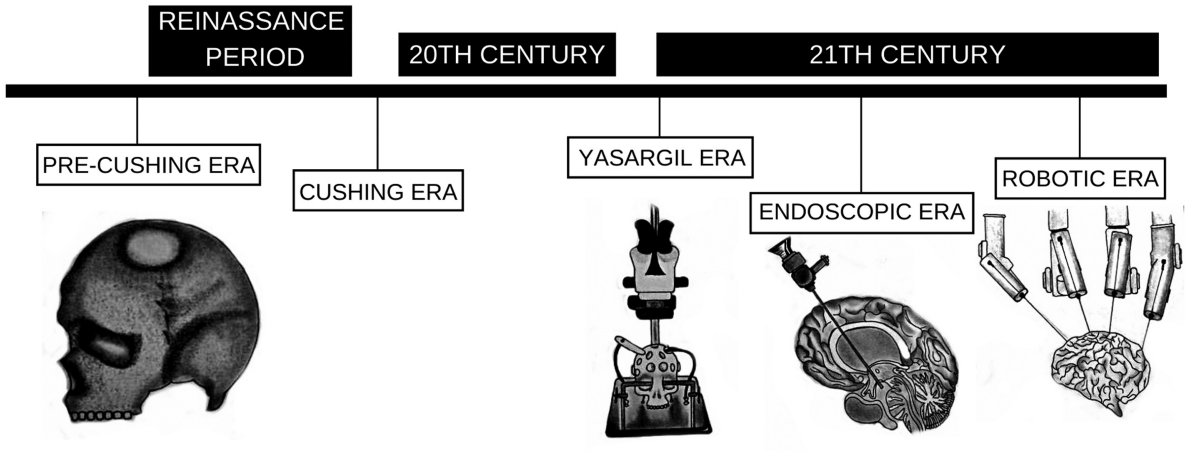

Fig. 2 Timeline illustrating the ages.

their ramifications, variations, and extensions have been described, and for this reason, detailed and topographic studies have become more accurate. In this sense, the studied ages allow the understanding of a history that needs to be understood and valued by all scholars of the neurological and neurosurgical sciences. From the Pre-Cushing era to the Robotic Era, many techniques, procedures, surgery systems, and scientific knowledge were achieved.

The application of neuroimaging linked to stereotaxic procedures was an indisputably unique advance regarding the success of neurosurgeries. The then Endoscopic Era used a device, called a neuroendoscope, which in a safe and minimally invasive manner brought the possibility of neurosurgeons to reach important territories such as those of the cerebral ventricles. Soon, many pathologies began to be treated, such as obstructive hydrocephalus, through an endoscopic third ventriculostomy. The Robotic Era, bringing intraoperative MRI with the procedures that, this time, with the arrival of robotics, brought not only safety to the neurosurgeon, but also better success, better chances of success, and expansion of the necessary interventions.

The present article allows not only a time travel around all the protagonists who have made neurosurgical science one of the most innovative and updated scientific fields, as well as through the historical landmarks that, from age to age, have been delimited and, gradually, led humanity to the point we have reached. The past, the present, and the future have never been described and analyzed in such a close and temporal way.

Contribution of the Authors

Study supervision: Bem Junior L. S. and Azevedo Filho H. R. C.;

Drafting of the first version of the article: Souza F. S. and Silva R. P. S;

Revision of the first draft: all authors;

Revision of the final version: all authors.

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The authors have no conflict of interests to declare.

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Complex Regional Pain Syndrome: A Quantitative Review of Current Treatments

Síndrome dolorosa regional complexa: Uma revisão quantitativa dos tratamentos atuais

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Abstract

Introduction Complex regional pain syndrome (CRPS) is a disease that causes intense pain mainly in the upper and lower limbs of the patients, impairing the quality of life of those affected by the syndrome. Its pathophysiology has not yet been fully discovered and described. Also, treatments need to advance in the search for pain relief in those affected by the disease. The present article aims to describe the pathophysiology of CRPS and, mainly, to quantitatively analyze the efficiency of new treatments against pain caused by the disease.

Methods Several articles on clinical trials described in a table were included in the present study, and a systematic review of the effectiveness of current treatments was performed.

Results A total of 29 articles from clinical trials were selected using the preselection criteria. Surgical treatments against CRPS had a 56.9% efficiency in reducing painful sensation, and conservative treatments against CRPS had a 40.82% efficiency in reducing pain sensation.

Conclusion Complex regional pain syndrome is a disease that causes pain in patients and worsens the quality of life of those affected by it. The treatments are diverse, and their efficiencies vary from bad to excellent.

Keywords
- complex regional pain syndromes
- neurosurgery
- therapeutics
- pathology

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Resumo

Introdução A síndrome dolorosa regional complexa (SDRC) é uma doença que causa dor intensa principalmente nos membros superiores e inferiores dos pacientes, prejudicando a qualidade de vida dos afetados pela síndrome. Sua fisiopatologia ainda não foi completamente descoberta e descrita. Ademais, tratamentos precisam avançar na busca do alívio da dor naqueles afetados pela doença. O objetivo do presente artigo é descrever a fisiopatologia da SDRC e, principalmente, analisar quantitativamente a eficiência dos novos tratamentos contra a dor causada pela doença.

Métodos Foram incluídos no presente estudo diversos artigos sobre ensaios clínicos descritos em uma tabela e foi feita uma revisão sistemática sobre a eficiência dos tratamentos atuais.

Resultados Foram selecionados 29 artigos de ensaios clínicos por meio do critério de pré-seleção. Tratamentos cirúrgicos contra a SDRC tiveram uma eficiência de 56,9% na redução da sensação dolorosa e os tratamentos conservadores contra a SDRC tiveram uma eficiência de 40,82% na redução da sensação dolorosa.

Conclusão A SDRC é uma doença que causa dor nos pacientes e piora da qualidade de vida dos afetados por ela. Os tratamentos são diversos e suas eficiências variam de ruim a excelente.

Palavras-chave

- síndrome da dor regional complexa
- neurocirurgia
- terapêutica
- patologia

Introduction

Complex regional pain syndrome (CRPS) is a disease that was discovered and described by Silas Weir Mitchell. The American doctor described this pathology when he realized that some patients who suffered gunshot wounds in the US secession war developed pain and hyperalgesia in the extremities of the limbs.[1]

This syndrome has been known by several names since its discovery. Known today as CRPS, names like post-traumatic pain syndrome, sudeck's atrophy, and reflex sympathetic dystrophy have already been used.[2]

Complex regional pain syndrome is classified into two different groups: type 1, the most common, is the one in which the patient does not have an identifiable nerve injury. This type was formerly known as "reflex sympathetic dystrophy"; and CRPS type 2, previously called "causalgia", is the one that presents a proven associated nerve injury.[2,3]

Based on the diagnosis from doctors in general, the incidence of CRPS is of 26.2/100,000 people per year. As for the diagnosis made and confirmed by specialists, this number decreased to 19.5/100,000, and with specialists who diagnose following the criteria of the International Association for the Study of Pain (IASP) we have a rate of 16.8/100,000 inhabitants.[4]

The incidence related to gender shows a big difference, with predominance in women. Men are 22.7% of those affected by the CRPS, while women are 77.3% of the patients. The upper extremities are 10% more affected than the lower ones, with no preference for laterality. Furthermore, the most common triggering factors are fractures and sprains, with fractures leading in percentage.[4]

The pathophysiology of CRPS is not yet fully understood, with only a few hypotheses that contribute to clarify the mechanism that causes this pathology. In the following paragraphs, the hypotheses most commonly related to CRPS are presented.

The main mechanisms that explain the pathophysiology of CRPS are nerve injury, ischemic reperfusion injury or oxidative stress, central sensitization, peripheral sensitization, altered sympathetic nervous system function or sympathetic-afferent coupling, inflammatory and immune-related factors, genetic factors, brain plasticity, and psychological factors.

Nerve Injury

Even though the pathophysiology of CRPS is not fully comprehended, it is known that persistent inflammation in the affected limb is something common in all patients affected by this condition. The phenomenon that explains the onset of this inflammation is a nerve injury, which in cases of CRPS type 2 has a clear and determined origin. In cases of CRPS type 1, however, this lesion cannot be explained, largely because the lesion was caused in small fibers, structures that often cannot be identified in imaging exams. About 90% of patients with CRPS do not have an identifiable nerve injury; thus, CRPS type 2 represents only 10% of the patients affected by this syndrome.[5,6]

Reperfusion Injury or Oxidative Stress

The mechanism of reperfusion ischemia is also pointed out as one of the factors that contribute to the development of CRPS type 1. Patients who experienced trauma and had to immobilize the injured limb after surgery were more likely to develop the syndrome.[7] The mechanism of reperfusion ischemia is already well-known. The process results in an accumulation of free radicals leading to oxidative stress. The oxygen supplied after reperfusion generates reactive oxygen species (ROS), a situation made possible by the lack of production of antioxidant agents by the ischemic tissue. Reactive oxygen species promote endothelial dysfunction and DNA damage, in addition to inflammation, which can lead to a cascade of cytokinins that will result in cell death

and symptoms related to the pathophysiology of the inflammatory process.[8,9] Studies that carried out ischemia experiments with consecutive reperfusion in rats showed that the animals triggered symptoms similar to those of SDRC type 1. Hyperalgesia and allodynia were observed even though no nerve damage was found in rodents.[10,11]

Central Sensitization

Sensitization of the central nervous system is also one of the hallmarks of complex regional pain syndrome. The lesion triggers the release of neurotrophic factors and proinflammatory substances, such as bradykinins and prostaglandins that, together, activate phosphokinases A and C, which in turn phosphorylate specific sodium channels of sensory neurons. This mechanism leads to peripheral sensitization of afferent nociceptors. This entire process of peripheral sensitization leads to continuous depolarization that will lead to a blockage of magnesium ions in NMDA receptors, the main receptor of the glutamatergic system located in the postsynaptic membrane of neurons. The blocking of magnesium ions causes these receptors to be activated, thus leading to depolarization of the pain pathway and amplifying its signal, finally causing central sensitization.[12]

Peripheral Sensitization

After a tissue injury to the peripheral, as to the central, nervous system provides a sensitization that protects the body against unnecessary movements. This sensitization in the peripheral nervous system occurs thanks to the increase in the firing rate of the nociceptors and its response to normally painful stimuli, with an antagonist decrease in the firing threshold for thermal and mechanical stimuli.[13–15] Inflammatory mediators such as proinflammatory cytokines (TNF-alpha, IL-1beta), prostaglandin E2 (PGE[2]) , bradykinin, and nerve growth factor (NGF) increase the sensitivity and excitability of nociceptors by enhancing the activity of pronociceptive receptors and ion channels.[13]

Moreover, a study developed by Moy et al. in 2017 demonstrates that phosphorylation of the 5′ cap-binding protein eIF4E by its specific mitogen-activated protein kinase (MAPK) interacting kinases (MNKs) 1/2 is a key factor in nociceptor sensitization and the development of chronic pain.[14] The authors, by these studies, advocate in favor of a new pain pathway of nociceptive plasticity; thus, it is clear that the pathophysiology of CRPS is, indeed, intriguing and multifactorial.

Altered Sympathetic Nervous System Function or Sympathetic–afferent Coupling

The medical literature also assumes that modifications in the sympathetic nervous system contribute to CRPS, which in the past was known as reflex sympathetic dystrophy. This information, nevertheless, is controversial, since a prospective study in patients early after fractures shows that those with reduced sympathetic outflow after the injury are at greatest risk of developing subsequent CRPS symptoms.[16]

Localized injuries have been shown to result in the expression of catecholamine receptors on nociceptive fibers, so the circulating catecholamines released after the stress and pain might directly increase the firing of nociceptors, a reflex known as sympathetic-afferent coupling, observed in various studies that hypothesized that this mechanism plays a role in the severity of the symptoms.[17–22] These, once again, demonstrate a multifactorial principle in the genesis of CRPS with the intersections of sympathetic and peripheral sensitization theories.

A common symptom of CRPS that is explained in part by the sympathetic system is the temperature asymmetry. Vasodilating drugs and sympathetic blockade have been cornerstones of therapy in cold CRPS for years. However, only a limited part of these patients improves on this kind of therapy. Research has shown a pivotal role for inflammation in the pathophysiology of CRPS,[23] which will be discussed below.

Inflammatory and Immune-related Factors

Here we will discuss what may be the latest and most complex mechanism involving CRPS.

This concept seems to link the many other mechanisms and to participate decisively in the elucidation of pathophysiology.

Evidence of the involvement of inflammatory mechanisms, especially in the acute phase, is present in studies documenting raised concentrations of proinflammatory neuropeptides and mediators, such as substance P, calcitonin gene-related peptide, bradykinin, and cytokines interleukin-1β (IL-1β), interleukin-2 (IL-2), and interleukin-6 (IL-6), tumor necrosis factor α (TNF- α) in the systemic circulation, cerebrospinal fluid, and affected limbs of patients with CRPS, which can explain the symptoms of vasodilation causing a warm red appearance in the affected area, and may increase hair growth and sweating.[24–37]

In humans, increased numbers of proinflammatory monocytes (CD14 + ; CD16 +) in addition to altered innate immune responses and mast cells have been reported in patients with CRPS compared with healthy controls.[38–41] A new theory advocates that antibodies from people with CRPS may be capable of transferring the condition to previously unaffected individuals, also supporting a role for immune mechanisms.[42] In a work by Goebel et al. from 2011, immunoglobulin G (IgG) from patients with CRPS when injected into mice in the absence of any injury induced motor changes, characteristic of CRPS.[43] This autoimmune model[44] can explain the link between the autonomic nervous system and the CRPS, since the presence of autoantibodies directed against β2 adrenergic and muscarinic type 2 receptors were found in patients with CRPS.[45–47]

Furthermore, a study with mice model conducted in 2019 demonstrated that, in CRPS, IgG is significantly increased and seems to prolong swelling and induce stable hyperalgesia. The author also says that CRPS IgG-injected mice displayed sustained microglia and astrocyte activation in the dorsal horn of the spinal cord and pain-related brain regions, indicating a link with central sensitization. Even more interesting, genetic deletion of interleukin-1 (IL-1) using IL-1αβ knockout mice and perioperative IL-1 receptor type 1 blockade with the drug anakinra prevented these changes,

showing one other possible correlation between various theories such as inflammatory, autoimmune, and genetics hypothesis to the CRPS pathophysiology.[48]

Although well explained, the autoimmune theory is not yet totally elucidated. One parallel, randomized, placebo-controlled, multicenter trial tried to confirm the efficacy of low-dose IVIg compared with placebo in reducing pain during 6 weeks in adult patients who had CRPS from 1 to 5 years but did not succeed, emphasizing once again the multifactorial genesis of CRPS.[49]

Brain Plasticity

Neuroimaging testing suggests that several brain changes are associated with CRPS.[50–54] Although recent studies point out that the change in the brain is associated with the onset of the syndrome, it is not known for sure if this is what occurs or if it is the syndrome that causes the change in the brain.[50] However, the longer you develop the syndrome, the greater the change in neuroplasticity.[53]

In CRPS, there is an asymmetry between the corresponding brain regions. A reduction (structure or function) occurs on the side of the affected brain or there is an increase on the side of the unaffected brain.[50]

The main brain areas where this difference in asymmetry occurs are endogenous pain inhibitory pathways (opioid-mediated), primary and secondary somatosensory cortices, the primary motor cortex, the insula, and the cingulate cortex.[50–54]

Genetic Factors

There is a lack of studies of genetic factors in CRPS. However, some family-based studies reported a potential genetic predisposition.[51] The studies have identified polymorphisms at the genes encoding α1a adrenoceptors and the human leukocyte antigen (HLA) system (HLA-DQ8, HLA-B62), tumor necrosis factor-alpha (TNFα) gene and the angiotensin-converting enzyme gene.[50,51] Due to the lack of studies on the genetic factors involved in CRPS, the pathophysiological mechanism related to genetics is still not completely understood.[52]

Psychological Factors

It is not known for certain whether psychological factors are directly related to the development of CRPS, but it is suspected that anxiety and depression are related to the syndrome.[50,51] It is suspected that psychological factors alone do not contribute to the onset of the syndrome; however, psychological factors linked to tissue damage may imply an increase in the severity of the syndrome, which might represent an increase in the intensity of the pain.[50,54] It is also suspected that psychological factors, especially before invasive procedures, provide an increase in the chance of developing CRPS.[50]

The main signs and symptoms found in patients with CRPS are spontaneous pain; hypoesthesia and hyperpathia; edema; skin blood flow abnormality; color change; abnormal sudomotor activity; tissue atrophy; and involuntary movements.[4,55]

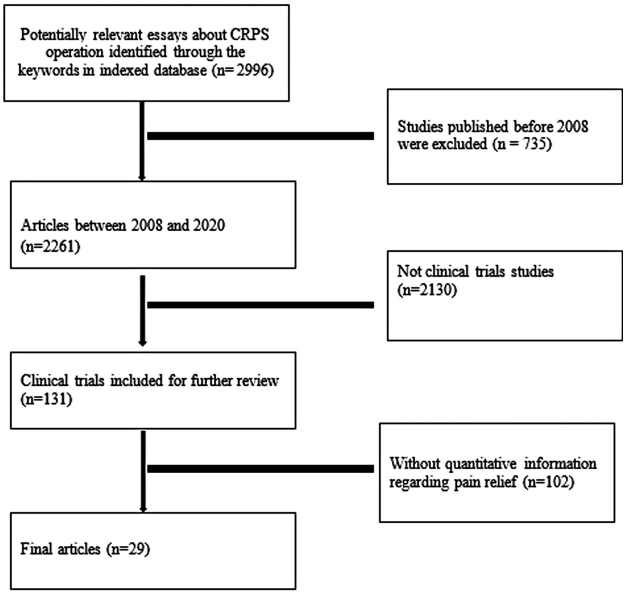

Fig. 1 Clinical trial inclusion criteria.

The diagnosis of CRPS is clinical, without imaging indicators or precise serum markers that indicate this pathology. The Budapest criteria is the one adopted to perform the diagnosis.[56]

The objective of the present systematic review is to show the results of the most recent unconventional treatments that add quality of life and improve the prognoses of CRPS patients.

Materials and Methods

To perform the systematic review, a broad review was conducted on the PubMed databases in the literature until September 2020. The search was initially performed with the keywords *complex regional pain syndrome*. A total of 2,996 articles were found in this search. Studies published before 2008, studies that were not clinical trial, and articles without quantitative information regarding pain relief were excluded. On this research, 29 results were obtained ►**Fig. 1**.

Results

►**Table 1** aimed to analyze how quantitatively the level of pain decreases in a given treatment against CRPS.

For that, we analyzed some initial quantitative mathematical quantities (average of pain, the median of pain, maximum pain) given by the articles in the baseline. We adopted these mathematical numbers as the initial average of the table at 100%.

Later, in the analysis of the article, with the quantitative number of the pain level given by the articles after the treatment (final average) of the last follow-up, we were able to arrive at how much the pain decreased in that particular treatment. This value was calculated by subtracting the final average multiplied by 100%, followed by dividing

Table 1 Description of Clinical Trials studies for CRPS treatment

REFERENCE	NUMBER OF PATIENTS (EFFECTIVE/CONTROL)	CRPS TYPE	TREATMENT	FOLLOW-UP (MONTHS)	PAIN RELIEF TREATMENT COMPARED WITH BASELINE	CONTROL PAIN RELIEF COMPARED WITH BASELINE (%)	CLASSIFICATION
[57]	54 (36/18)	1	spinal cord stimulation	60	25.37	14.28	fair
[58]	22 (22/0)	1	stellate ganglion blockade	0.5	87.5	–	excellent
[59]	13 (7/6)	1	low-dose intravenous immunoglobulin	0.83	25	12.5	fair
[60]	67 (33/34)	1	ct-guided radiofrequency neurolysis	24	67.6	21.2	good
[61]	42 (42/0)	1	intrathecal baclofen	12	22.4	–	bad
[62]	14 (14/0)	1	spinal cord stimulation	6	71.8	–	good
[63]	29 (15/14)	1	Ketamine	3	71.4	22.6	good
[64]	56 (29/27)	1	intravenous magnesium	3	14.8	10	bad
[65]	13 (6/7)	1	infliximabe	1.5	38	0	fair
[66]	74 (40/34)	1	amino-bisphosphonate neridronate	1.3	65.6	32.1	good
[67]	22 (12/10)	1	intramuscular magnesium sulphate	0.75	8.21	–	bad
[68]	29 (15/14)	1	thoracic sympathetic block	12	36	5.19	fair
[69]	51 (51/0)	1	spinal cord stimulation of the dorsal root ganglion	12	66.3	56.7	good
[70]	28 (14/14)	1	mirror therapy in stroke patients	6	50	–	good
[71]	53 (27/26)	1	pain exposure physical therapy	9	28.6	30.1	fair
[72]	29 (29/0)	1	oral corticosteroids	1.5	13.33	–	bad
[73]	52 (C.O.T.)	1	prednisolone	2	57.2	–	good
[74]	30 (15/15)	1	transcutaneous electrical nerve stimulation	UNK	70	–	excellent
[75]	33 (18/15)	1	exposure in vivo	6	49	47.5	fair
[76]	105 (55/50)	1 and 2	dorsal root ganglion stimulation	12	81.39	67.16	excellent
[77]	28 (C.O.T.)	1 and 2	spinal cord stimulation	2.5	45.24	12.37	fair
[49]	108 (56/52)	1 and 2	low-dose intravenous immunoglobulin treatment	1.5	6.76	3.5	bad
[78]	22 (11/11)	1	transcranial direct current stimulation	1.5	16.23	8.77	bad
[79]	9 (4/5)	1	mycophenolate treatment	5.5	45.45	–	fair
[80]	15 (C.O.T.)	UNK	paravertebral block performed at the t2 level	UNK	50.06	–	good
[81]	52 (26/26)	1	bioptron light therapy combined with conventional therapy	0.5	93.65	80.1	excellent
[82]	30 (15/15)	1	fluidotherapy combined with conventional therapy	0.75	50	37.5	good
[83]	12 (12/0)	1	short term glucocorticoid	0.2	50	–	good
[84]	24(12/12)	1 and 2	selective l4 dorsal root ganglion stimulation	3	37.72	–	fair

Abbreviations: C.O.T., crossed over treatment; CT, computed tomography; UNK, uninformed.

it by the initial average, from 100%. It is worth mentioning that this analysis was performed in the effective therapy group (100% of the articles in the table) and the control when it presented quantitative data.

Furthermore, the number of patients in the table does not necessarily reflect the initial number, but rather the final present number described in each article. According to the quantitative data obtained in pain relief, we classified the treatment as bad, fair, good or excellent.

For the treatment to be considered bad it should reach a maximum of 24.9%, fair should be between 25 and 49.9%. To be evaluated as good, it should be between 50 and 74.9%, and for excellent, the range was from 75 to 100%.

Of the 29 articles that completed our selection criteria, 20.7% (6/29) of the performances of the treatments were bad, 31% (9/29) were fair, 34.5% (10/29) were good, and 13.8% (4/29) were excellent. The average painful reduction of all articles was 46.37% 7 months of follow-up (average).

Among these, surgical treatments (10/29) showed an average pain reduction of 56.9% and follow-up of 14.67 months; in contrast, conservative treatments (19/29) had a reduction of 40.82% and a follow-up of 3.16 months.

Moreover, the table shows an average of 38.48 patients in an average follow-up of 7 months. It is worth mentioning that the ratio between the average number of patients in the experimental group and in the control group is 1.52 (616/405, excluding crossed-over treatment).

Discussion

►**Table 1**

According to the data in ►**Table 1**, surgical treatments (10/29) showed an average pain reduction of 56.9% and a follow-up of 14.67 months. In contrast, conservative treatments (19/29) had a reduction of 40.82% and a follow-up of 3.16 months. Thus, we conclude that invasive treatments are more effective in combating one of the symptoms of CRPS: pain.

Among the surgical treatments, according to ►**Table 1**, in descending order, the procedures that most reduce pain are: stellate ganglion blockade, dorsal root ganglion stimulation, spinal cord stimulation,[62] computed tomography-guided radiofrequency neurolysis, spinal cord stimulation of the dorsal root ganglion, paravertebral block performed at the t2 level, spinal cord stimulation,[77] selective l4 dorsal root ganglion stimulation, thoracic sympathetic block, and spinal cord stimulation.

However, the most efficient treatment for pain reduction was a nonsurgical treatment, bioptron light therapy combined with conventional therapy.

Conclusion

Complex regional pain syndrome is a severe issue that affects the quality of life of the patients and interferes with one's well-being. This illness does not have a well-established pathophysiology; thus, the option of treatments is diverse in the literature. In the present study, we reviewed the literature to explain the possible treatments of CRPS. We conclude that surgical treatments are more efficient in decreasing pain in patients with CRPS. We suggest that further studies that analyze pain reduction in CRPS are needed.

Ethics Approval and Consent to Participate

The National Health Council of Brazil, by resolution 466/2012, exempts this type of study from the research ethics committee, since it is a transversal study and all data is available on the internet free of charge and anonymously.

Conflict of Interests

The authors have no conflict of interests to declare.

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Oncotic (Myxomatous) Aneurysms: A Review of Management

Aneurismas oncóticos (mixomatosos): Revisão das opções de tratamento

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Abstract

Atrial myxomas are the most common primary cardiac tumors and may manifest with neurological symptoms in ~ 30% of cases. Cerebral ischemia, aneurysmal formation, and extravascular metastases are mechanisms that lead to these neurological manifestations. Perilesional changes on computed tomography (CT) and magnetic resonance imaging (MRI) may help in the diagnosis of myxomatous aneurysms, which are usually located in the distal middle cerebral artery (MCA) and in the posterior cerebral artery (PCA) circulation territories. Careful resection of the cardiac lesion is essential for preventing embolism. However, treatment of myxomatous aneurysms is controversial due to the limited understanding of the natural history of this condition. Treatment may include clinical observation in asymptomatic patients, surgical resection, endovascular approaches, adjuvant chemotherapy, and low-dose radiation therapy. We present one case of a female patient with myxomatous aneurysm secondary to an atrial myxoma who presented with neurological symptoms and another case of a female patient who developed neurological symptoms after initial surgical treatment of the primary lesion. Lesion growth rate, topography, morphology, and the patient's clinical condition must be considered when choosing a therapeutical method. Further clinical studies are needed to achieve a better understanding and treatment of this disease.

Keywords

- oncotic aneuryms
- myxomatous aneurysm
- intracranial aneurysm
- fusiform aneurysm
- atrial myxoma
- embolization

Resumo

Mixomas atriais são os tumores primários cardíacos mais comuns. Podem levar a manifestações neurológicas em cerca de 30% dos pacientes devido a: isquemia cerebral, formação de aneurismas e metástases extravasculares. Alterações perilesionais encontradas tanto nas de tomografia (TC) ou ressonância magnética (RM) podem

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ajudar no diagnóstico de aneurismas mixomatosos, que geralmente envolvem ramos distais das artérias cerebral média e posterior. Ressecção cirôrgica cuidadosa da lesão cardíaca é essencial para prevenção de eventos embólicos. Entretanto, por sua história natural mal conhecida devida à raridade da condição, o tratamento dos aneurismas mixomatosos é controverso, incluindo conduta conservadora em pacientes assintomáticos, abordagem cirôrgica, endovascular, quimioterapia adjuvante e radioterapia em baixas doses. Discutiremos dois casos clínicos de pacientes femininas com aneurismas mixomatosos, tendo o primeiro caso o acometimento neurológico como manifestação inicial e o segundo com sintomas posteriores ao tratamento cirôrgico do tumor primário. Determinação da melhor escolha do tratamento deve levar em consideração taxa de crescimento da lesão, sua topografia, morfologia e clínica do paciente. Mais estudos clínicos são necessários para melhor compreensão e definição de conduta desses pacientes.

Palavras-chave
- aneurisma oncótico
- aneurisma mixomatoso
- aneurisma intracraniano
- aneurisma fusiforme
- mixoma atrial
- embolização

Introduction

Atrial myxomas are the most common primary cardiac tumors, and usually arise in the left atrium. Complete surgical resection can cure these lesions, but embolism can occur before and during total resection. Most importantly, cranial metastasis can occur even after years of total resection of the tumor, without any evidence of remaining atrial lesion.[1] Thus, neurological deficits may appear long after a successful removal of the primary cardiac tumor, stressing the need of long-term neurological follow-up.

Subendocardial multipotential mesenchymal cells originate these tumors. Macroscopically, these lesions are generally soft and pedunculated. They occur between the 3rd and 6th decade of life and show a 2:1 female-to-male ratio.[2]

The cranial vasculature is one of the most susceptible areas to myxoma embolization, most often resulting in ischemic strokes. Atrial myxomas are diagnosed by echocardiography. Atrial myxomas with walls with irregular surface are associated with a high risk of embolic events. Early diagnosis and treatment of these cardiac lesions is essential to the prevention of embolic events.[3] There is controversy about the pathogenesis and treatment of secondary cerebral lesions. We report two cases and review the literature on the pathogenesis, clinical-radiological aspects, and management of intracranial myxomatous aneurysms.

Methods

We present a series of two consecutive cases cared for by the main author and obtained from the neurosurgical databases of the institutions where the present study was conducted. These databases are approved by the Ethics and Research Committee of both institutions. The inclusion criteria were patients with cardiac myxoma and intracranial aneurysms.

A systematic review was performed using the PubMed and Scielo databases. To perform the search, the keywords *oncotic* AND *myxomatous* AND *intracranial aneurysm* were used, including the past 25 years in English publications.

After magnetic resonance imaging (MRI) studies, we performed digital 3D subtraction angiography, and the location of the lesions was classified as follows: internal carotid artery (ICA), anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), basilar artery (BA), and posterior inferior cerebellar artery (PICA).

Case Reports

Case 1

A 14-year-old girl presented with sudden-onset aphasia and right-sided weakness. She had a history of generalized tonic-clonic epileptic seizures from the age of 11.

A computed tomography (CT) scan showed hypodensity in the left MCA territory. On echocardiography, a 39×17 mm tumor in the left atrium was identified, suggesting atrial myxoma. Surgical excision of the myxoma was performed in another hospital. The neurological condition of the patient improved, but a learning disability ensued, as well as preserved oral comprehension with slower verbal information processing and oral expression characterized by hesitation and moderate anomia. Speech therapy and persistence of school activities enabled continued improvement.

On digital cerebral angiography performed after the cardiac surgery, multiple aneurysmatic lesions in the anterior and posterior circulations were identified. The most evident lesions were in the bifurcation of the left MCA, in the A2 and A3 segments of the ACA, and in the right PICA (►**Fig. 1**). We proposed endovascular treatment, preceded by a test occlusion and occlusion, if possible, but the parents did not accept the risks of a cerebellar infarction even after explanation of the hemorrhagic risk and its consequences. Therefore, a conservative treatment was chosen.

We performed a control MRI angiography, that showed the aforementioned lesions with no significant change compared with the previous test, and an additional lesion located inside a sulcus in the posterior temporal region. Digital

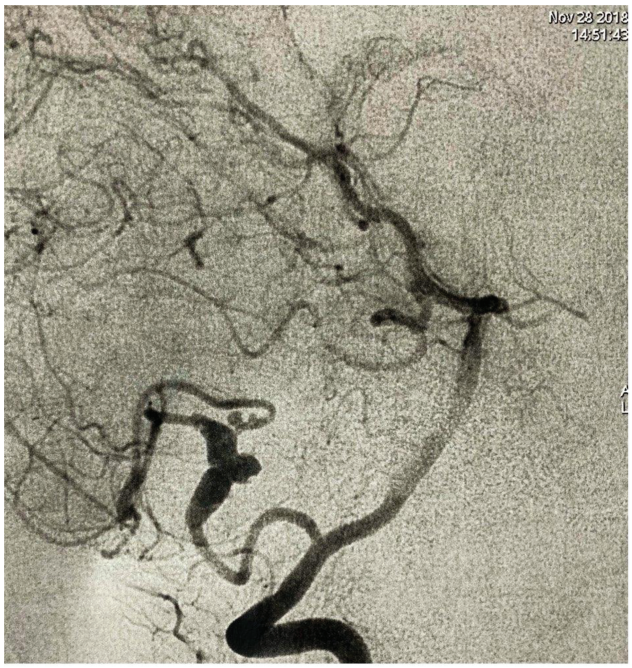

Fig. 1 Diagnostic cerebral angiogram showing a right posterior inferior cerebellar artery aneurysm. Notice the fragility spots represented by lobulation and the two small aneurysms in the superior branch.

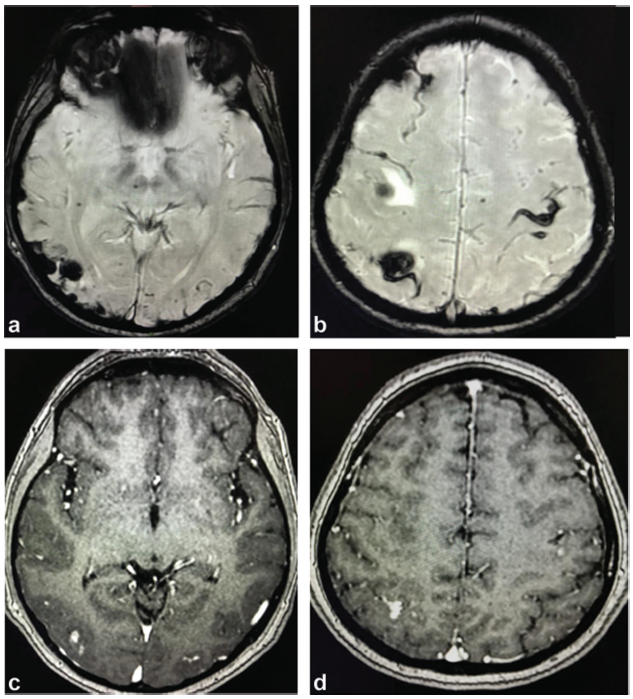

Fig. 2 Follow up magnetic resonance imaging studies obtained 2 months after initial presentation. Axial susceptibility weighted images (SWI) (**a, b**) and 3D axial T1 weighted images (**c, d**) at the same anatomic level for comparison. Note the round blooming artifact in SWI in the right parietal region, consistent with hemorrhage, as well as small amounts of linear blood in the sulci diffusely. There is contrast enhancement in the right parietal lesion, corresponding to the larger aneurysm seen on digital subtraction angiography.

cerebral angiography showed stable lesions, and there was no increase in size or number of lesions in a 2-year outpatient follow-up.

Case 2

A 47-year-old woman was admitted to our hospital with generalized tonic-clonic seizures. A CT scan showed two areas of hemorrhagic stroke on the right parietal lobe, on the posterior right MCA territory. The patient was awake and oriented, with a slight left hemiparesis on physical examination. She had a history of a cardiac myxoma surgery 3 months before, without surgical or postsurgical complications.

Magnetic resonance imaging depicted multiple foci of sulcal and intraparenchymal lesions, one of which showed evidence of hemorrhage (a small 1 cm parietal hematoma), suggesting multiple intracranial cavernomas. The clinical information provided to the radiology did not mention her cardiac history.

Clinical treatment of the low volume hematoma was chosen, with general clinical improvement, cessation of seizures, and residual occasional headaches.

After 2 months, the headaches worsened, and a follow-up MRI made in another institution (►**Fig. 2**) depicted several foci seen before, but which now showed an increase in volume in 2 lesions, with perilesional hemorrhage in 1 of them. Gadolinium-enhanced T1 images showed continuity of the lesions with distal blood vessels, suggesting fusiform aneurysms, the larger one located in the right precentral gyrus, with vasogenic edema in the surrounding parenchyma. Minute hyposignal foci in SWI-weighted imaging in the cerebellum, brainstem, and cerebral hemispheres suggested microhemorrhages.

Digital subtraction 3D angiography (3D DSA) showed 7 fusiform aneurysms in the territory of the right MCA (►**Fig. 3**), 5 in the left MCA territory and four aneurysms in the distal PCA territory (2 on the left and 2 on the right side). Most of these lesions remained opacified until the late venous phase.

A diagnostic echocardiography showed no remaining atrial myxomas. Based on the symptoms and on the findings of increased lesion volume, a multidisciplinary team comprised of therapeutical neuroradiologists, oncologists and radiation therapists chose radiation therapy as the best course of action. Two lesions were irradiated, 1 in the frontal and another in the parietal region, measuring 1.6 and 1.3 cm, respectively. The treatment was performed with stereotactic ablative radiotherapy (SABR, also known as radiosurgery), with a single dose of 1200 cGy, in a linear accelerator with Agility multileaf collimators (Elekta Corporation, Stockholm, Sweden). We decided to only treat these lesions due to the evidence of volumetric progression when compared with previous diagnostic images, which was lacking in the other lesions.

Follow-up brain MRI and cerebral angiogram performed after 2 years of follow-up, in January 2021, showed stability of both treated and untreated lesions, with no evidence of disease progression or new lesions. The patient was clinically

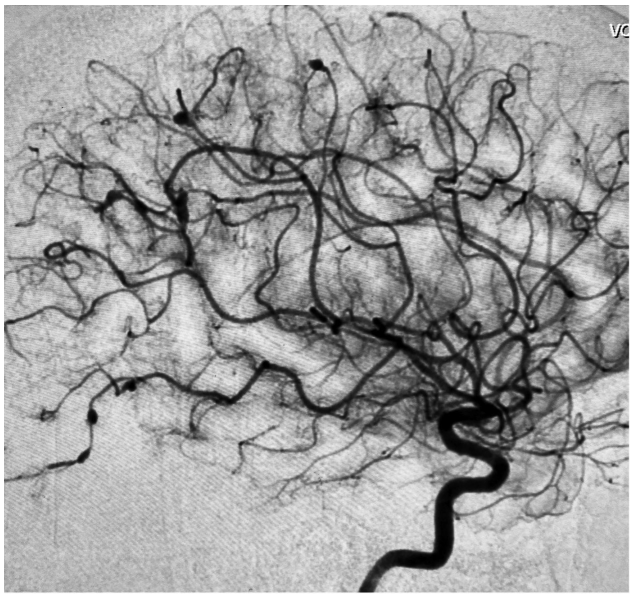

Fig. 3 3D digital subtraction angiography showing multiple fusiform aneurysms on the right middle cerebral artery distal branches.

stable, without new seizures. Annual MRI and MRA follow-up was decided as the management strategy for the patient, with digital subtraction angiography as a possible choice in case the noninvasive images showed progression of the lesions.

Discussion

Clinical Presentation and Pathogenesis

Cardiac myxomas are benign lesions originated from subendocardial mesenchymal cells commonly located in the left atrium, at or near the interatrial septum. There is a female-to-male ratio of 2:1 and they are more frequent between the 3rd and 6th decades of life, although children and elderly individuals may be affected.[4]

They can be solid or soft (papillary subtype) and, in these cases, they may be pedunculated, and intermittently stop the flow across the mitral valve, leading to syncope. Most of the times the lesions are benign but may recur after initial surgical treatment if incompletely resected. Malignant transformation has been reported. Recurrence has been reported in the familial myxoma syndrome.[5]

The clinical presentation may range from asymptomatic to sudden death. Cardiac symptoms such as dyspnea, syncope, and cardiac murmur may occur when the tumor is solid, and/or embolization when the papillary subtype is involved.[6]

The triad of symptoms of cardiac myxoma include:[7]

1. Inflammatory syndrome, with symptoms such as myalgia, arthralgia, fever, with elevated erythrocyte sedimentation rate and C-reactive protein (CRP) levels.
2. Embolic presentation, most commonly to the brain or systemic circulation, as tumors are often left-sided in the heart
3. Valvular heart obstruction, leading to pulmonary edema with dyspnea and, less commonly, right heart failure.

Myxomas produce growth factors such as vascular endothelial growth factor (VEGF), resulting in angiogenesis, which may explain why they are more invasive to blood vessels than other tumors. They proliferate under the intimal layer of the artery, and may progress to invade the whole vessel wall, leading to rupture.

Overproduction of interleukin-6 (IL-6) could be responsible for the inflammatory presentation, recurrence, and distal embolization of cardiac myxomas.[8] High levels of IL-6 leads to upregulation of matrix metalloproteinases, consequently with degradation of the arterial wall collagen and aneurysmal genesis.[9]

Interleukin-6 may be a more sensitive biomarker than CRP for evaluation of the inflammatory status of patients with cardiac myxoma. The normalization of circulating IL-6 levels can be of value in the follow-up of patients after cardiac tumor resection.[10]

About 30 and 40% of patients will suffer tumor embolism in the lungs, in the brain or in the systemic circulation. Factors associated with an increased risk of embolism include:

1. Echocardiographic irregular tumor surface (polypoid tumors) embolize much more frequently than round tumors (58 versus 0%).[11]
2. Atrial fibrillation, larger tumor size, and an increased left atrial diameter.[12]

The tumor location (left or right atrium) and/or presence of a persistent foramen ovale will determine the site of embolism.[13]

Neurologic symptoms will occur in $\sim$ 30% of patients with an atrial myxoma, and in almost half of these, the neurologic manifestation will precede the cardiac symptoms.[14]

Three distinct neurological presentations have been described:[15]

1. Embolic ischemic stroke.
2. Intracranial aneurysms.
3. Intracranial metastases (the most uncommon presentation).

The aneurysm cases we present here are of two women, both with multiple lesions. We will summarize the characteristics and treatment options of these aneurysmal lesions.

The initial presentation of both patients was tonic-clonic seizures. Patient 1 did not bleed, but patient 2 had a hemorrhagic stroke due to a ruptured distal fusiform aneurysm. Only after that, the cardiac myxoma was found.

Also, in both patients, the main patterns of aneurysm distribution were multiplicity and always had a distal location. The topography was most frequently in the MCA and PICA territories, but also in the PCA. No aneurysm was found in the ACA territory. The shape of the lesions was always fusiform. In patient 2, there were significant irregularities in the PICA aneurysms (►**Fig. 1**), which indicated test occlusion

and occlusion, if possible, but the parents did not accept the risks.

In patient 2, some aneurysms coexisted with hypodense areas on MRI (old hemorrhagic sites), which presented as gyral pattern of marked signal loss on T2WI and SWI. Of note, homogenous enhancement surrounding the aneurysms was detected on contrast-enhanced MRI.

The neurologic presentation may occur before, at the time, months or even years[16] after the clinical manifestation or diagnosis of the primary tumor. In our cases, the presentation consisted of seizures and only after the imaging features of the brain (MRI angiography) it was thought to be related to an embolic event.

The histopathological type of both tumors was papillary myxoma. The mobility, but not the size of the myxoma appears to be related to the embolic potential,[3] and the friable and gelatinous papillary myxomas embolize more often than solid lesions.

All patients had multiple fusiform aneurysms in distal locations. There are three hypotheses for the genesis of these lesions:[3]

1. Embolic fragments of the tumor leading initially to vascular occlusion and destruction of the arterial wall and/or myxoma cells would proliferate without apoptosis, leading to occlusion.
2. Hematogenous dissemination of lesions with cerebral vasa vasorum invasion, leading to destruction of the arterial wall, particularly of the internal elastic lamina, resulting in aneurysm formation.
3. A combination of the two mechanisms above: myxomatous tumor emboli leading to invasion of the vasa vasorum, apoptosis and destruction of the vessel wall, widening of the arterial lumen, and fusiform aneurysm formation.[17]

Differential Diagnosis

Echocardiography should be performed in all patients with suspected embolic events, especially when cerebral infarcts or hemorrhages in multiple arterial territories are identified. On noncontrast CT, the aneurysms are spontaneously hyperdense, due to accumulation of myxoid matrix or to calcification in their walls. Also, there are abnormal findings surrounding the myxoid aneurysms, like signal loss on T2-weighted images, enhancement in contrast-enhanced T1 images and on CT, due to myxoid accumulations, angiogenesis, or granulation tissue. These perilesional changes may contribute to differentiate these aneurysms from other lesions, as described below:

Cavernoma: Cavernomas are not seen on angiography, but on MRI images, both may appear as large-volume lesions surrounded by an irregular hemosiderin ring; different degrees of perilesional edema can exist simultaneously and both show a blooming effect on gradient-echo and susceptibility images, but only the myxoid aneurysms are clearly identifiable on T1-weighted images.[4]

Mycotic aneurysms: angiographic findings of myxoid aneurysms are not different from the most common mycotic (septic) aneurysms: multiple lesions that are fusiform in shape and peripheral in topography. The finding of persistent hyperdensity in noncontrast enhanced CT scan may suggest a myxoid origin: histopathological studies showed accumulation of myxoid, hemosiderin, and iron from recurrent chronic hemorrhages, but not calcification.[18] Septic aneurysms are more prone to rupture, resulting in subarachnoid hemorrhage or hematoma around the lesions.[2]

Other neoplastic intracranial aneurysms: choriocarcinoma and lung carcinoma metastases generally are single lesions and may lead more frequently to intracranial hemorrhage (100% in choriocarcinoma and 84% in lung carcinoma). Instead, myxoid aneurysms are almost always multiple and the rate of intracranial hemorrhage is much lower (19.6%).[19]

Treatment Options for Myxomatous Intracranial Aneurysms

Early cardiac surgery with extreme caution not to allow the myxoma to embolize intraoperatively is the best treatment to reduce the possibility of embolic complications or sudden death, as well as for optimally preventing these serious lesions from reaching the central nervous system.

After cardiac surgery, these patients need frequent neurological examination, as well as echocardiography, brain MRI and MRA, and must be made aware of the need to seek medical attention should any neurological symptom arise.

In a study of 58 patients with myxomatous intracranial aneurysms, the incidence of rupture was 19.6% in 11 years.[19] A meta-analysis[20] of 37 patients with multiple myxomatous intracranial aneurysms showed 76% of stability or regression of these lesions, enlargement of 21%, and mortality of 3.4%.

The management of intracranial myxomatous aneurysms is controversial. The resection of the atrial lesion does not avoid the continuous growth of these lesions in the central nervous system, if they are already present, with risk of hemorrhage.

There is no definitive guideline available in the current literature, so decisions should be made case by case. Surgery, embolization, and surgery with adjuvant chemotherapy have been proposed, with or without adjuvant low-dose radiation therapy.[21]

Conservative Treatment

Given the poor understanding of the natural history of these lesions, a conservative management is mandatory in most asymptomatic patients with stable and nonhemorrhagic lesions.[22]

Follow-up imaging may show stability or even regression of some lesions after cardiac tumor removal.[20,23] In a series of 37 cases, 78.4% were managed conservatively and 75,9% with stable or even regression, with a mortality of 3.4%. In the present study, 20.7% of the cases demonstrated aneurysmal enlargement, without symptoms or bleeding.[19]

Noninvasive Methods

The pathogenesis and further growth of myxomatous aneurysms is linked to the proliferation of neoplastic cells inside the arterial wall. Therefore, radiation and chemotherapy

have been used in selected cases to try to halt their growth.[24] There are limited reports of such treatments, so their efficacy remains unproven.

Radiation Therapy

The effects of radiation in metastatic myxomas are extrapolated from the response seen in the setting of tumors and especially of brain arteriovenous malformations,[25] including endothelial damage, arterial wall smooth muscle proliferation, and intraluminal platelet aggregation with microthrombosis, resulting in vessel obliteration. The parent vessel occlusion with radiation has a slow course, allowing for the opening of collateral circulation, avoiding ischemic events. Furthermore, given the differential response to radiation of neoplastic cells, it could interrupt the proliferation of myxomatous cells and, consequently, aneurysmal enlargement.[24]

There are many reports of successful treatment of metastatic myxoma,[21] but for the treatment of myxomatous intracranial aneurysms, we have found only two literature reports of radiation therapy for multiple lesions located in eloquent areas, in which parent artery surgical or endovascular ligation would be highly deleterious.

One single case report used 45 Gy low-dose fractionated radiation in multiple myxomatous aneurysms, with occlusion of the lesions and parent vessels on control angiograms.[17] The other report treated with 14 Gy, obtaining the same effect (aneurysmal and parent vessel occlusion), claiming to minimize the risks of adverse effects of radiation.[24]

The main issue with monotherapy with radiation is similar to its use in treating hemorrhagic brain arteriovenous malformations[26]: in hemorrhagic myxomatous aneurysms, the latency period until radiation promotes protection may put the patient at risk of new bleeding episodes.

Chemotherapy

In cases of evolving symptomatic masses, chemotherapy might be considered. Etoposide and carboplatin have been used[27] in severe cases, but their efficacy is poor, and most medical centers are cautious about their use due to a lack of clinical experience and of high-quality studies.

Invasive Methods

As most lesions occur in distal branches, surgical excision remains the option of choice in selected cases. In determining the best treatment option, lesion topography, morphology, and clinical and aneurysm size evolution are important factors to help decide between surgical or endovascular approach. The same patient may even need both methods of treatment for multiple lesions.[28]

Surgical Treatment

In cases in which there is significant increase in lesion size, craniotomy may be indicated for decompression. In the subdural space, thrombi may be seen on the brain surface, as well as mucinous masses and yellow staining. It is often not possible to remove the aneurysms due to the eloquent territory irrigated, and the low risk of bleeding. Thus, postoperative MRI or DSA may show persistence of the aneurysms, with amelioration of the mass effect.

In those cases in which the lesion is close to the cortical surface, and with small parent vessels, the use of a neuronavigational system to guide craniotomy may be chosen, followed by exploration of the sulcus harboring the lesion. After identification of the dilated fusiform artery, coagulation and/or clipping of the afferent and efferent artery is performed, allowing for safe removal of the aneurysm. Bypass should be considered for those lesions in eloquent areas, since clip reconstruction is impossible due to the friability of the aneurysms.[16,29]

Endovascular Treatment

For acute vascular occlusion, intravenous thrombolysis has been attempted in emergency stroke care scenarios, without the knowledge of a cardiac myxoma as the underlying condition.[30] From a practical standpoint, this can be effective in restoring the blood flow and improve the prognosis in patients with cerebral embolism due to a cardiac myxoma, but the possibility of a hemorrhagic complication in the setting of a coexisting myxoid aneurysm must be remembered.

Consequently, unstable (growing) and symptomatic intracranial myxoid aneurysms, although with a low risk of rupture, may need to be occluded. As a fusiform lesion, they must be occluded sacrificing the artery closely proximal and distally to them (the so-called "deconstructive approach") with a liquid embolic. This may pose a very difficult decision, as neurological deficits may appear after ligation.

One advantage of the endovascular method is the possibility of performing balloon test occlusion before this decision, with the patient awake, in an attempt to predict the clinical consequence of sacrificing the vessel. Rarely, some deficits may appear lately, only after increased metabolic demands such as that due to physical exercise.

After aneurysm and vessel occlusion, although the hemorrhagic risk is eliminated, the lesion itself or its surroundings may continue to grow as a tumor. This would be the case to treat with chemotherapy or radiotherapy soon, although in most reported cases these embolized lesions remained stable on follow-up after embolization,[20] possibly because embolization devascularizes the region, causing decreased blood flow to neoplastic cells and lowering the risk of tumoral growth.

Conclusions

Myxomatous intracranial aneurysms may present a therapeutic dilemma, as their natural history is relatively unknown. Most of the unruptured cases seem to have a benign course, and all the possible open interventions have potential morbidity (sacrificing the parent artery is almost always necessary).

Once the aneurysmal lesions are diagnosed, periodic follow-up noninvasive images are warranted, as well as close clinical evaluation. Increasing and symptomatic lesions in

low eloquence areas should receive further investigation with DSA followed by treatment with surgery or embolization, and targeted radiation therapy should be considered for lesions in eloquent areas.

There is no time limit to stop follow-up, due to literature cases presenting with hemorrhage decades after tumor removal, as cited above.

Further clinical studies are needed to elucidate the appropriate management of asymptomatic evolving lesions in eloquent areas.

The doubt persists for those increasing lesions in eloquent areas but in asymptomatic patients.

Conflict of Interests

The authors have no conflict of interests to declare.

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Historical Aspects and Surgical Nuances on the Craniocervical Approach to the Jugular Foramen

Aspectos históricos e dicas do acesso craniocervical ao forame jugular

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Abstract

Context Tumors of the jugular foramen present a challenge to skull base surgeons. Their rarity, coupled with the complex anatomy of the region require exquisite knowledge and surgical technique. We present the history of the craniocervical approach to the jugular foramen, as well as surgical advice on how to manage the different extensions these tumors may present. The surgical nuances come from the experience of our skull base team managing over 150 tumors of the jugular foramen over the past 30 years. The history of the craniocervical approach was obtained by reviewing articles on surgery of the jugular foramen published on PUBMED over the past 100 years.

History The first craniocervical approach may be attributed to Gardner et al. in 1891, with posterior contributions from Shapiro and Neues, Gejrot, Kempe et al, Hilding and Greenberg, and Glasscock.

Nuances Cervical dissection with identification of the jugular vein, carotid bifurcation, and IX to XII cranial nerves was performed. Mastoidectomy with exposition of the fallopian canal, labyrinth, middle ear, sigmoid sinus, followed by a trans-sigmoid craniotomy with transposition of the vertebral artery gave access to the temporal and intracranial region.

Conclusion Approaching the jugular foramen is the epitome of skull base surgery. Several modifications of the standard approach may be necessary depending on the extension of the tumor.

Keywords
- jugular foramen
- schwannoma
- meningioma
- paraganglioma
- skull base neoplasms

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Resumo

Contexto Os tumores do forame jugular apresentam um desafio para os cirurgiões da base do crânio. A sua raridade e a anatomia complexa da região requerem conhecimento específico da técnica cirúrgica. O presente manuscrito apresenta a história do acesso crâniocervical ao forame jugular, assim como dicas cirúrgicas para manejar as diferentes extensões que os tumores podem apresentar. As dicas são derivadas da experiência da nossa equipe em mais de 150 tumores do forame jugular nos últimos 30 anos. A história do acesso crâniocervical foi obtida da revisão de artigos em PUBMED dos últimos 100 anos.

História A primeira abordagem craniocervical pode ser atribuída a Gardner et al. em 1891, com contribuições posteriores de Shapiro e Neues, Gejrot, Kempe et al, Hilding e Greenberg e Glasscock.

Descrição A dissecção cervical necessita identificação da veia jugular, bifurcação carotídea, e dos nervos cranianos de IX a XII. A mastoidectomia com exposição do canal de falópio, labirinto, ouvido médio e seio sigmoide foi seguida por uma craniotomia transsigmoide com transposição da artéria vertebral, permitindo abordar a região temporal e intracraniana.

Conclusão Acessar o forame jugular é o epítome da cirurgia da base do crânio. Múltiplas modificações do acesso tradicional podem ser necessárias dependendo da extensão do tumor.

Palavras-chave

- forame jugular
- schwannoma
- meningioma
- paraganglioma
- base do crânio

Context

Tumors of the jugular foramen have been a challenge to diagnose, define its origin, classify and treat. For the past century, otolaryngologists and neurosurgeons have transformed management of tumors in this region, achieving high rates of gross total resection and low rates of neurological deficits and death.[1] Due to their rarity, the learning curve for approaching the jugular foramen is particularly steep, probably steeper than for any other region of the body, therefore centering their management in a few high-volume centers. There is a myriad of approaches to the jugular foramen,[2] each with specific indications and complications, and due to their complexity, it may not be possible to become proficient in all of them, which is why we advocate the use of the same approach whenever possible. Of all the described approaches, we believe the craniocervical approach is the most versatile, allowing exposure of the cervical, mastoid, and intracranial regions, thus, being the most suitable for skull base groups to rely on. In the following text, we present the history of the craniocervical approach, and the different variants that may be performed according to the particular characteristics of the lesion to be resected.

Evidence Acquisition

We reviewed the PUBMED database to identify articles describing surgical techniques for the jugular region. The surgical nuances are derived from our experience with more than 150 tumors of the jugular foramen treated over the past 33 years by the skull base team of the Neurological Institute of Curitiba, Brazil. The present manuscript was approved by the institutional review board of our center.

Results

Tumors of the Jugular Foramen

Tumors of the jugular foramen may be broadly classified into primary lesions, arising from within the jugular foramen, such as paragangliomas, schwannomas, meningiomas, and aneurysmal bone cysts, as well as into lesions with secondary extension into the jugular foramen, such as chondrosarcomas, chordomas, cholesteatomas, and meningiomas of the cerebellopontine angle that grow into the jugular foramen.[3] Paragangliomas are by far the most frequent, followed by schwannomas, and, then, meningiomas.[4] In the present article, we will focus on the surgical nuances for primary lesions, as they represent the basic concepts and details that may be extrapolated to secondary tumors.

History of the Craniocervical Approach

The history of the surgery of the jugular foramen has been exquisitely detailed in previous publications.[1] Since most tumors present with ear symptoms, early literature was dominated by otolaryngologists, with the first reports of neurosurgical exploration for jugular tumors arising in 1951,[5,6] and a further report of a glomic tumor arising from the jugular foramen successfully resected through a suboccipital approach in the same year.[7] The description of the craniocervical approach as such may be attributed to Shapiro and Neues in 1864[8] and Gejrot in 1965.[9] They described the cervical resection, radical mastoidectomy and transposition of the facial nerve, but they did not dare entering the posterior fossa, leaving intracranial tumors for radiation therapy. In the 70s, with the advent of skull base teams composed of neurosurgeons, otolaryngologists, and head and neck surgeons, tumors of the jugular foramen were

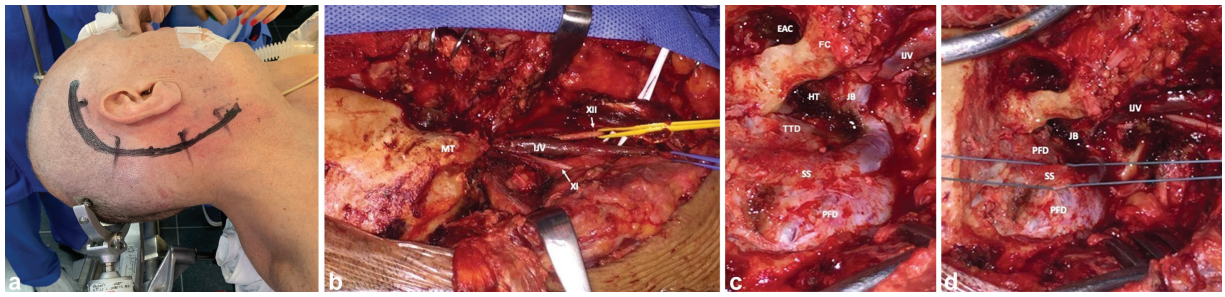

Fig. 1 Steps of a classic right craniocervical approach. (**a**) Head positioning and skin incision, beginning above the pinna and extending into the cervical region. (**b**) Neck dissection, identifying the internal jugular vein (IJV), hypoglossal nerve (XII), accessory nerve (XI), and mastoid tip (MT). (**c**) Mastoidectomy and craniectomy, with exposure of the posterior fossa duramater (PFD), sigmoid sinus (SS), jugular bulb (JB), IJV, hypotympanum (HT), external auditory canal (EAC), Treutmann triangle duramater (TTD), and fallopian canal (FC). (**d**) Ligature of the sigmoid sinus. The superior petrosal nerve is not exposed during the approach.

now thought of as neurosurgical, otological, and cervical problems.[10] In 1971, Kempe et al.[11] performed a suboccipital craniotomy and mastoidectomy to resect a glomus jugulare tumor of the middle ear and intracranial compartment. They also described the ligation of the sigmoid sinus and jugular vein, with resection of the tumor inside the jugular bulb. In the same year, Hilding & Greenberg[12] reported a similar approach that included exposure of the internal carotid artery through the glenoid fossa and packing of the inferior petrosal sinus after resection of the tumor. In 1974, Glasscock et al.[13] proposed a protocol for the diagnosis and treatment that described the use of the extended facial recess to remove tumor from the hypotympanum without transposing the facial nerve, and reconstruction of the tympanic membrane when the external auditory canal was exposed (both techniques had been previously described, but not for glomus jugulare tumors). Finally, Gardner et al.[14] published their series of combined cervical, temporal, and intracranial resection of glomus jugulare tumors in 1981, and then, Al-Mefty et al.[15] reported its use for large tumors in 1987. Afterwards, several authors have added small changes to the approach, according to particular extensions, which we will further discuss below.

The Modern Craniocervical Approach

The craniocervical approach has been described at length in previous articles.[1] Briefly, a complete approach consists of a C-shaped incision extending from the temporal region to the cervical region anterior to the sternocleidomastoid muscle (►**Fig. 1a**). Dissection of the neck consists of identification of the cervical tumor, cranial nerves IX to XII, carotid artery, jugular vein, and vertebral artery (►**Fig. 1b**). Then, a mastoidectomy is performed to expose the jugular foramen and sigmoid sinus, labyrinth, middle ear, and fallopian canal. A small craniectomy fully exposing the sigmoid sinus with transposition of the vertebral artery is also performed. (►**Fig. 1c**) After complete exposition of the region, the jugular vein and sigmoid sinus are ligated, and the tumor is removed *en bloc* from the temporal and cervical areas. The duramater medial to the sigmoid sinus is opened afterwards to resect the intracranial tumor, and, after hemostasis, the skull base is reconstructed.

Rationale for Using the Craniocervical Approach

As previously stated, the rarity of tumors of the jugular foramen limits the exposure skull base surgeons have to different approaches, so we must rely on a few of them that allow us to solve most problems and develop an adequate learning curve. Here, the craniocervical approach is unmatched, giving access to all the compartments the tumor may grow into; therefore, it may be tailored to each particular case. After incision and exposure of the craniocervical region and neck dissection, mastoidectomy and craniotomy are performed according to extension of the tumor into each compartment. (►**Fig. 2a**).

The first tailoring may be performed according to the histology of the tumor. A paraganglioma almost always

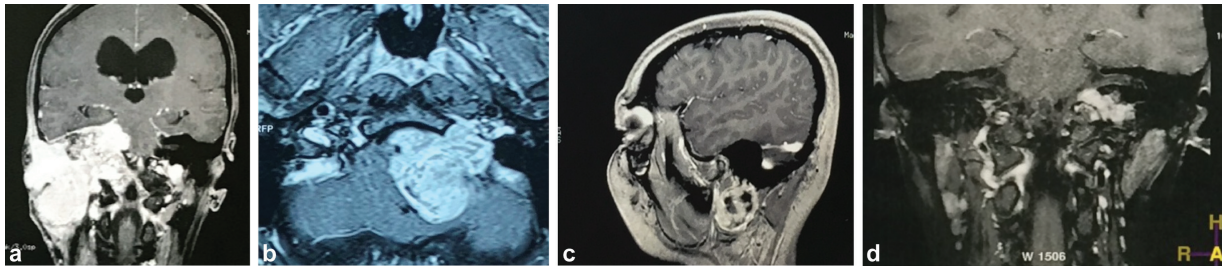

Fig. 2 Several extensions of jugular foramen tumors. (**a**) Giant **right** glomus jugulare tumor, occupying the entire mastoid bone and extending intracranially and into the cervical and retropharyngeal space. (**b**) Left jugular foramen schwannoma from the cerebellopontine angle with limited extension into the jugular foramen by the glossopharyngeal canal. (**c**) Vagal schwannoma of the cervical region, extending up into the skull base, but without entering the jugular foramen. (**d**) glomus tympanicum extending into the hypotympanum, below the internal auditory canal.

grows into the venous system, so regardless of the compartment it occupies, the cranial and caudal poles of the tumor inside the jugular vein and sigmoid sinus must be exposed. Schwannomas, on the other hand, usually grow medial to the jugular bulb and vein, needing greater anterior exposure but usually without needing to sacrifice the venous system. Meningiomas are probably the most difficult to completely resect, given their extension into the internal auditory canal, fallopian canal, middle fossa, infratemporal fossa, and paranasal sinuses,[16] with frequent invasion of the sigmoid sinus and jugular bulb, thus needing to be removed. The craniocervical approach does allow for complete resection; however, reconstruction of the skull base must be thoroughly planned beforehand.

Perhaps the only exception for the use of the craniocervical approach is when a tumor is located mostly in the intracranial compartment and less than 1 cm within the jugular foramen (►**Fig. 2b**), in which case a retrosigmoid infralabyrinthine (suprajugular) approach may be suitable for some lesions,[17,18] though the principles stated above must be considered. This makes schwannomas and meningiomas ideal for a suprajugular approach, whereas paragangliomas and chordomas/chondrosarcomas usually need more extensive bone resection.

Technical Nuances

Cervical Extension

This is the most variable part of the approach, and the cervical extension of the incision is tailored to the tumor extension on preoperative imaging. In most cases, identification of the bifurcation of the carotid artery is usually necessary to have proximal arterial control in case of bleeding. Using the carotid bifurcation is a good landmark to properly expose the inferior pole of a paraganglioma inside the jugular vein, as well as to identify the cranial nerves IX to XII in the upper cervical region and avoid unintended traction of the IX and X nerves during dissection. In cases in which the tumor does not invade the venous system nor extends into the cervical region, we advocate for a limited upper cervical dissection, so as to expose the extracranial jugular foramen and to provide an adequate angle of attack to the mastoid region.

Management of Vascular and Nervous Structures

Before the advent of endovascular embolization, the external carotid artery was often ligated in paragangliomas and meningiomas, given that their primary arterial supply comes from the ascending pharyngeal and occipital arteries. Nowadays, both the internal and external carotid arteries are usually left in place, and the bifurcation is used to identify the hypoglossal nerve travelling 2cm cranial to it. In rare cases, the internal carotid artery may be eroded by the tumor, and, in those cases, the use of an extracranial-to-intracranial bypass must be considered before resection. Management of the jugular vein depends mostly on the histology of the tumor. For schwannomas, the venous system is usually displaced by the tumor, and, therefore, there is no need to sacrifice it. In some meningiomas and all paragangliomas, the venous system is compromised, and the jugular vein must be resected *en bloc* with the tumor. For that matter, the jugular vein must be completely freed from the adjacent carotid artery and vagus nerve (passing between them), and then ligated below the inferior pole of the tumor. Of note, the accessory nerve follows a posteroinferior course after leaving the jugular foramen, crossing the jugular vein in its anterolateral surface, and must be carefully preserved when performing *en bloc* resection (►**Fig. 1b**). In case of schwannomas, differentiation of the origin from the glossopharyngeal or vagus nerve is of uttermost importance when the tumor presents cervical extension, since a glossopharyngeal schwannoma will be located medial and anterior to the carotid artery, displacing it posteriorly, whereas a vagal paraganglioma will be located between the carotid and jugular vein, displacing the carotid anterior and medial, and the jugular vein posterior and lateral. Finally, the craniocervical approach exposes the greater auricular nerve during superficial (suprafascial) dissection. The nerve must be preserved and dissected throughout its cervical course to avoid auricular hypesthesia or paresthesia, and, eventually, it can also be used as a cable graft if needed, though sural grafts are preferred.

Temporal Extension

Mastoidectomy is the most crucial part of the approach, and several modifications may be needed according to the extension of the tumor. The basic mastoidectomy includes drilling of air cells until identification of the bony labyrinth, identification of the fallopian canal, opening of the mastoid antrum, exposition of the duramater of the Treutmann triangle, skeletonization of the jugular bulb and sigmoid sinus up to the sinodural angle, and removal of the mastoid tip (►**Fig. 1c**). In selected cases in which a mainly cervical tumor only occupies the inferior pole of the petrous bone and there is no invasion of the venous system (►**Fig. 2c**), a limited mastoidectomy with resection of the mastoid tip may be performed.

Extension into Hypotympanum and Facial Nerve Transposition

Particularly in paragangliomas extending through the tympanic plexus (►**Fig. 2d**), the skin of the external auditory canal may be peeled off the tympanic bone, the tympanum detached from its posterior insertion, and the posterior wall of the external auditory canal drilled down to get the tumor through the facial recess, without opening the fallopian canal (►**Fig. 1c**). Nowadays, the only indication to expose and reroute the facial nerve is when the tumor itself invades the canal/nerve, such as in some meningiomas or paragangliomas, though it is the exception.

Management of Inner and Middle Ear Structures

Due to earlier diagnosis, tumors of the jugular foramen usually present with normal hearing, making hearing preservation a goal of surgery. A retrolabyrinthine mastoidectomy is sufficient to approach tumors of the jugular foramen,

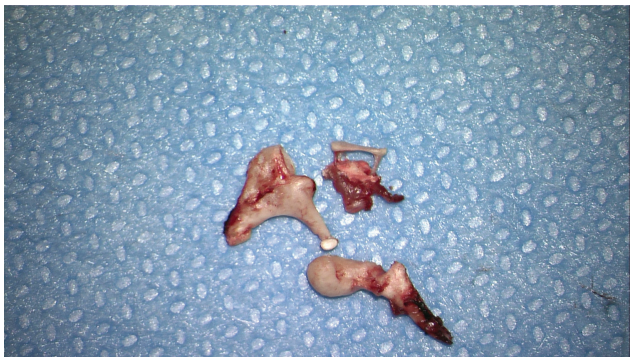

Fig. 3 Auditory ossicles from a patient with a glomus jugulare tumor and preserved hearing. Resection of the ossicles was necessary due to invasion of the stapes by tumor.

since their intracranial extension is removed via trans-sigmoid craniotomy, avoiding the need of a transcrural/translabyrinthine extension. The middle ear, however, needs to be exposed during the approach, especially because the short process of the incus is an important landmark to identify the tympanic segment of the facial nerve. Special care must be taken to avoid disarticulating the ossicles when hearing preservation surgery is attempted; however, if the tumor invades the middle ear (even with preserved hearing), the ossicles are frequently compromised and must be resected (►**Fig. 3**). In cases in which the tympanum has to be detached, tympanoplasty with temporal fascia[19] must be attempted to preserve conduction. In cases in which hearing was already compromised, the external auditory canal may be closed, or, most frequently, left open to the mastoid cavity, which allows for postoperative endoscopic evaluation of the surgical site.

Management of Vascular and Nervous Structures

In the temporal bone, early identification of the facial nerve is paramount. The tympanic segment of the facial nerve lays 1.5 cm medial to the spine of Henle, between the short process of the incus and lateral semicircular canal. At the level of the stylomastoid foramen, the nerve is identified by the tarsal "pointer." After removing the mastoid tip, the mastoid segment of the facial nerve may be delineated by joining both reference points in the anterior mastoid. In the jugular foramen, it is important to remember that nerves run medial to the jugular bulb, so paragangliomas will most likely displace bulbar nerves medially, whereas schwannomas will displace the jugular bulb laterally. Moreover, the glossopharyngeal nerve passes through its own canal, located more anterior and superior to the vagal and accessory nerves, and it is separated by a dural fold. All these anatomical details are extremely important to foresee the location of those structures in order to preserve them. In the same way, the carotid artery is located inside the carotid canal, anteromedial to the jugular foramen, and though it is not usually exposed, a dehiscent canal may be encountered, the tumor may erode into the carotid artery, or in case of paragangliomas and meningiomas, they may be fed by caroticotympanic branches arising from the petrous carotid artery, so preoperative images must be evaluated for these possibilities. Finally, in cases in which the venous system must be sacrificed, the sigmoid sinus must be ligated below the sinodural angle so as to preserve circulation between the transverse and superior petrous sinuses (►**Fig. 1d**). After *en bloc* resection of the tumor, brisk bleeding is expected from the inferior petrous sinus, which can be stopped with packing with oxidized cellulose.

Intracranial Extension

A limited, 3-cm craniectomy anterior and posterior to the sigmoid sinus is usually sufficient to approach an intradural tumor. Since the jugular foramen lays in the inferior part of the posterior fossa, transposition of the vertebral artery from the vertebral sulcus of C1 (and partial resection of the transverse process of C1) provides ample space to work in the lateral cerebellomedullary cistern. We perform this transposition in most cases when there is intracranial extension of the tumor, and we consider leaving the vertebral artery in place only when the intracranial extension is small, particularly in schwannomas.

Management of Vascular and Nervous Structures

In the lateral cerebellomedullary cistern, the same relationship between bulbar nerves and the jugular bulb is encountered. The microsurgical technique for separating the tumor from the nerves depends on the histology of the lesion. Meningiomas and paragangliomas are adherent to the surrounding nerves, whereas schwannomas are more easily dissected (except for the nerve it originates from). If the bulbar cranial nerves are infiltrated, and the patient presents previously deficits, radical tumor removal with the infiltrated nerves is performed. Damage of these nerves should be avoided if their function has not been already compromised by the tumor. The intradural vertebral artery and branches are not usually compromised, but, rarely , they may feed the tumor (►**Fig. 4**).

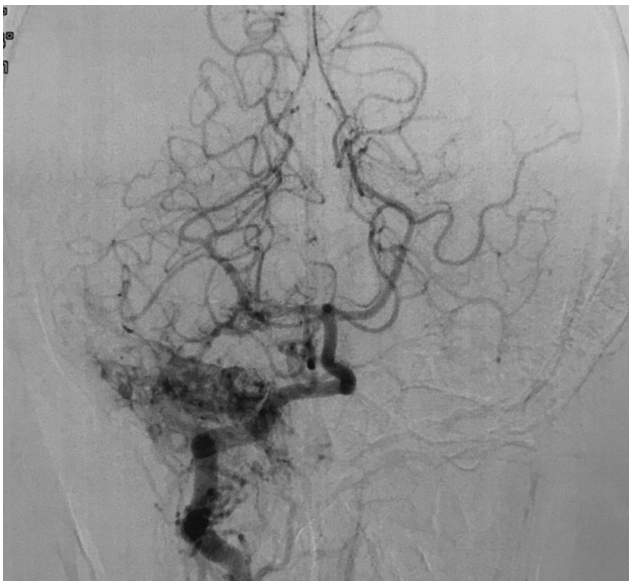

Fig. 4 Right vertebral digital subtraction angiography showing filling of a glomus jugulare tumor by fine branches of the V3 (atlantic) and V4 (intradural) segments of the vertebral artery.

Closure and Postoperative Care

Closing the surgical defect must be planned preoperatively. We advocate for the use of a multilayered closure with pedicled flaps in lieu of avascular fat grafts. Our group has previously published a technique using temporo-cervical fascia anchored in the sternocleidomastoid muscle, and temporal and digastric muscles to avoid cerebrospinal fluid leaks and achieve good cosmetic outcomes.[20]

After surgery, the decision to extubate depends on the degree of manipulation of bulbar nerves during surgery. Most cases are extubated immediately after surgery, when irritation of the cranial nerves was minimal according to intraoperative monitoring readings. When in doubt, it is appropriate to wait until the patient is fully awake to ensure that the airway is sustained before removing the tube. All patients benefit from early phonoaudiological evaluation to assess pharyngeal function and begin early oral feeding, if possible.

Conclusion

Approaching the jugular foramen is the epitome of skull base surgery. Extensive exposure by means of bone removal with minimal manipulation of neural tissue, based on anatomical knowledge, allows for total resection with minimal morbidity. Variable extension of tumors in this region warrants small but significant modifications to the standard approach.

Conflict of Interests

The authors have no conflict of interests to declare.

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Dealing with a Pediatric Posterior Fossa Tumor after COVID-19 Infection: Report of One Case

Manejo de um tumor da fossa posterior em paciente pediátrica após infecção por COVID-19: Relato de um caso

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Plain Language Summary

Having the issue of coronavirus disease 2019 (COVID-19) in mind, there is always a dilemma surrounding elective and non-urgent neurosurgical operations. The unanswered question is regarding whether there is any post-COVID-19 complications that hinder a patient from becoming a candidate for a neurosurgical operation. If that is the case, what should we do?

In the present article, we report our single-center experience with an unusual bleeding during the operation of a huge cerebellar tumor in a girl previously infected with COVID-19. In the end, we recommend our experience to our colleagues.

Abstract

There are still some conditions that pediatric neurosurgeons may face in the context of coronavirus disease 2019 (COVID-19) which have not been fully addressed so far. Authors have postulated an ongoing inflammatory myocardial status in a significant proportion of patients who have recovered from COVID-19. We report our experience with a 10-month-old girl who had recovered form COVID-19 and had a case of fourth-ventricle mass in the midline of the posterior fossa. She was scheduled for micro-neurosurgical resection of the mass following the insertion of a ventriculoperitoneal shunt. There were no significant issues regarding the induction of anesthesia. A midline suboccipital approach was chosen, and the patient was fully prepared and draped. Suboccipital soft tissues and muscles were dissected layer by layer through the midline avascular line. A marked gush of blood off the midline was observed during the opening in Y of the dura mater. Then, we started to approach the occipital sinus. However, there was an unusual loss of $\sim$ 200 mL of blood lost from this area. Despite the proper packed-cell transfusion, the patient developed bradycardia and a sudden rhythm of asystole. The cardiopulmonary cerebral resuscitation (CPCR) was initiated immediately. Despite

Keywords
- COVID-19
- posterior fossa tumor
- pediatrics
- myocardial damage

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the maximal effort, the heart rate did not change and remained asystole. We recommend that pediatric neurosurgeons postpone the procedures to be performed in patients who have recovered from COVID-19 for more than one month after a thorough preoperative cardiac evaluation has been performed.

Resumo

Ainda existem algumas condições que os neurocirurgiões pediátricos podem enfrentar no contexto da doença por coronavírus 2019 (COVID-19) que não foram totalmente abordadas até agora. Os autores postularam um estado inflamatório miocárdico contínuo em uma proporção significativa de pacientes que se recuperaram da COVID-19. Relatamos nossa experiência com uma menina de 10 meses que se recuperou da COVID-19 e teve um caso de massa no quarto ventrículo na linha média da fossa posterior. Ela foi programada para ressecção microneurocirúrgica da massa após a inserção de uma derivação ventrículo-peritoneal. Não houve problemas significativos em relação à indução da anestesia. Uma abordagem suboccipital na linha média foi escolhida e a paciente foi totalmente preparada e coberta. Tecidos moles e músculos suboccipitais foram dissecados camada por camada através da linha avascular da linha média. Durante a abertura em Y da dura-máter observou-se um jorro marcado de sangue na linha média. Em seguida, iniciamos a abordagem do seio occipital. No entanto, houve uma perda incomum de 200 ml de sangue perdido nesta área. Apesar da transfusão de hemácias adequada, a paciente evoluiu com bradicardia e ritmo súbito de assistolia. A ressuscitação cerebral cardiopulmonar (RCCP) foi iniciada.

Palavras-chave
- COVID-19
- tumor da fossa posterior
- pediatria
- dano miocárdico

Background and Importance

The relatively small number of pediatric neurosurgical subjects that coped a COVID-19 course of disease makes it a matter of debate to deal with these patients in their neurosurgical procedures.[1] Guidelines suggest the postponement of non-urgent procedures until the period of crisis is over.[2] The present article points out that patients who have recovered from COVID-19 would require of thorough work-ups that could be lifesaving prior to specific procedures. There are still some conditions that pediatric neurosurgeons may face in the context of COVID-19 which have not been fully addressed so far.[3] The presence of acute ischemic events and fat embolism are common in children with hemoglobinopathies and COVID-19. Shchedrygina et al.[4] have postulated an ongoing inflammatory myocardial status in a significant proportion of patients who have recovered from COVID-19. They have concluded that the initiation and propagation of the inflammatory cascade following viral invasion takes place irrespective of the severity of COVID-19. This process would involve patients in all age groups, including pediatric patients. Hence, COVID-19 could lead to a significant chance of progressive heart failure. We herein report our experience with a 10-month-old girl who had recovered form COVID-19 and had a case of fourth-ventricle mass in the midline of the posterior fossa. She was scheduled for micro-neurosurgical resection of the mass.

Case Presentation

The patient was had been born through normal vaginal delivery without any known peripartum complications, and was brought to the Shiraz pediatric neurosurgery ward, a referral center in the south of Iran, with a chief complaint of repeated episodes of nausea and vomiting despite thorough gastrointestinal investigations. A non-contrast brain computed tomography (CT) scan revealed a fourth-ventricle mass in the midline with severe obstructive hydrocephalus and a globular third ventricle. Insertion of a ventriculoperitoneal shunt (VPS) was scheduled, as our policy is to proceed with the VPS, but we chose to give the patient at least one week to try to cool the brain edema via cerebrospinal fluid diversion along with dexamethasone in an outpatient setting.

During this period, she developed a COVID-19 infection that was confirmed. So, we delayed the next operative stage for three weeks until she tested negative for severe acute respiratory syndrome coronavirus 2 (SARS-COV-2).

The patient was admitted about a month later in a stable condition. She was brought to the operating theater in an elective setting for microneurosurgical resection of the posterior-fossa lesion. It is worth noting that a thorough preoperative evaluation was performed by the pediatric anesthesiology team.

There were no significant isssues regarding the induction of anesthesia. A central access line was drawn, and we changed her to a prone position. A midline suboccipital approach was chosen, and the patient was fully prepared and draped. Suboccipital soft tissues and muscles were dissected layer by layer through the midline avascular line, from the inion to the level of the C2 vertebrae. No significant bleeding occurred during this stage of dissection. A total of two burr holes were made using the Medtronic (Dublin, Ireland) Midas Rex Legend AD03 Perforator Driver, and craniectomy was carried out exposing the posterior fossa from the confluent sinus to the rim of the magnum. A marked

gush of blood off the midline was observed during the opening in Y of the dura mater. Hemostasis was achieved using surgical and two cotton balls. We proceeded with the opening of the midline portion of the dura mater, but, suddenly, ~ 100 mL of blood was lost despite the millimeter-by-millimeter advancement of the dural opening. We packed the field and filled it with copious amount of normal saline. The vital signs were still stable except for relative tachycardia (180 beats per minute). The anesthesiologist replaced the amount of blood lost drop by drop throughout the operation. We started to approach the occipital sinus. However, there was an unusual loss of ~ 200 mL of blood from this area. Despite the proper packed-cell transfusion, the patient developed bradycardia and a sudden rhythm of asystole. The cardiopulmonary cerebral resuscitation (CPCR) was initiated immediately, and the position of the patient was changed to supine while the surgical field remained wide open and just packed with enough gauze. The CPCR continued for ~ 90 minutes. Despite the maximal effort, the heart rate did not even change to one beat per minute. In the meantime, chest tubes were inserted bilaterally, but no pneumothorax was found. The electromechanical dissociation rhythm did not change. The patient passed away regardless of the attempts to reverse the rhythm.

Discussion

Valverde et al.,[1] in a thorough investigation on cardiovascular involvement in pediatric COVID-19 patients, stated that the SARS-COV-2 infection resulted in direct myocardial damage, a vicious inflammatory cascade which could lead to myocardial dysfunction and ventricular arrhythmia. Furthermore, COVID-19 would exhibit a kindling phenomenon, known in cases of temporal-lobe epilepsy, which would result in myocardial dysfunction and arrhythmia. This kindling phenomenon induces fever, increased oxygen consumption, ion alterations, and, finally, a metabolic crisis.[1] Ludvigsson et al.[5] reported their experience with five children in who had recovered from COVID-19, and reviewed the literature for the long-term effects of the disease on the heart, such as perimyocarditis. The authors[5] claimed that these symptoms follow a similar trend in children and adults. Ley-Vega[6] pointed out the potential cardiac problems in a population of Cuban children previously diagnosed with convulsion. The author[6] found myocarditis, pericarditis, and arrhythmias in 18% of the sample (20 patients out of 110 cases), and an interesting finding was that the patients evolved satisfactorily following several weeks of monitoring and treatment. Ley-Vega[6] stated that these abnormalities may be reversible, but potentially time-consuming for proper recovery.

The retrospective analysis of the preoperative brain magnetic resonance imaging scan of our patient revealed nothing unusual regarding the occipital sinus. There are two plausible scenarios for our case: a post-COVID-19 subclinical myocardial damage that made this patient decompensated following a blood loss; the second scenario is based on air embolism. However, the latter is less likely because the embolus would theoretically pass through the right ventricle following our vigorous CPCR.

Conclusion

We recommend that pediatric neurosurgeons postpone the procedures to be performed in patients who have recovered from COVID-19 for more than one month after a thorough preoperative cardiac evaluation has been performed, even if there is no frank clinical disorder to estimate the cardiac reserve of a given patient.

Highlights

- A review of specific considerations on COVID-19 in pediatric neurosurgery patients.
- A correlation between myocardial injury after COVID-19 infection and perioperative neurosurgical complications.
- A possible salvation from the perioperative neurosurgical complications related to COVID-19.

Ethical Considerations

Approval from the institutional review boardd was obtained following the initial drafting of the present article.

Conflict of Interests

The authors have no conflict of interests to declare.

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Primary Extraskeletal Ewing Sarcoma of the Thoracolumbar Epidural Space: Rare Case Report in a Child

Sarcoma de Ewing extraesquelético primário no espaço epidural toracolombar: Raro relato de caso em criança

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Abstract

Introduction Ewing sarcomas are a family of tumors that can be of skeletal or extraskeletal origin. We report a rare case of a child with extraskeletal Ewing sarcoma in the thoracolumbar epidural space.

Case Report The patient was a 1-year-old female child with sphincter alteration, flaccid paraplegia, and areflexia. A magnetic resonance imaging (MRI) scan showed a large extensive epidural lesion with compression of the dural sac in the D6–L2 segment, and a left paravertebral extension through the L1–L2 foramen. Laminotomy was performed, with subtotal resection of the lesion. The histopathological and immunohistochemical analyses indicated Ewing sarcoma. Due to the child's age, radiotherapy was not performed, only chemotherapy, due to the aggressiveness of the neoplasm. The patient showed rapid tumor recurrence and ended up dying.

Discussion Extraskeletal Ewing sarcoma can appear in different locations in the body. They are aggressive tumors with local recurrence and distant metastases. In our case, a combination of MRI and positron-emission tomography–computed tomography scan presented a clearer result, especially in the presence of metastasis. In the histopathological analysis, small blue cells with a clear cytoplasm and indistinct nucleoli were observed. In the immunohistochemical analysis, CD99 (*MIC2*) expression is

Keywords
- Ewing sarcoma
- thoracolumbar
- epidural
- radiotherapy
- chemotherapy

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highlighted. The best treatment outcome would have been surgical resection with chemotherapy and radiotherapy.
Conclusion We reported a rare case of thoracolumbar epidural Ewing sarcoma in which, despite surgery and chemotherapy, the tumor behaved very aggressively, leading to an unfavorable prognosis.

Resumo

Introdução Os sarcomas de Ewing constituem uma família de tumores que podem ser de origem óssea ou extraesquelética. O caso aqui relatado é o de uma criança com raro sarcoma de Ewing extraesquelético no espaço epidural toracolombar.
Relato de caso Criança do sexo feminino, de 1 ano de idade, com quadro de alteração de esfincter, paraplegia flácida, e arreflexia. O exame de ressonância magnética (RM) revelou volumosa lesão expansiva epidural com compressão do saco dural no segmento de D6-L2, e extensão paravertebral esquerda através do forame L1-L2. Realizou-se laminotomia, com ressecção subtotal da lesão. O exame histopatológico e a imunohistoquímica indicavam sarcoma de Ewing. Por conta da idade da criança, ela não foi submetida a radioterapia, apenas a quimioterapia, e, devido à agressividade da neoplasia, a paciente evoluiu com rápida recidiva tumoral e terminou falecendo.
Discussão O sarcoma de Ewing extraesquelético pode aparecer em diferentes locais do corpo. São tumores agressivos com recorrência local e metástase à distância. Na investigação, a combinação de RM e tomografia por emissão de pósitrons–tomografia computadorizada apresenta melhor resultado, principalmente na presença de metástase. No exame histopatológico, observaram-se pequenas células azuis com citoplasma claro e nucléolos indistintos. Na imunohistoquímica, se destaca a expressão principalmente do CD99 (*MIC2*). A conduta com melhor resultado no tratamento seria ressecção cirúrgica, com quimioterapia e radioterapia.
Conclusão Relatamos um caso raro de uma criança com sarcoma de Ewing epidural na coluna, e apesar da realização da cirurgia e de quimioterapia, o tumor se comportou de modo extremamente agressivo, o que levou a um prognóstico desfavorável.

Palavras-chave
- sarcoma de Ewing
- toracolombar
- epidural
- radioterapia
- quimioterapia

Introduction

Ewing sarcoma is a rare malignant neoplasm that was first described by James Ewing in 1921. He described it as a small-blue-round-cell tumor. Initially, Ewing sarcoma was believed to originate in the undifferentiated endothelial and mesenchymal cells of the bone marrow, but, with the advent of immunohistochemistry and cytogenetic tests, its neuroectodermal origin was discovered.[1–3] It is the second most common bone tumor in children and adolescents.[4]

The Ewing sarcoma family of tumors (ESFT) includes peripheral primitive neuroectodermal tumors (pPNETs) and Askin tumors. They are morphologically similar in terms of malignancy, and they can be of skeletal or extraskeletal origin. Extraskeletal Ewing sarcomas account for 6% to 47% of all tumors in the ESFT.[5,6]

The patient in the case herein reported was a child with a rare extraskeletal Ewing sarcoma of the thoracolumbar epidural space.

Case Report

A 1-year-old female child presented to the hospital with difficulty in walking, with motor deficit progressively worsening and dorsalgia for 30 days. Upon physical examination, she presented with intestinal constipation, bladder dysfunction (neurogenic bladder), flaccid paraplegia, and areflexia. Up to one year of age, the developmental milestones were normal, and during pregnancy the obstetric ultrasound was also normal. Regarding the imaging studies, a computed tomography (CT) scan of the thoracolumbar spine showed a massive heterogeneous lesion (D8–L2) in the vertebral canal. A magnetic resonance imaging (MRI) scan of the thoracolumbar spine showed a large extensive epidural lesion with compression of the dural sac in the D8–L2 segment, and a left paravertebral extension through the L1–L2 foramen (►**Fig. 1**). The chest CT scan and the ultrasound examination of the abdomen were normal. Laminotomy was performed from D7 to L3, with subtotal resection of the lesion (►**Fig. 2a** and **b**). In the postoperative period, the areflexia and paraplegia persisted, and only improvement in terms of pain were observed. The histopathological results indicated undifferentiated malignant blue-round-cell neoplasm (►**Fig. 2c**). The immunohistochemical analysis suggested Ewing sarcoma/PNET with Ki67 (85% positive)/epithelial membrane antigen (EMA) positive/CD56

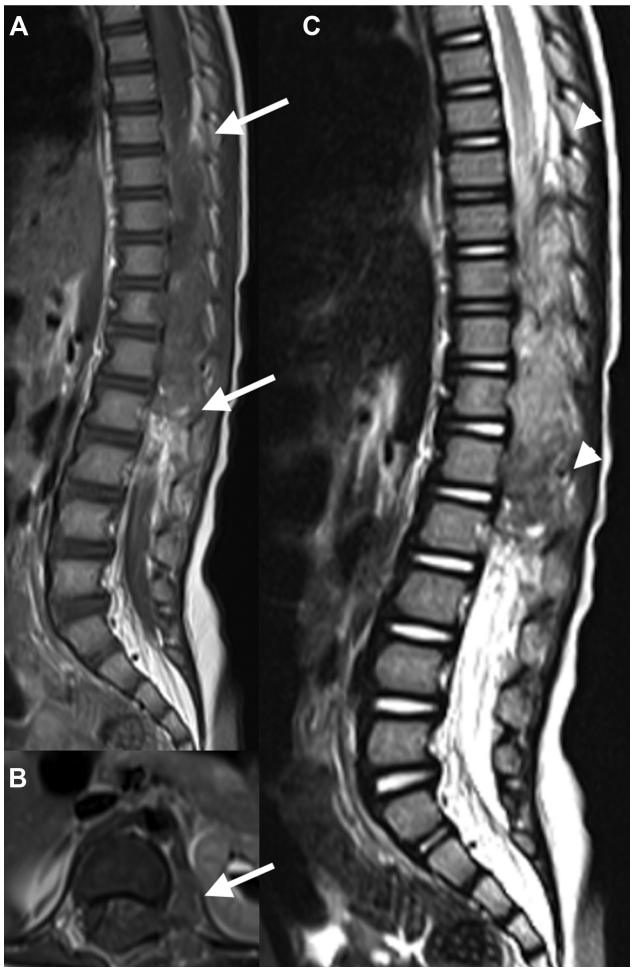

Fig. 1 (A) Sagittal T1-weighted MRI scan with contrast showing a heterogeneously-enhancing epidural mass at T8-L2 (arrows); (**B**) axial T1-weighted MRI scan with contrast showing an extension to the left intervertebral foramen (L1 / L2) with a paravertebral mass and homogeneous enhancement (arrow); (**C**) sagittal T2-weighted MRI scan showing a heterogeneously-enhancing epidural mass at T8-L2 (arrowheads).

positive/pan-cytokeratin positive/CD99 positive/friend leukemia integration-1 (FLI-1) positive.

Due to the patient's age, radiotherapy was not performed, only chemotherapy. The patient then presented with rapid lesion recurrence (►**Fig. 3**), with tumor lysis, septic shock and, after several days in the intensive care unit (ICU), she died.

Discussion

In 1969, Tefft et al.[7] first described four patients with paravertebral soft-tissue tumors that were histologically similar to Ewing sarcoma. In 1975, Angervall and Enzinger[8] reviewed 39 patients with paravertebral malignant soft-tissue tumors that did not originate in the bone, but were morphologically similar to skeletal Ewing sarcoma.

Extraskeletal Ewing sarcoma ia part of the ESFT. This group of tumors affects bones and soft tissues. The peak incidence is between 10 and 15 years of age, with a specific translocation t (11; 22) (q24; q12) in > 90% of the cases.[2,9,10]

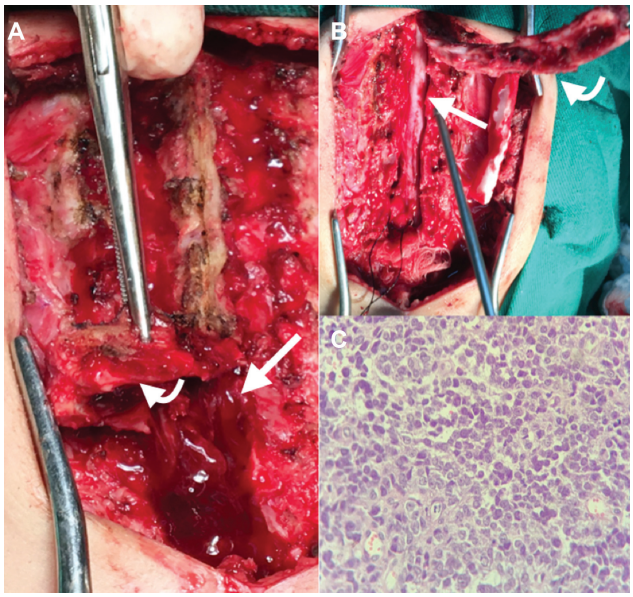

Fig. 2 (A) Laminotomy (curved arrow) with epidural mass (arrow); (**B**) D7-L3 laminotomy (curved arrow) and dural sac after tumor resection (arrow); (**C**) the tumor shows the a small-round-blue-cell appearance and scanty cytoplasm with mitotic figures (hematoxylin-eosin stain, x 400).

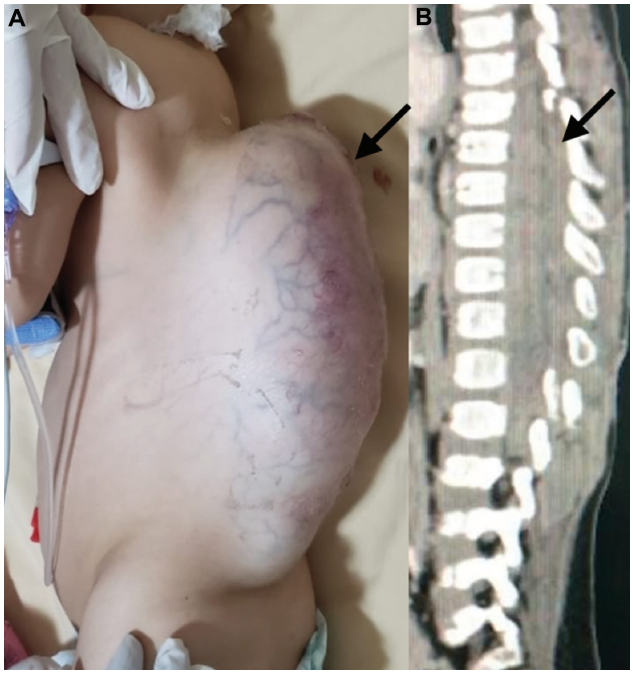

Fig. 3 (A,B) Massive recurrence in the thoracolumbar epidural space (arrows).

Extraskeletal Ewing sarcoma can appear in different locations of the body, such as the central nervous system, the chest wall, the retroperitoneum, the skin, the kidneys, the small intestine, the pelvis, the rectum, the vagina, the fingers, the arms, the scalp, the lips, the nasal passages, the paravertebral region, and the perineum.[1] They are aggressive tumors with a high incidence of local recurrence and distant metastasis, mainly to the lungs, spine, and brain. These

tumors have worse prognosis compared with that of other bone tumors of the ESFT.[2,6]

Extradural tumors account for 30% of all spinal-cord tumors in children. Therefore, the differential diagnoses may be: benign bone tumors (such as osteoid osteoma, osteochondroma, giant-cell tumor, aneurysmal bone cyst, and hemangioma), Langerhans cell histiocytosis, and fibrous dysplasia; and malignant tumors, such as sarcomas, teratomas, chordomas, and metastatic lesions.[11]

For the diagnosis, imaging techniques like CT be used to look for heterogeneous masses, and the MRI, for hypo- or isointense signals in T1-weighted images and hyperintense signals in T2-weighted images. Fluorodeoxyglucose positron emission tomography has not shown good results in the diagnosis and staging of soft-tissue sarcomas.[2,12]

A combination of MRI and positron-emission tomography–computed tomography (PET-CT) has been shown to yield satisfactory results, mainly in the identification of metastasis.[2,12]

As clinical findings are inaccurate and the diagnosis of extraskeletal Ewing sarcomas by imaging is nonspecific, the histopathological analysis becomes vital, and, on it, uniform proliferation of small blue round cells with a clear cytoplasm and indistinct nucleoli is observed. The immunohistochemical markers traditionally used in the differential diagnosis of ESFT are CD99 (*MIC2*), FLI-1, and human natural killer-1 (HNK-1). Other more specific markers are also used, such as enolase, S-100, CD56, chromogranin A, synaptophysin, cytokeratin, and EMA. The expression of Ki67 also represents an indicator of poor prognosis in ESFT.[2,9,13]

In terms of treatment, patients with extraskeletal Ewing sarcoma who underwent surgical resection (partial or total), chemotherapy, and radiotherapy had a 1-year survival rate compared with those who underwent surgery, chemotherapy, or radiotherapy.[14] Patients with metastasis had an even worse prognosis.[6]

In the present article, we reported a rare case of thoracolumbar epidural Ewing sarcoma, and due to the atypical age group (1 year of age) for the pathological condition, in which radiotherapy is not recommended, the tumor proved to be extremely aggressive. Despite surgery and chemotherapy, the tumor presented a rapid degree of recurrence, leading to an unfavorable outcome.

Conflict of Interests
The authors have no conflict of interests to declare.

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Cervical Primitive Neuroectodermal Tumor in an Adult: Case Report and Literature Review*

Tumor neuroectodérmico primitivo cervical em adulto: Relato de caso e revisão da literatura

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Abstract

Introduction Primitive neuroectodermal tumors are rare neoplasms of the central nervous system that occur in children, with few reports in adults. These tumors are found most often in the cerebral hemispheres, with spinal cord disorders being rare.
Case Report A 71-year-old man with motor and sensory deficits in the upper limbs, cervical pain, and urinary incontinence presented to the Neurosurgery Service. The physical examination revealed grade-III motor strength on the right side, grade IV- on the left upper limb, and grade IV+ on the left lower limb. A magnetic resonance imaging scan showed an expansive intramedullary lesion with a C3-C4 epicenter. Spinal decompression, lesional biopsy, and adjuvant radiotherapy were performed. The anatomopathological report showed a primitive neuroectodermal tumor. After a new treatment with adjuvant radiotherapy (20×1.8 Gy in the skull and neuroaxis and 5×1.8 Gy in tumor boost), the patient progressed without recurrence.
Conclusion Since the characteristics of the tumor are similar to those of medulloblastoma, it is necessary to expand the studies on these lesions, to better understand their pathophysiology and list better diagnostic and therapeutic methods, in addition to those already available.

Keywords
- primitive neuroectodermal tumors
- adult
- medulloblastoma

* *Study conducted at Hospital Erasto Gaertner, Curitiba, Paraná - PR, Brazil.*

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Resumo

Introdução Os tumores neuroectodérmicos primitivos são neoplasias raras do sistema nervoso central que ocorrem em crianças, com escassos relatos em adultos. Esses tumores são encontrados mais frequentemente nos hemisférios cerebrais, sendo raros os acometimentos medulares.

Relato de Caso Um homem de 71 anos com déficits motor e sensitivo em membros superiores, algia cervical e incontinência urinária apresentou-se ao Serviço de Neurocirurgia. O exame físico revelou força de grau III à direta, de grau IV- no membro superior esquerdo, e de grau IV+ no membro inferior esquerdo. Um exame de ressonância magnética denotou lesão expansiva intramedular com epicentro em C3-C4. Foram realizadas descompressão medular, biópsia lesional e radioterapia adjuvante. O laudo anatomopatológico evidenciou tumor neuroectodérmico primitivo. Após novo tratamento com radioterapia adjuvante (20 × 1,8 Gy no crânio e neuroeixo e 5 × 1,8 Gy em *boost* tumoral), o paciente seguiu sem recidiva.

Conclusões Uma vez que as características do tumor se assemelham às do meduloblastoma, torna-se necessário ampliar os estudos acerca dessas lesões, a fim de compreender melhor sua fisiopatologia e elencar melhores métodos diagnósticos e terapêuticos, além dos já disponíveis.

Palavras-chave
- tumor neuroectodérmico primitivo
- adulto
- meduloblastoma

Introduction

Primitive neuroectodermal tumors (PNETs) represent ~ 2.5% of neoplasms that affect the pediatric population, whereas, among adults, cases are scarce, with 57 cases reported in the literature.[1–4]

They affect the brain hemispheres more frequently, and may spread to the cerebrospinal fluid throughout the neuroaxis.[2,4,5] According to their location, extension and presentation, they can be clinically subdivided into "pineal tumors" and "non-pineal tumors," with the former being associated with a better prognosis.[4] Imaging methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), denote a lesion that resembles medulloblastoma; thus, it is necessary to perform a histological analysis of the lesion for diagnostic confirmation.[2–8]

Radical resection, followed by radiation on the entire neuroaxis, are the mainstays of the treatment, with better results when adding adjuvant chemotherapy to the treatment.[4,5,9–11] The models proposed to elucidate the long-term prognosis demonstrate that adults with PNETs have a survival rate that ranges from ~ 50% to 60% in 5 years, and from 40% to 50% in 10 years.[5]

In the present article, we report a case of PNET in an adult individual, whose infrequent presentation differs from the main data found in the literature. Although such a lesion can affect other regions of the neuroaxis, spinal disorders are rare, and even less frequent in individuals with advanced age.

Case Report

Male patient, 71 years old, referred to the Oncology Neurosurgery Service due to suspected primary neoplasia. He presented with altered sensitivity in the upper limbs, progressive loss of strength in the right dimidium, progression to reduced strength in the left dimidium, cervical pain, and urinary incontinence with 15 days of evolution. The physical examination revealed grade-III motor strength on the right side, grade IV- on the left upper limb, and grade IV+ on the left lower limb. An MRI scan showed an expansive intramedullary lesion with an epicenter in C3-C4. The hypotheses of astrocytoma, ependymoma, or metastatic process were raised. He was urgently admitted to undergo a cervical spine decompression procedure.

The patient underwent resection of an intramedullary tumor without complications. Upon postoperative examination, he was alert and communicative, with tetraparesis more pronounced on the right side. He was discharged from hospital three days after surgery.

The report of the surgical specimen revealed poorly-differentiated neoplasia. The immunohistochemical panel (►**Table 1**) yielded unspecific results, showing probable medulloblastoma.

After discharge, he presented symptoms of COVID-19 and evolved with clinical improvement. A Chest CT scan showed signs of pulmonary thromboembolism, requiring anticoagulation. He was followed up in an outpatient and physiotherapeutic basis. About two months after the surgery, he had relative strength recovery in the left dimidium, persisting with plegia in the right dimidium. In a discussion with a specialized team, craniospinal radiotherapy (36 Gy in the neuroaxis and 45 Gy boost) was indicated. A skull MRI scan did not reveal evidence of metastasis or expansive lesions.

Three months after the initial intervention, without having started the proposed adjuvant radiotherapy, he sought care for worsening of the left dimidial paresis and urinary retention lasting for four days.

A new MRI scan (►**Fig. 1**) showed an intramedullary image with intermediate signal on T1 and T2, with slight

Table 1 Immunohistochemical panel of the tumor specimen

Biomarker	Result
CD99	Positive
Vimentin	Positive
CD20	Negative
CK7	Negative
CKAE/AE3	Negative
EMA	Negative
CD45	Negative
p63	Negative
S100	Negative
Myogenin	Negative
Melan-A	Negative
Desmin	Negative

Note: The report stated that the set of morphological and immunohistochemical aspects with positivity for CD99 is suggestive of medulloblastoma. Negativity for cytokeratins and EMA does not favor primary neoplasms of epithelial origin. CD45 negativity does not favor lymphoproliferative neoplasms. Negativity for S100 does not favor the diagnosis of melanoma or undifferentiated malignancy.
Abbreviations: CKAE/A3, cytokeratin AE3; EMA, epithelial membrane antigen.

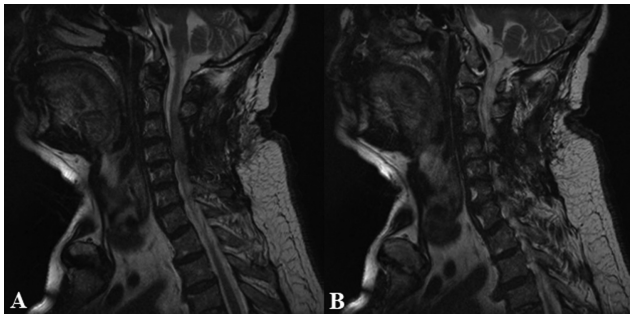

Fig. 1 Sequence of magnetic resonance imaging scans in sagittal section (**A, B**) showing intramedullary lesion with intermediate signal on T2, measuring ~33 mm in the craniocaudal axis at the height of C3-C4.

contrast enhancement, measuring ~ 33 mm in the longest axis (craniocaudal) at the height of C3-C4, nonspecific, which raised the suspicion of residual/recurrent injury. There was an extensive signal change in the adjacent spinal cord extending from C1 to T1, characterized by a high signal on T2. A new surgical approach was chosen, which was performed without complications. The patient did not present any infection in the postoperative period. He was discharged from hospital three days after the intervention, with hemiplegia on the right side and grade-II muscle strength on the left side. The anatomopathological analysis of the specimen revealed poorly-differentiated small-round-blue-cell neoplasm. The immunohistochemical panel (►**Table 2**) was compatible with a PNET, and the images can be seen in ►**Fig. 2**.

Table 2 Immunohistochemical panel of the specimen removed in the second surgical procedure

Biomarker	Result
CD99	Positive
GFAP	Positive
Vimentin	Positive
Ki67	Positive in 70% of the nuclei
CKAE1/AE3	Negative
Cromogranin-A	Negative
S100	Negative
Synaptophysin	Negative

Abbreviations: CKAE1/A3, cytokeratin AE1/AE3; GFAP, glial fibrillary acidic protein.

Adjuvant radiotherapy was started 1 month after surgery, with a dose of 20×1.8 Gy in the skull and neuraxis and 5×1.8 Gy in tumor boost, for 1 month. During the follow-up, the patient asked for the interruption of the physiotherapy.

A new MRI (►**Fig. 3**) revealed no tumor recurrence, with an area of evident thinning between C2 and C3 and posterior spinal cord retraction. In addition, control abdominal CT showed a renal nodule measuring $3.5 \times 3.2 \times 4.2$ cm, compatible with a probable neoplastic lesion, which was not present in the control CT that had been performed 4 months ago.

The case herein reported has been under follow-up for 9 months, and, since the last surgery – ~ 6 months ago – the patient has not presented a new tumor recurrence, despite the fact that the origin of the renal nodule of origin is yet to be clarified.

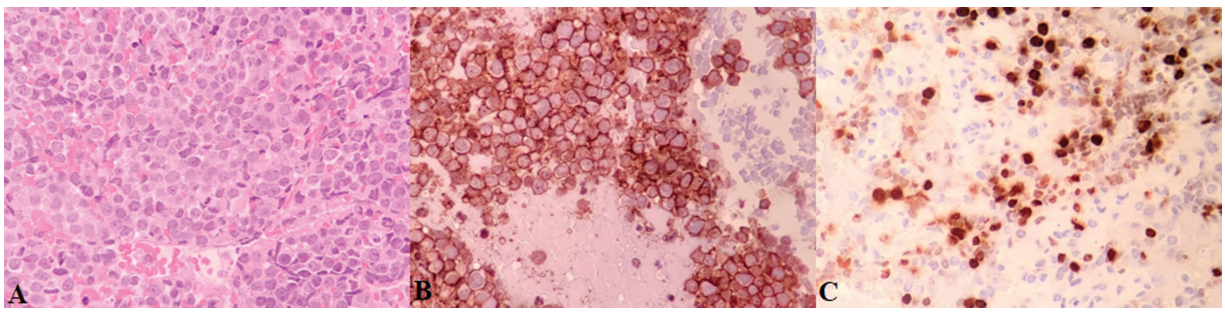

Fig. 2 (**A**) Histopathology of the tumor in hematoxylin and eosin staining showing small, round cells. (**B**) CD99 positive expression. (**C**) Reaction with K_i-67 antibody showing nuclear staining with ~ 70% of the neoplasia nuclei.

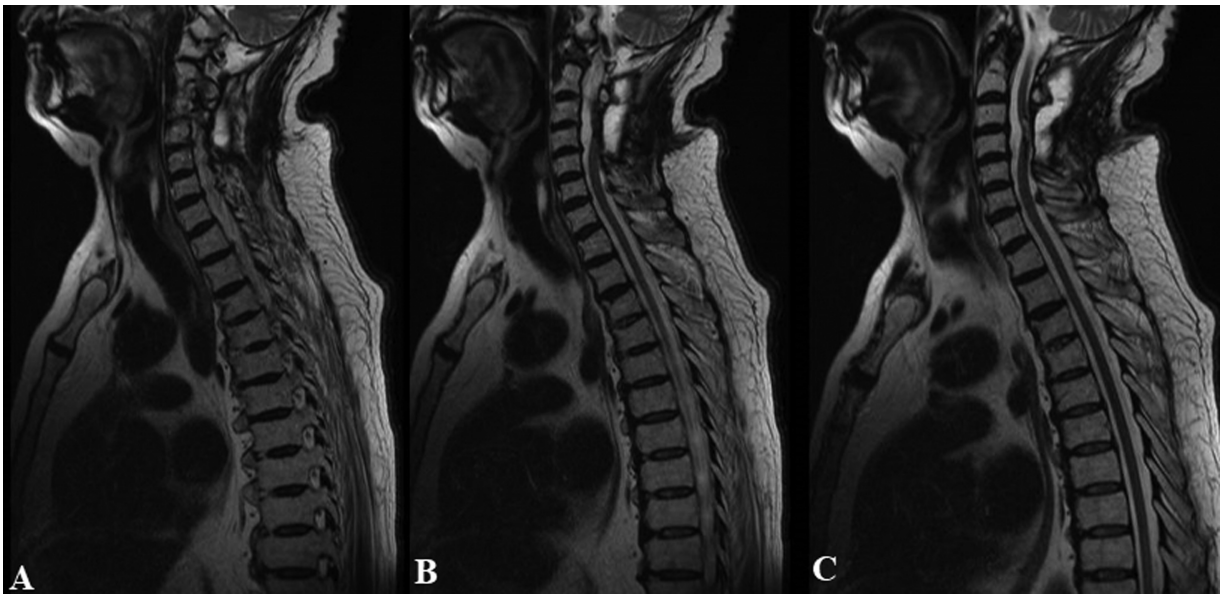

Fig. 3 Sequence of magnetic resonance imaging scans (**A-C**) in axial section, T2-weighted, showing thinning between C2 and C3 and subsequent retraction of the spinal cord, without tumor in this topography.

Discussion

Primitive neuroectodermal tumors are rare neoplasms of the central nervous system (CNS) that can affect children and adults.[1–9] When compared with other tumors in the pediatric population, PNETs represent ~ 2.5% of neoplasms, and, after medulloblastoma and astrocytoma, they are the most common embryonic tumor of childhood (the average age at diagnosis is 9 years old).[1–5] The incidence ratio among male and female individuals is of 1.1 and 0.8 per million inhabitants respectively.[2,3]

The pathophysiological mechanisms of PNETs are still not well understood; however, there is a small association with the mechanisms responsible for the development of medulloblastomas, in addition to a record of origin in the germ cell matrix of the primitive neural tube.[1–6] In addition, the location of these tumors is not specific, so they may be found in any portion of the CNS, such as the posterior fossa, the brainstem, and the spinal cord.[2,5] However, they are found more frequently in the cerebral hemispheres, and may spread to the CSF throughout the neuroaxis.[2,4,5] They can present malignant behavior, which is observed mainly in the most undifferentiated PNETs.[2,4,5]

In the present report, on spinal topography, the lesion showed signs and symptoms of involvement of the ascending and descending tracts. The clinical manifestations of these tumors vary according to their location.[2–5] Thus, signs and symptoms of intracranial hypertension, such as headache, nausea, vomiting, focal motor changes or even seizures can be observed.[2–5] The complementary evaluation with imaging methods and analysis of the CSF should be used to assist the diagnosis, identify possible spread throughout the neuroaxis, rule out other possible diagnoses, and establish a therapeutic plan.[1–6]

On CT and MRI scans, the lesions resemble a medulloblastoma; thus, it is necessary to perform a histological analysis of the lesion for diagnostic confirmation.[2–8]

In 2007, the WHO[12] defined four histological subtypes of PNETs according to the histological analysis: CNS neuroblastoma; CNS ganglioneuroblastoma; meduloepithelioma; and ependymoblastoma. Subsequently, another subtype was included in the classification, the so-called embryonal tumor with abundant neuropile and true rosettes (ETANTR). However, such subgroups are not uniform variants.[2]

Therefore, molecular studies[2–6] were conducted to more accurately determine the cell origin of PNETs. Based on the transcriptional signature of these lesions, it was possible to determine the occurrence of three molecular subgroups: group 1 consists of genes from neural stem cells; group 2 is associated with oligoneural genes; and group 3 is composed of genes involved in mesenchymal differentiation.[2]

Advances in immunohistochemistry techniques have enabled an even better differentiation between these groups, which can contribute to the diagnostic evaluation.[5–7] However, studies[2,4–7] demonstrate that these factors, when evaluated in isolation, can result in failures, given the presence of some of these signatures in other CNS tumors.

The following markers of histological analysis and immunohistochemical markers of these tumors are described in the literature: positivity for LIN28 and oligodendrocyte transcription factor 2 (OLIG2) in the tumors in groups 1 and 2 respectively. However, there is no specific correlation for tumors in group 3, which are classified as negative markers for LIN28/OLIG2, showing positivity for insulin-like growth factor 2 (IGF-2).[2]

Surgical resection, radiotherapy, and chemotherapy are the treatments that can be used in these tumors.[2,3,5,7,9] The therapeutic approach should be studied on a case-by-case basis, considering the different locations of these lesions.[2–11] However, studies[4,5,9–11] suggest that radical resection followed by radiation in the entire neuroaxis is the mainstay of treatment, with better results when adding adjuvant chemotherapy. When used, the chemotherapeutic agents that

have yielded the best therapeutic responses were CCNU (lomustina), vincristine, cisplatin, procarbazine, etoposide, temozolamide, cyclophosphamide, and carboplatin.[5,8]

Prognostic assessment and risk of recurrence can be estimated from the analysis of Ki-67 markers and nuclear proliferation antigen (NPA), while p53 protein positivity is associated with lower survival rates disease free.[5,6,8] This explains why most of the studies[1–3,5–9] found are case reports and molecular studies, considering that new therapeutic tests are being developed, which made it difficult to correlate postoperative outcomes and long-term prognoses with those of our patient.

The models proposed to elucidate the long-term prognosis show that survival in adults ranges from ~ 50% to 60% in 5 years, and from 40% to 50% in 10 years.[5] Furthermore, when the prognosis is compared among molecular subgroups, subgroup-1 tumors present a survival rate of 0.8 years, and subgroups 2 and 3, 1.8 and 4.3 years respectively.[2] Thus, the molecular assessment provided us with an overview of the prognosis, which was possible to observe during the follow-up of our patient.

Thus, the need for further studies on the molecular characteristics of PNETs is evident, as the different forms can have different outcomes, which directs the conduct toward more radical or palliative therapies.[1–9]

Conclusion

We report here a rare type of CNS tumor in an adult. Such a tumor is even less frequent in spinal topography. Given its uniqueness and reduced finding of similar cases in the literature, we suggest that further studies on PNETs be carried out. Thus, it will be possible to distinguish among other neoplasms that affect the CNS, and to predict better parameters for the diagnosis, treatment and long-term follow-up.

Ethics Statement

The present study complied with all institutional guidelines for studies on human beings. Informed consent was obtained from the person responsible for the patient.

Conflict of Interests

The authors have no conflict of interests to declare.

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Enterogenous Cyst and Glioblastoma: A Brief Histopathological Review of Two Uncommon Cystic Lesions of the Central Nervous System

Cisto entérico e glioblastoma: Uma breve revisão histopatológica de duas lesões císticas incomuns do sistema nervoso central

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Abstract

Intracranial cystic lesions are common findings in cerebral imaging and might represent a broad spectrum of conditions. These entities can be divided into nonneoplastic lesions, comprising Rathke cleft cyst, arachnoid cyst, and colloid cyst, as well as neoplastic lesions, including benign and malignant components of neoplasms such as pilocytic astrocytoma, hemangioblastoma, and ganglioglioma. Surgical resection and histological evaluation are currently the most effective methods to classify cysts of the central nervous system. The authors report two uncommon cases presenting as cystic lesions of the encephalic parenchyma—a enterogenous cyst and a glioblastoma—and discuss typical histological findings and differential diagnosis.

Keywords
- brain cyst
- glioblastoma
- central nervous system
- pathology
- prognosis

Resumo

Lesões císticas intracranianas são achados comuns em imagens cerebrais e podem representar um amplo espectro de condições. Essas entidades podem ser divididas em lesões não neoplásicas, compreendendo cisto da bolsa de Rathke, cisto aracnoide e cisto colóide, e lesões neoplásicas, incluindo componentes benignos e malignos de neoplasias, como astrocitoma pilocítico, hemangioblastoma e ganglioglioma. A ressecção cirúrgica e a avaliação histológica são atualmente os métodos mais eficazes para classificar os cistos do sistema nervoso central. Os autores relatam dois casos incomuns que se apresentam como lesões císticas do parênquima encefálico, um cisto entérico e um glioblastoma, e discutem achados histológicos típicos e diagnósticos diferenciais.

Palavras-chave
- cisto cerebral
- glioblastoma
- sistema nervoso central
- patologia
- prognóstico

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Introduction

Cystic lesions of the central nervous system (CNS) parenchyma comprise distinct pathological entities.[1–3] Benign cystic process arising in CNS include arachnoid cyst, epidermoid and dermoid cysts, colloid cyst, ependymal cyst, pineal cyst, Rathke cleft cyst, or even infectious diseases such as cysticercosis and abscesses.[1–4] Slow-growing CNS neoplasms such as ganglioglioma, hemangioblastoma, and pilocytic astrocytoma may exhibit cystic areas. Cysts differ from cystic neoplasms in that they lack a solid nodular area.[1,2,4] This typical finding is fundamental to distinguish glial cysts from cystic gliomas with mural nodules, and cystic craniopharyngiomas from epithelial cysts. In adults, glioblastomas and metastatic carcinomas can develop into cystic variations.[1,4,5] Mural nodule biopsy is recommended to obtain an accurate diagnosis. However, in some cases, the mural nodule may be difficult to detect.[2,4–6] In this case report, the authors describe two distinct cystic lesions, a developmental disorder and a high-grade glial neoplasm, to discuss characteristic histological findings and differential diagnosis.

Case 1

A 60-year-old female patient presented with an incidental finding of an expansive brain lesion during hospitalization for coronavirus disease 2019 (COVID-19). The patient reported frequent episodes of chronic headache, systemic arterial hypertension, dyslipidemia, patent foramen ovale, and myocardial revascularization. Neurological examination showed no abnormality. Magnetic resonance imaging (MRI) revealed a cystic lesion near the suprasellar cistern (►**Fig. 1**), extending toward the interpeduncular cistern and defining a bulging area of the inferior wall of the third ventricle, with obliteration of the infundibular recess. The signal intensity of the lesion was similar to that of the cerebral spinal fluid, and the lesion measured 4.6 × 3.6 × 3.5 cm (►**Fig. 2**).

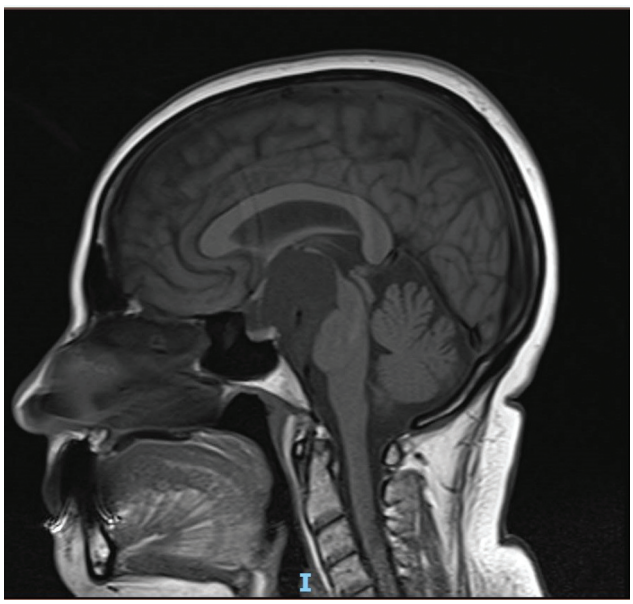

Fig. 1 Enterogenous cyst: MRI exhibiting a cystic lesion near the suprasellar cistern.

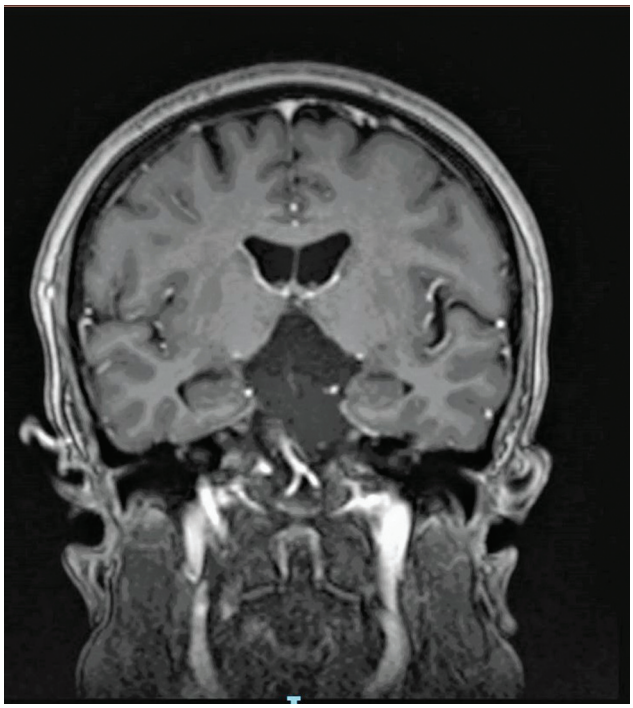

Fig. 2 Enterogenous cyst: MRI showing a cystic lesion measuring 4.6 × 3.6 × 3.5 cm and arising in inferior wall of the third ventricle.

The patient underwent left pterional craniotomy, dissection of the Sylvian fissure, and visualization and resection of the lesion close to the interpeduncular fossa. The specimen was sent for anatomopathological examination with a clinical–surgical hypothesis of a parasitic lesion. Microscopic examination of the process revealed a benign cystic lesion with walls consisting of connective tissue and internally covered by cuboidal and/or cylindrical epithelium, sometimes simple, sometimes pseudostratified, with ciliated or muciparous cells (►**Fig. 3**), compatible with an enterogenous cyst.

Case 2

An 18-year-old, previously healthy, male patient was referred to the hospital with complaints of severe headache and hypertensive peaks associated with temporary deviation of the rima oris for the past 7 days. He also reported episodes of fever, tremors, and sweating. On physical examination, the patient was somnolent and disoriented, with dysarthria, left hemiparesis, and a score of 13 on the Glasgow scale. Computed tomography and MRI revealed a solid cystic lesion in the topography of the third ventricle, measuring 5.4 × 5.0 × 4.7 cm (►**Fig. 4**) and causing hydrocephalus, compression of the interpeduncular region of the midbrain, a significant reduction in the amplitude of perimesencephalic cisterns, and cerebral edema, (►**Fig. 5**) suggestive of craniopharyngioma. The patient developed nausea, vomiting, intracranial hypertension, and Parinaud syndrome.

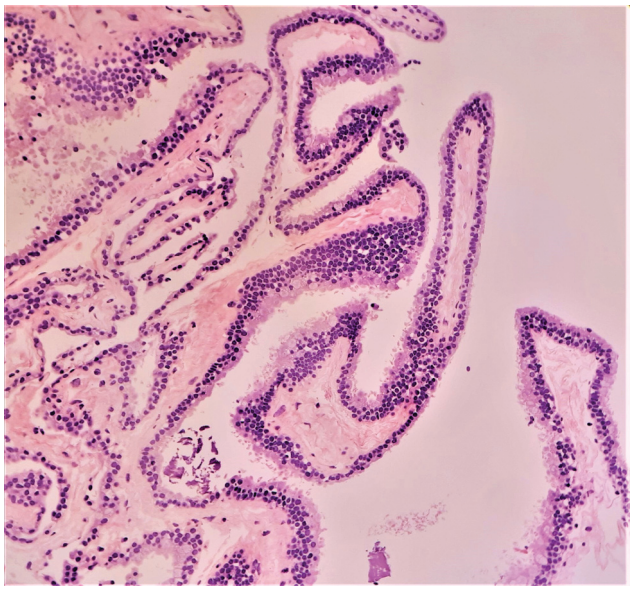

Fig. 3 Enterogenous cyst: benign cystic lesion covered by cuboidal and/or cylindrical epithelium, hematoxylin-eosin, 100x.

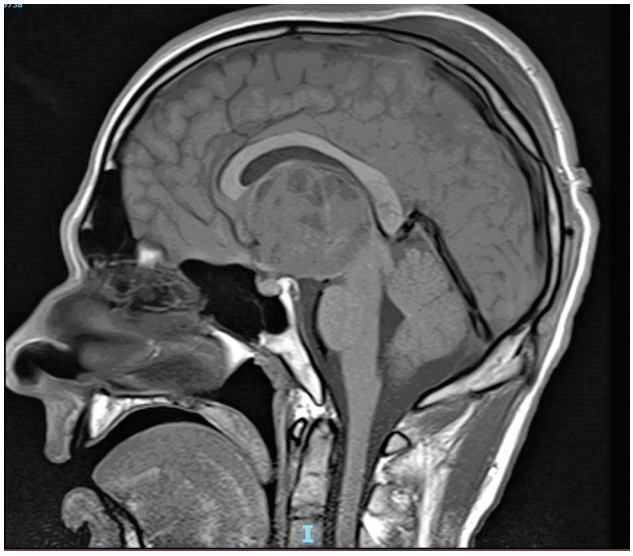

Fig. 4 Glioblastoma: MRI revealed a solid cystic lesion in the topography of the third ventricle.

External ventricular drainage was performed, leading to partial improvement of symptoms. The patient progressed to spasticity, anisocoria without light reflexes, tachycardia, tachypnea, and decorticate and decerebrate posturing, with no eye opening. Orotracheal intubation was then performed. The electroencephalogram showed slow and dysfunctional background activities, dominated by diffuse delta waves and a small amount of superimposed theta activity, compatible with diffuse dysfunction of brain activity without epileptiform paroxysms. The patient underwent resection of the lesion. Pathological examination revealed a poorly differentiated, pleomorphic, malignant neoplasm characterized by epithelioid/polygonal cells with high mitotic index and areas of necrosis (►**Fig. 6**).

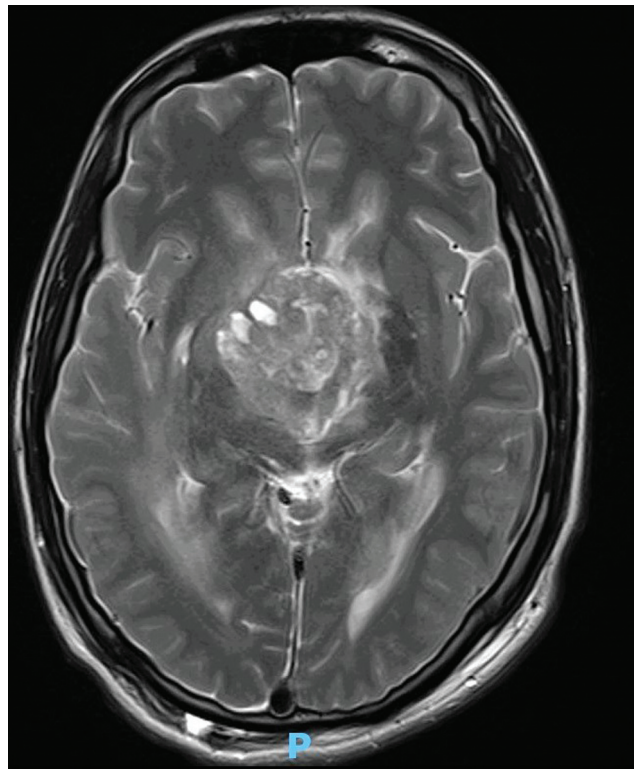

Fig. 5 Glioblastoma: MRI exhibiting a solid-cystic lesion, which determined hydrocephalus, compression of the interpeduncular region of the midbrain, a reduction of perimesencephalic cisterns, and edema.

The lesion exhibited strong and diffuse positive immunoexpression for GFAP, OLIG2, synaptophysin, CD99, INI-1, and ATRX, and was negative for IDH, p53, H3K27M, PHOX2B, SALL4, and HCG. The K_i-67 expression was observed in 95% of neoplastic cells (►**Fig. 7**). These histopathological findings were compatible with glioblastoma associated with an area of primitive neuroectodermal characteristics and some giant tumor cells, grade 4 according to the World Health Organization (WHO) 2021 system.

The patient evolved with diabetes insipidus, central hypothyroidism, secondary adrenal insufficiency, fever, leukocytosis with deviation, thrombosis in the left upper limb, progressive worsening of the neurological condition, and nonreactive mydriasis associated with septic shock. Death occurred 9 weeks after the surgical procedure.

Discussion

Intracranial cystic lesions are a heterogeneous group of processes, including parasitic infections, abscesses, developmental cysts, and primary and metastatic neoplasms.[1,2,4] In the case of primary and metastatic neoplasms, analysis of medical history often leads to the correct diagnosis.[1,2,4] Recently, imaging, especially new MRI techniques, has proven to be particularly useful for the diagnosis of these challenging lesions. However, it is only after histological analysis that a definite diagnosis can be made.[2,4–6]

Infectious diseases, such as neurocysticercosis, echinococcosis, cryptococcosis, tuberculosis, amebiasis, and

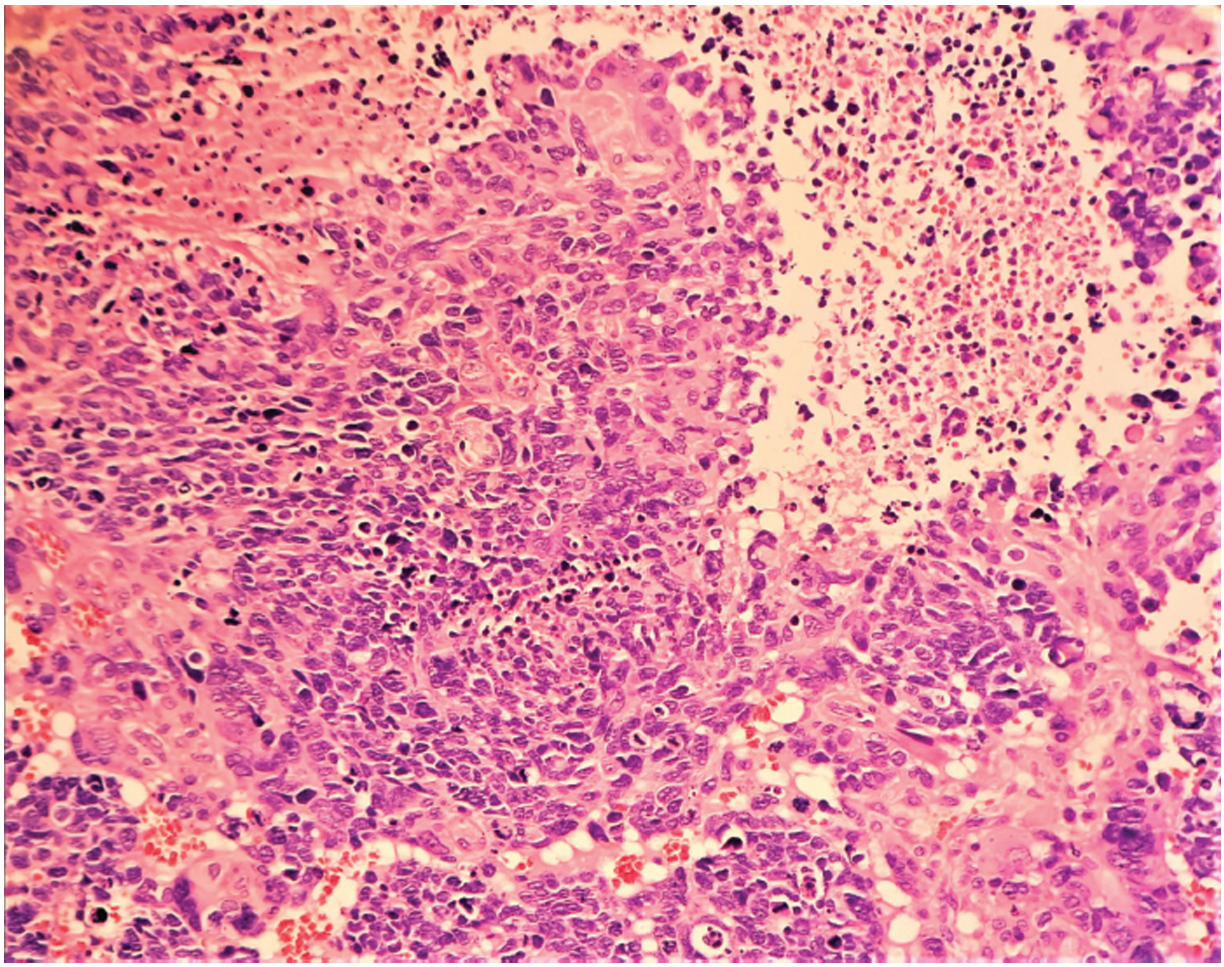

Fig. 6 Glioblastoma: A high-grade glioma with high mitotic index and necrosis, hematoxylin-eosin, 200x.

toxoplasmosis, are often suspected in patients with a cyst, as revealed by imaging, and presenting with severe headache, convulsion, fever, or delirium. By contrast, incidentally found intracranial cysts are commonly congenital.[2,4,5,7] Arachnoid, pineal, epidermoid, dermoid, ependymal, Rathke cleft, and enterogenous cysts are some of the nonneoplastic diagnostic possibilities.[2,5,7–9] Benign neoplastic intracranial diseases include craniopharyngiomas, usually suspected when located at the suprasellar region, having excellent survival rates. Intratumoral necrosis or hemorrhage is responsible for cystic presentation of both intracranial metastases and higher-grade primary tumors. The former usually presents as a multifocal lesion.[1,5,7–10]

In our first report, we described a rare case of an intracranial enterogenous cyst, also called endodermal cyst. This entity is a benign developmental lesion of endodermal origin.[2,3,11–13] Its pathogenesis is not fully understood, but probably arises after failure of obliteration of the neurenteric canal, with displacement of endodermal cells. It is more commonly found in the spine, rarely as an encephalic lesion.[2,11–13] Histologically, the cyst is lined by gastrointestinal or respiratory-type epithelium, with or without cilia, cuboidal to columnar, and simple to pseudostratified. It is sometimes impossible to histologically distinguish a Rathke cleft cyst from an enterogenous cyst; the former is often diagnosed when the lesion is intra- or suprasellar.[1,5,7,8,13,14] Given the nonneoplastic nature of enterogenous cysts, symptoms depend on lesion size and location, ranging from headaches (in almost 50% of patients) to seizures and deficits. Treatment in most cases is by surgical resection. Follow-up is recommended, as recurrence is common.[1,5,7,8,14,15]

In our second report, we described the case of an H3-/IDH-wildtype glioblastoma, with giant cells and primitive neuroectodermal component, presenting as an acute, aggressive, solid cystic lesion of the third ventricle. Glioblastoma is a high-grade glioma featuring nuclear atypia, pleomorphism, mitotic activity, diffuse growth pattern, microvascular proliferation, and necrosis.[1,4,7,11,15,16] It is the most frequent malignant brain tumor in adults, very rarely occurring in the pediatric population. In the latter case, the malignancy is defined as pediatric-type high-grade diffuse glioma, according to the 2021 WHO CNS classification.[10] Glioblastomas develop rapidly, primarily manifesting as focal neurological deficits, as in our case. Imaging reveals irregularly shaped and ring-shaped zones of contrast enhancement around a dark central area of necrosis, sometimes interpreted as a cystic area in the lesion.[2,3,10,14,16,17] Surgical excision is the primary

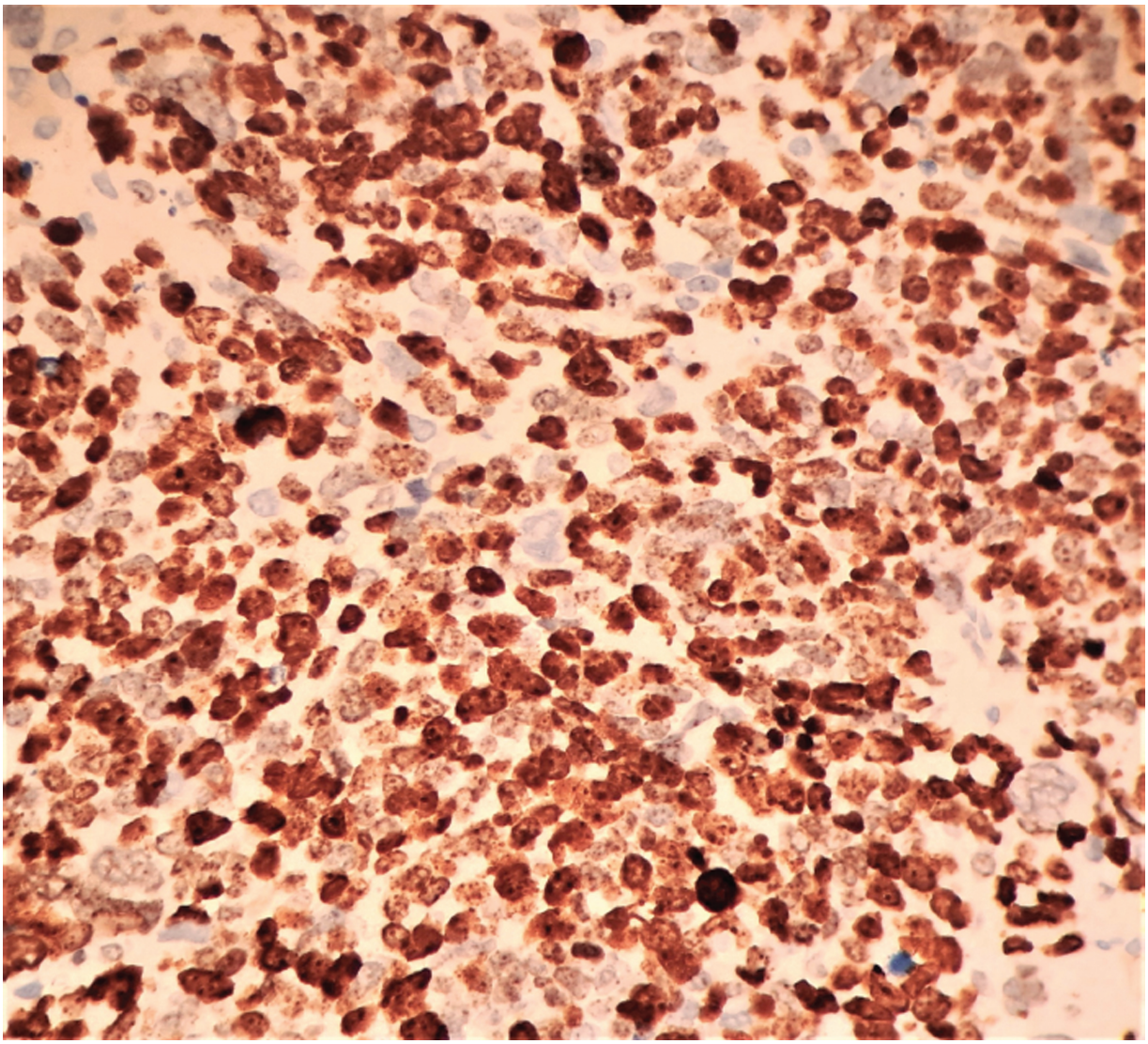

Fig. 7 Glioblastoma: High proliferative index estimated by K_i-67 imunoexpression, Ventana Systems, 400x.

treatment, although the disease is almost invariably fatal. An abrupt change in morphology may reflect new clone proliferation through new genetic alterations.[1,2,5,9,10] The primitive neuronal component represents a variation in glioblastoma, with one or more solid-looking nodules showing primitive neuronal morphology sharply demarcated from adjacent glioma, markedly increased cellularity, higher N/C ratio, mitotic activity, karyorrhexis, and anaplastic cytology similar to that of other CNS embryonal neoplasms.[2,3,5,7,8,11,13,17] It usually shows synaptophysin positivity, loss of GFAP expression, and a high K_i-67 index. This subtype has a high frequency of MYC gene amplification and p53 immunoreactivity. Although the survival time is similar to that of other glioblastomas,[9] our case presented as a very aggressive acute disease, with 2 months from first symptoms to death.[1,5,9,10,18] We add this unfortunate case to the very few literature reports of this aggressive high-grade glioma variant in the pediatric population.

Conflict of Interests
The authors have no conflict of interests to declare.

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Surgical Treatment for Refractory Aggression after Bacterial Meningitis Complicated by Stroke: Case Report

Tratamento cirúrgico para agressividade refratária pós-meningite bacteriana complicada por acidente vascular encefálico: Relato de caso

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Abstract

Bacterial meningitis remains a public health problem. One of the complications of this group of diseases is cerebral ischemia, an important indicator of severity and an independent predictor of poor prognosis. It is already known that, in many cases, pathological aggressiveness is the result of brain abnormalities in individuals with mental illnesses. The indication of neurosurgeries for psychiatric disorders (NPDs) relies on numerous studies based on scientific evidence that correlate psychiatric illnesses with the limbic system and the pathophysiology of emotions. The development of sophisticated stereotactic target localization techniques, brain atlases, and imaging methods made stereotaxis possible, a procedure that increased the precision of neurosurgery and reduced brain damage. Nowadays, multiple targets can be treated during NPD, according to the particular characteristics of the patient. Moreover, the combination of lesions leads to more significant improvements compared with isolated procedures. The present study aimed to report the rare case of a patient with a history of bacterial meningitis who developed stroke and chronic pathological aggressiveness refractory to clinical treatment and underwent ablation using the multitarget stereotactic technique.

Keywords
- bacterial meningitis
- psychosurgery
- neurosurgery for psychiatric disorders
- limbic system
- aggression

Resumo

A meningite bacteriana continua sendo um problema de saúde pública. Uma das complicações deste grupo de doenças é a isquemia cerebral, um importante indicador de gravidade e um preditor independente de mau prognóstico. Já se sabe que, em muitos casos, a agressividade patológica é o resultado de anormalidades cerebrais em indivíduos com doença mental. A indicação das neurocirurgias para doenças psiquiátricas (NDPs) se fundamenta em inúmeros estudos com base em evidências científicas, os quais correlacionam as enfermidades psiquiátricas com o sistema límbico e a fisiopatologia das emoções. O desenvolvimento de técnicas sofisticadas de localização

Palavras-chave
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- psicocirurgia
- neurocirurgia para doenças psiquiátricas
- sistema límbico
- agressão

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de alvos estereotáxicos, atlas cerebrais e métodos de imagem tornaram a estereotaxia possível, um procedimento que aumentou a precisão da neurocirurgia e reduziu os danos cerebrais. Atualmente, múltiplos alvos podem ser tratados durante a NDP, de acordo com as características individuais do paciente. Ademais, a combinação das lesões leva a melhorias mais significativas em comparação com os procedimentos isolados. O presente estudo teve como objetivo relatar o caso raro de uma paciente com histórico de meningite bacteriana que evoluiu para acidente vascular encefálico e agressividade patológica crônica refratária ao tratamento clínico e foi submetida a ablação utilizando a técnica estereotáxica de múltiplos alvos.

Introduction

Bacterial meningitis remains a public health problem,[1] and in 2019, 2,330 cases were confirmed in Brazil.[2] One of the complications of this group of diseases is cerebral ischemia, an important indicator of severity and an independent predictor of poor prognosis.[3] Among the main repercussions of bacterial meningitis are hearing loss, language disorders, mental retardation, motor abnormalities, and visual disturbances.[4] Although no articles describing the evolution from bacterial meningitis to aggressive pathological behavior have been found, it is already known that, in many cases, pathological aggressiveness is the result of brain abnormalities in individuals with mental illnesses.[5]

The normal aggressive behavior in the human species aims to maintain the physical integrity, subsistence, territory establishment/maintenance of the individual, and perpetuation of the species.[5,6] Aggressiveness becomes pathological when its manifestation becomes exaggerated in response to a stimulus that would normally not cause danger or even in the absence of a stimulus.[7] Unfortunately, for patients with affective disorders resistant to treatment and their families, pathological aggressiveness represents an extreme emotional and psychological burden, in addition to an increased risk of suicide.[8]

Among the brain nuclei used as targets in stereotactic neurosurgeries for psychiatric disorders (NPDs) to control pathological aggressiveness, the following are considered the most important ones: the amygdala, the posteromedial hypothalamus, the ventral part of the internal capsule and the striatum, the cingulate, the substance innominate, and the nucleus accumbens (NAcc).[9] These multiple targets can be used during the procedures according to the individual characteristics of the patient and to the experience of the neurosurgeon. Also, the combination of lesions leads to more significant improvement compared with isolated procedures.[10] Therefore, the present study aimed to report the rare case of a patient with a history of bacterial meningitis who developed stroke and chronic pathological aggressiveness refractory to clinical treatment and underwent ablation using the multitarget stereotactic technique.

Case Report

The legal guardian of a 30-year-old female, with a pathological history of acute bacterial meningitis, previously healthy and with no comorbidities until she developed ischemic stroke at 15 years old, looked for medical assistance in 2019 because of her aggressive behavior. After the diagnosis of bacterial meningitis and the appropriate treatment, the patient presented with dysarthria, left upper limb hemiparesis with loss of movement at light touch, mental retardation, episodes of pathological aggressive behavior manifested as verbal aggression (screaming with anger, temper tantrums), property damage (slamming doors, throwing objects on the floor), self- injury (hitting herself and hitting her fists on the wall), and hetero-aggression (making threatening gestures, hitting and pushing others, even causing minor injuries). She scored 47 points on the Modified Overt Aggression Scale (MOAS)[11] and also presented with intense sexual impulse, motor tic (clapping), vocal tic (recurrent sounds), and binge eating disorder.

The legal guardian claimed to have made use of grills and restraints on household utensils and objects to protect the patient, belongings, and property. Additionally, the family had to adopt social distancing due to embarrassment, conflicts, and compromised coexistence.

The magnetic resonance imaging (MRI) performed in 2019 (►**Figs. 1** and **2**), prior to the stereotactic NPD to control aggressiveness, shows most of the following injuries caused by the evolution of the bacterial meningitis and the stroke: 1) extensive area of encephalomalacia and gliosis, affecting the temporal lobes bilaterally, including the amygdala, the uncus, and the hippocampus, the insular lobes bilaterally, the frontobasal region, the right anterior cingulate gyrus, and the genu, trunk, and splenium of the corpus callosum; 2) areas of encephalomalacia/gliosis in the lower part of the cerebellar hemispheres; 3) relative preservation of the occipital lobe and of the nucleus-capsular region. In the same year, stereotactic NPD was indicated to control her aggressive behavior, respecting the protocol of the Federal Council of Medicine and with the consent of the family and of the legal guardian. Using software planning and the stereotactic technique, the NAcc, the hypothalamus, the cingulate, and the anterior limb

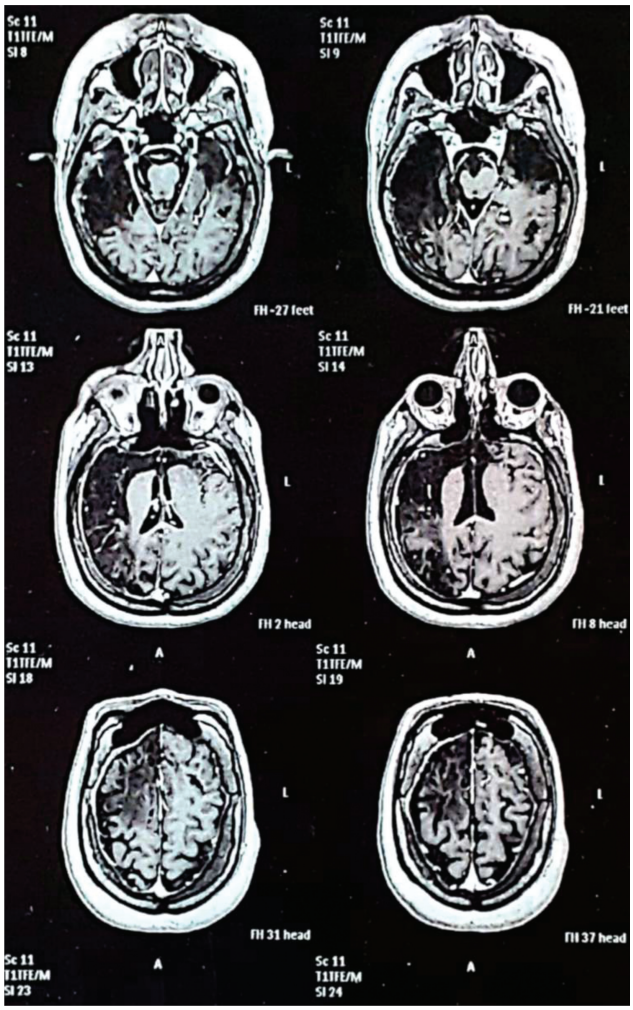

Fig. 1 Magnetic resonance imaging performed prior to the stereotactic neurosurgery for psychiatric disorder showing injuries caused by bacterial meningitis and stroke. T1 axial section: extensive area of encephalomalacia and gliosis in the right insular lobe, the genu of the corpus callosum, the temporal lobes, and the frontobasal region bilaterally, with predominance on the right; relative preservation of the occipital lobe and of the nucleus-capsular region.

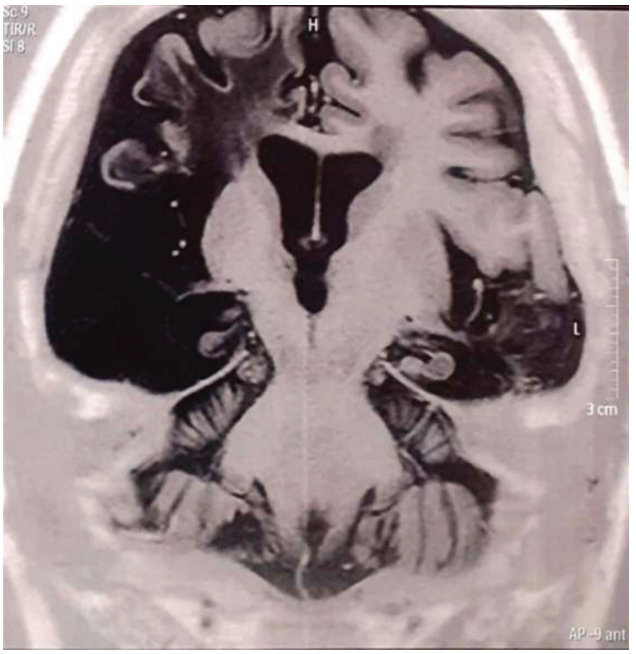

Fig. 2 Magnetic resonance imaging performed prior to the stereotactic neurosurgery for psychiatric disorder showing injuries caused by bacterial meningitis and stroke. T1 inversion recovery coronal section: encephalomalacia and gliosis affecting the right insular lobe, the right frontobasal region, and the temporal lobes bilaterally, with predominance on the right.

of the internal capsule, all of them to the left, underwent thermocoagulation at 80°C for 80 seconds. The range of the NAcc coordinate values was between 5 and 6 mm under the line joining the anterior and posterior commissure, 17 mm anterior to the brain midpoint, and 5 mm lateral to the brain midline; the anterior cingulotomy involved lesions 20 mm posterior to the anterior extent of the frontal horn of the lateral ventricles, between 5 and 7 mm off the midline, and 5 mm above the corpus callosum; the lesions in the anterior capsule were performed in the middle of the anterior limb of the internal capsule, ~ 4 mm above the level of the mid-commissural plane. The hypothalamus was located by macrostimulation, using a 2-mm exposed tip electrode, with frequency between 5 Hz and 100 Hz and voltage ranging from 1 V to 10 V. As an electrophysiological response, the patient presented autonomic signs, including mydriasis, increase in mean arterial pressure and heart rate, and ipsilateral eyeball inversion. The target point chosen was 2 mm laterally, 2 mm posteriorly, and 2 mm inferiorly from the midpoint of the intercommissural line. No complications occurred during the surgical procedure or in the postsurgical period.

The prescribed medication, quetiapine hemifumarate and clonazepam, was discontinued without medical advice shortly after the surgery, because the family considered that the patient had achieved a stable condition with no return of symptoms. One year after the surgery, the patient still showed no postsurgical complications, with improvement in her aggressive condition, with a decrease in verbal aggression and property damage, a partial decrease in sex drive, and absence of self-harm and heteroaggression (MOAS score 5).

The present study was approved by the Ethics Committee of the Pontifícia Universidade Católica de Goiás (CAAE: 29424920.0.0000.0037). It was conducted according to the Helsinki Declaration, and the written consent was signed by the legal guardian of the patient.

Discussion

Meningitis and its Neurological Complications

Bacterial meningitis is a group of diseases characterized by the inflammatory process of the subarachnoid space and of the leptomeningeal membranes (arachnoid and pia mater), the protective covering for the brain and the spinal cord.[12] It is a serious and life-threatening condition and remains a major public health challenge. The main microorganisms involved are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*.[13]

After invading the nasopharynx mucosa, these bacteria overcome the defense barriers of the central nervous system and penetrate the subarachnoid space, which lacks mechanisms capable of controlling bacterial replication. Pathogens release active subcapsular components such as lipopolysaccharide or peptidoglycan and teichoic acid, compounds that stimulate astrocytes and microglia cells to produce cytokines such as tumor necrosis factor and interleukin-1, which, in turn, trigger the meningeal inflammatory response, with neutrophil adhesion to endothelial cells and their passage to the subarachnoid space.[1,14,15]

The inflammatory response causes endothelial damage, increases the permeability of the blood-brain barrier, and allows the entry of serum proteins into the subarachnoid space, generating vasogenic edema.[16] Bacteria and neutrophils release toxic substances and produce inflammatory exudates that alter cerebrospinal fluid dynamics, resulting in interstitial edema. Both forms of edema are responsible for the increase in intracranial pressure, causing a decrease in cerebral perfusion, hypoxemia, and anaerobic metabolism, which determines the consumption of glucose and hypoglycorrhachia, leading to brain damage.[1,14,17]

Strokes are a particular complication of bacterial meningitis. Among the mechanisms that cause cerebral ischemia, the increase in cerebral blood flow velocity, vasculopathies, and intravascular thrombosis result from inflammation. The progression of the infection to sepsis affects the vascular self-regulation of the central nervous system, making the cerebral blood flow dependent on systemic pressure. In cases of systemic hypotension, a reduction in brain irrigation and tissue ischemia occur.[3]

The interaction and synergy of the events described above can cause focal or diffuse irreversible damage to the brain. It has been long believed that diffuse brain lesions result in psychic changes.[18]

The patient that has a stroke in a certain cerebral hemisphere can have hemiplegia on the opposite side of the lesion due to the crossing of the motor pathways in the brainstem.[19,20] Other symptoms associated with a stroke are dysphagia, hemianopsia, and urinary and fecal incontinence. The most common psychological consequences reported are anxiety, depression, as well as sleep, sexual, motor, sensory, cognitive, and communication disorders.[21]

Brain Injury and Etiology of Behavioral Changes

Lesions to the frontal lobe as well as to both temporal lobes can trigger aggressive behavior. The association of orbitofrontal cortex lesions with inappropriate behaviors such as impulsivity, anger, little expression of happiness, and personality disorders has been reported.[21] The frontal cortex and the ventromedial frontal cortex are involved in the inhibition and control of emotions, whereas the orbitofrontal cortex plays a role in anger and pathological aggressive behavior, is directly involved in the modulation of reactive aggression, and regulates the calculation of consequences and punishments to aggressive responses.[22,23]

Aggressive and impulsive patients have shown decreasing activation of inhibitory regions in the left anteromedial cortex when compared with control subjects. These patients also presented deactivation of the anterior cingulate gyrus and activation of the posterior cingulate gyrus.[22] The cingulate gyrus is the structure involved in evaluating the approach of stimuli capable of triggering the aggressive response. However, different patterns of brain activation can occur in individuals with an impulsive and aggressive personality.[22,24]

The effects caused by the lesion of the midtemporal lobe, which includes subcortical structures such as the amygdala and the hippocampus, are still controversial. The amygdala is responsible for detecting, generating, and maintaining emotions related to fear, as well as for coordinating appropriate responses to threat and danger. Thus, injuries to the amygdala in humans reduce the expression of emotions and the ability to recognize fear. Some studies have indicated that, in apes, bilateral lesions in the temporal lobe, which reach the contralateral amygdala, cause loss of fear, adoption of docile posture, extreme curiosity, quick forgetfulness, tendency to put objects in the mouth, and intense sexual impulse.[25] Humans with damage to both temporal lobes (Klüver-Bucy syndrome) react in a similar way, with apathy, lethargy, emotional insensitivity, hypersexuality, psychic blindness or visual agnosia, strong oral tendencies, and hypermetamorphosis.[25,26]

Other studies have demonstrated a correlation between temporal lobe abnormalities, such as reduced tissue volume and/or activity, and exacerbated aggressive behavior.[27] New functional and structural neuroimaging techniques for examining abnormalities of the temporal lobe have revealed temporal irregularities, including asymmetric gyratory patterns in the parietal-temporal region, decreases in the volume of the anterior-inferior temporal lobe (encompassing the amygdala-hippocampus region or adjacent areas), increases in the volume of the left temporal lobe, and specific pathologies of the amygdala.[28]

In patients with borderline personality syndrome, the glucose metabolism is increased in the anterior cingulate, bilaterally in the upper frontal gyrus, in the lower right frontal gyrus, and in the operculum of the precentral gyrus, and is decreased in the left hippocampus and in the cuneus. The hippocampus is involved in fear responses and stressful situations, participating in the regulation of emotions. Dysfunctions in this region, therefore, can generate symptoms of anxiety and impulsivity. Glucose hypometabolism has also been found in the ipsilateral cuneus, even though the interconnections between the hippocampus and the cuneus are not fully known.[29]

Damage to the frontal lobe has been associated with exacerbated and targeted aggressive responses, while temporal lobe dysfunction generates bursts of misdirected anger.[30] Neuropathologies that occur in both areas can increase the risk of exacerbated aggressive behavior compared with those that affect only one or the other area.[27]

Prefrontal and insular regions are also implicated in eating disorders such as obesity, with a gray matter volume reduction in the medial prefrontal cortex, the anterior cingulate, the frontal pole, the caudate nucleus, and the

uncus, as well as a white matter volume decrease in the anterior limb of the internal capsule, adjacent to the caudate nucleus. These regions are involved in the decision, motivation, and reward processes, which suggests a relationship between the anatomical structures described, atypical behaviors, and polyphagia.[31]

The corpus callosum can be anatomically subdivided into the rostrum, the genu, the anterior body, the anterior middle body, the posterior middle body, the isthmus, and the splenium.[32] Among the major psychiatric diseases associated with morphological changes in the corpus callosum are those originating from injuries to the splenium or to the posterior middle body. Splenial lesion is associated with depression, a syndrome characterized by loss of pleasure in daily activities, with cognitive and sleep alterations, loss of appetite and of sexual interest. Injury to the posterior trunk of the corpus callosum is associated with Tourette syndrome.[32,33] This chronic tic disorder is manifested by fluctuating motor and vocal tics (emission of sounds with differing degrees of intensity and frequency, or sudden, repetitive, involuntary, rapid movements, rhythmless and stereotyped, with unpredictable durations). They usually occur as attacks, are reduced by sleep, and may cause social and occupational limitations.[33,34]

It has been recognized that the cerebellum, in addition to its motor functions, also acts in several cognitive processes. Cerebellar damage may be associated with dysfunctions in executive tasks, learning, procedural and declarative memory, language processing, visual and spatial functions, as well as with dysfunctions in personality, affection, and cognition.[12] In 1998, a new concept related to the cerebellum was created: "dysmetria of thought" or "cognitive dysmetria." According to this concept, the cerebellum would be responsible for the chronology of reasoning and of ideas, and it would be altered in several diseases such as schizophrenia, autism, dyslexia, and bipolar mood depression.[35] The cerebellum has the capacity to regulate the mood via the nuclei. Emotional control is achieved through its influences on the prefrontal cortex and on the hypothalamus. Anatomically, posterior lobe injuries are associated with cognitive changes, while lesions in the cerebellar vermis are associated with affective disorders. The anterior lobe is directly involved in motor functions, showing little correlation with cognitive and affective symptoms.[36]

In the case reported in the present article, the synergy of the lesions found in the patient before the stereotactic NPD resulted in the behavioral changes described. This is a rare and extremely interesting case, since the patient, despite presenting with bilateral lesions of the amygdala, was not diagnosed with Klüver-Bucy Syndrome, but with an exacerbation of aggressive behavior as a complication of the stroke. Targets used in surgical procedures in the right hemisphere can lead to a functional imbalance between these behavioral structures. Thus, the treatment can be more effective using a bilateral approach and multiple targets. Other findings about this patient are consistent with the literature, showing a relationship, even if not yet completely clarified, between neuroanatomical structures and the human psyche. The role of the cerebellum in aggressive behavior cannot be ruled out in the present case, and may become a surgical target in the future, after further studies.

Limbic System

The indication of NPDs is based on scientific evidence that correlates psychiatric illnesses to the limbic system and the pathophysiology of emotions.[37] Psychiatric disorders considered eligible for NPD are not yet fully understood from a pathological perspective, since injured brain areas are part of a large neuronal network, which has only been empirically defined. The smaller and more precise targets currently used in surgical procedures are the result of nearly a century of improvement in surgical techniques, neuroanatomy, neurophysiology, and neuropsychiatry.[38]

The term "limbic system" was first used by MacLean in 1955,[39] but Willis and Broca were the first ones to describe the limbic lobe, in 1664 and 1828, respectively.[40] In 1937, Papez was a pioneer who suggested the existence of a circuit of specific brain structures responsible for human emotion. From the observation that the hypothalamus played a significant role in the expression of emotions, and that higher cognitive thoughts arose from activity in the cortical areas (frontal lobes), Papez postulated that since emotion can be influenced by thought, and thought can be influenced by emotion, the hypothalamus (emotion) would be connected with other upper cortical areas (thought). Thus, he proposed a circuit in which the cortex connects to the cingulate gyrus, which connects to the hippocampus, which in turn connects to the mammillary bodies (hypothalamus) through the fornix. The mammillary bodies project to the anterior thalamic nuclei, which connect back to the cingulate gyrus, and then to the cortical areas. He considered that the cingulate cortex is the cortical region receptive to emotional impulses.[41]

In 1955, MacLean[39] added other structures to the limbic system, such as the septal area, the NAcc, the orbitofrontal cortex, the anterior temporal cortex, the dorsomedial thalamic nuclei, and the amygdala. Later, Goldenberg divided the limbic system into three limbic subcircuits: 1) the medial limbic circuit, including the classic Papez circuit; 2) the basolateral circuit, including the orbitofrontal cortex, the anterior temporal cortex, the amygdala, and the magnocellular division of the dorsomedial nucleus of the thalamus (frontothalamic pathway); and 3) a defense reaction circuit, including portions of the hypothalamus, the stria terminalis, and the amygdala.[38,42] The circular nature of these pathways may explain why surgical injuries performed at different locations within the same circuit can alleviate the same symptoms, and why injuries in two or more circuits produce better results than isolated lesions.[38] These pathways and their interactions with the basal ganglia (corticostriatothalamic pathways) constitute the anatomy of human emotion, and disturbances in these routes are considered the substrate of behavioral psychiatric illness.[38]

Neuropsychosurgery History and Targets

Most probably, neurosurgery began in the Antiquity era, through the practice of trepanation, a surgical removal of

sections of the cranial vault during life,[43] performed with the aid of a cylindrical instrument of varying size and shape called a trephine.[44] The use of trepanation to relieve neuropsychiatric symptoms has been shown to date back to 5100 BC; therefore, the history of psychosurgery, currently named NPD,[45] is as old as the history of psychiatric illnesses.[46]

In the 19th century, during the neuroscientific era of brain-behavior correlation, Broca and Wernicke established a clinicopathological parallelism between the neuroanatomical substrate and cognitive functions such as language.[40] Influenced by these discoveries, in 1888, the Swiss psychiatrist Johann Gottlieb Burckhardt inaugurated modern psychosurgery, performing the first procedure of the modern era. He excised various brain regions from six chronic psychiatric patients under his care. As a result, three progressed successfully and one died. The difficulty in establishing a good outcome in the postoperative period led to the discredit of the technique and to the consequent abandonment of the project even before its publication, in 1891.[47]

In spite of this, neurosurgeons continued their investigation of ablative brain surgery: the Estonian Lodovicus Puusepp performed frontal lobotomies with relative success;[40] the American-Canadian Wilder Graves Penfield obtained symptomatic psychological relief after resection of tumors, abscesses, and other brain injuries[48]; in 1935, at the Second World Congress of Neurology, the American John Farquhar Fulton presented, together with the American animal psychologist Carlyle F. Jacobsen, the resection of the anterior frontal cortex with behavioral changes in apes,[9,40] whereas the Portuguese António Egas Moniz proposed, for the first time, the ablation of the frontal cortex in humans with psychiatric diseases.[40]

In fact, Moniz was the first one to introduce the term "psychosurgery", and following the footsteps of Fulton and Jacobsen, in 1936, he and Pedro Almeida Lima performed the first neurosurgery to treat psychiatric disorders in humans, called "prefrontal lobotomy." The surgery performed by the Portuguese neurosurgeons achieved good effectiveness, but a relevant number of patients had frontal lobe syndrome as a complication (apathy, euphoria, distraction, and disinhibition), returned to nursing homes, and were no longer seen.[9,40]

Between 1936 and 1949, the American neurologist Walter Jackson Freeman and neurosurgeon James W. Watts modified the technique of Moniz and Lima and developed the transorbital lobotomy. Between 1936 and 1956, $\sim$ 60,000 lobotomies were performed in the USA, some of them without precise indications and in poor conditions, generating a large number of complications, ranging from convulsive disorders in the postoperative period to infection and death.[9,40] This surgical intervention was received with prejudice and discrimination, especially during World War II, when it was indiscriminately used in humans in the absence of a bioethical protocol.[49]

The development of sophisticated stereotactic target localization techniques, brain atlases, and imaging methods made stereotaxis possible. This surgical procedure is performed with a geometric orientation device fixed on the head, which directs the instrument to the coordinates of the target, increasing the precision of neurosurgery and reducing brain damage.[5,50]

In the 1940s, the Austrian neurologist Ernest A. Spigel and the American neurosurgeon Henry T. Wycis performed stereotactic surgery in humans using dorsomedial thalamotomy in schizophrenic patients for the first time. Their technique increased the accuracy of neurosurgery and decreased brain damage.[51] Since the 1950s, the demand for psychosurgery has significantly decreased due to the development of psychotropic drugs.[9,40,49] Nonetheless, for some patients presenting with psychiatric diseases refractory to clinical treatment, the use of psychosurgery remains valid. Stereotactic surgeries are, therefore, used especially in these cases, mainly for obsessive compulsive disorder (OCD), chronic pain, and Parkinson disease, among others.[52–54]

Nowadays, the main targets addressed in psychosurgery for pathological aggressiveness are the hypothalamus, the amygdala, the anterior capsule, the cingulate gyrus, and the NAcc. The procedures can be neuromodulatory and ablative, used separately or together.[55] The most used ablative procedures are posteromedial hypothalamotomy, amygdaloidotomy, anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy, and limbic leucotomy.[52,55]

In 1966, bilateral lesions of the posteromedial hypothalamus resulted in a significant reduction in aggressiveness. An interval of 7 to 10 days between the completion of the 2 lesions was recommended, since severe and potentially fatal hypothalamic dysfunction was observed in cases in which they were performed simultaneously.[56] This procedure is based on the hypothalamic functions, namely processing information from the external environment, controlling aggressive behavior, and ceasing the activity of the middle-basal hypothalamus (area of aggression). Therefore, posteromedial hypothalamotomy leads to reduced activation of the limbic system and, consequently, of aggressive behavior. This target has also been used in deep brain stimulation (DBS), leading to improvement in epileptic seizures.[9,51,53]

Amygdaloidotomy is performed especially by thermocoagulation. It is based on the association between the amygdala and the modulation of aggressive behavior, its connections with the prefrontal, parietal, and insular cortexes, the cingulate gyrus, the hypothalamus, and the reticular formation, and its role in controlling neuroendocrine and autonomic responses.[9] A reduction in aggressive behavior has been reported as a result of bilateral lesions to the central nucleus of the amygdala.[57,58] Nonetheless, this procedure has the rare complication of Klüver-Bucy syndrome.[58]

Anterior capsulotomy, developed by the Swedish neurosurgeon Lars Leskell and the French psychiatrist and neurosurgeon Jean Talairach in 1949, is based on the disruption of the orbitofrontal cortex and of the limbic system by targeting the fibers that connect them, located between the caudate nucleus and the putamen. This procedure has adverse effects such as mental confusion, weight gain, nocturnal enuresis, headache, and impaired memory.[40,55] Although these effects rarely occur, they can last long in the postoperative period.

This procedure has been indicated in cases of intractable OCD, with a success rate of up to 70%.[9,53]

Anterior cingulotomy was developed by the American neurosurgeon H. Thomas Ballantine in the early 1960s as a treatment for patients with anxiety, intractable pain, and mood disorders.[40] Bilateral MRI-guided thermocoagulation is used to create ablation lesions of fibers that connect the cingulate cortex, the orbitofrontal cortex, and the limbic system. Currently, it is mainly used in the treatment of OCD.[40,53,55] This procedure has a low rate of adverse effects. A study listing > 800 cases of cingulotomy at the Massachusetts General Hospital over a 40-year period revealed no casualties and only 2 cases of infection.[53]

Subcaudate tractotomy, developed by the British neurosurgeon Geoffrey Knight in 1964, is the interruption of the fibers that connect the orbitofrontal cortex to the subcortical limbic structures through the ablation of the innominate substance in the area inferior to the head of the caudate nucleus.[53] Since 1970, the Brook General Hospital in London has reported > 1,300 cases of subcaudate tractotomy performed in patients with affective disorders such as OCD and chronic anxiety. An improvement has been observed in between 40 and 60% of the patients 1 year after the procedure.[59] Complications are usually induced edema, transient postoperative disorientation, and long-term seizures.[9,53,55]

Limbic leucotomy, introduced by Desmond Kelly and Nita Mitchell-Heggs in England in 1973, is a combination of bilateral cingulotomy and subcaudate tractotomy[40] that causes the interruption of the Papez circuit by disconnecting the frontolimbic and the corpus callosum. The lesion is made on the lower side of the head of the caudate nucleus and on the anterior cingulate gyrus, and also involves the mid-lower quadrant of the frontal lobe.[55] In the first 24 to 48 hours after surgery, patients may experience confusion and drowsiness, with subsequent recovery.[53]

Since the NAcc plays a role in immediate reward circuits and also in modulating repulsive stimuli, it has also been proposed as a target to control aggressive behavior.[60] Its stimulation is effective to control addiction to drugs, nicotine, and alcohol, as well as to reduce aggressive behavior in patients with OCD, Tourette syndrome, and pathological obesity.[61]

All the multiple targets described can be used, isolated or in combinations, in NPDs, depending on the psychiatric illness and on the experience of the neurosurgeon.[10] A 27-year-old male patient diagnosed with organic delusional disorder, absence epilepsy, and pathological aggressiveness underwent NPD using the stereotactic technique, combining left medial hypothalamotomy and bilateral anterior capsulotomy. Although schizophrenia and epilepsy remained unchanged, the patient had important improvement in his aggressive behavior immediately after the procedure.[9]

A 14-year-old and a 16-year-old male patient, both diagnosed with severe pathological aggressiveness refractory to clinical pharmacological treatment, were operated on using the multitarget stereotactic technique. In the former, four interventions were performed with 3-month intervals between the procedures: 1) left posteromedial hypothalamotomy; 2) anterior capsulotomy; 3) right posteromedial hypothalamotomy and bilateral reinforcement of the lesion to the anterior limb of the internal capsule; 4) NAcc lesion. In the latter, 2 procedures were performed: left posteromedial hypothalamotomy and, after 1 year, right posteromedial hypothalamotomy associated with anterior capsulotomy. Both patients experienced significant improvement in symptoms and no recurrence of aggressive behavior.[60]

Bilateral anterior capsulotomy was performed in 13 patients with epilepsy and psychiatric comorbidities such as psychotic symptoms, pathological aggressiveness, impulsivity, anxiety, depression, and intellectual disability. The neurosurgical procedure was considered an effective treatment for epileptic patients presenting with refractory psychotic symptoms and aggressive behavior. It also improved the compliance of the patients with antiepileptic medication regimens. The most common but transient side effects of this surgery were fatigue and laziness.[62]

The combination of anterior cingulotomy and anterior capsulotomy was employed for the treatment of pathological aggressiveness in 10 patients, who showed improvement in their condition and reintegration into society. A total of 13 adverse effects related to the surgical procedure were reported, but all complications were temporary.[63]

Additionally, the combination of NAcc DBS with anterior capsulotomy is an effective treatment for drug addiction. A 28-year-old male patient who had a polysubstance use disorder (bucinnazine, morphine, and hypnotics) for 13 years, severe depression, and anxiety underwent a combination of bilateral NAcc DBS with bilateral anterior capsulotomy. After the procedure, he had an evident decrease in his craving for the three drugs. Furthermore, he showed significant improvements in depression, anxiety, sleep, quality of life, and most aspects of cognitive functioning.[64]

In the case reported in the present article, the patient underwent multitarget stereotactic surgery to control chronic pathological aggressiveness refractory to clinical treatment. The targets were selected based on the clinical manifestations of the patient. The procedure was uneventful and resulted in a decrease in the aggressive behavior and in a partial decrease in sexual impulse, leading to improvement in the quality of life of the patient and her family. The patient also showed improvement in the symptoms of binge eating disorder, with reduced searches for food. Our outcomes corroborate the findings that lesions to the NAcc address behaviors associated with vandalism and irritability,[10] and also confirm its role in compulsive behavior, which may be connected with binge eating disorder.[61]

Conclusion

The reported case and several publications bring to light the discussion of refractory aggressiveness therapy, a complex scenario, and show that multitarget stereotactic NPD, well-performed in properly selected patients, is capable of producing satisfactory results, controlling symptoms, and

improving quality of life. However, it is clear that further studies on the correspondence between brain injuries and symptoms are still needed, since no formal consensus has been reached on the targets that should be used in each case.

Scientific knowledge is still limited to fully understand the pathophysiology of pathological aggressiveness of the patient in the present case, who had brain injuries caused by bacterial meningitis and stroke that resulted in lesions to targets normally used in NPD for aggressiveness, leading to aggressive behavior. Interestingly, the destruction of these structures in the ablation procedure causes significant improvements in pathological aggressiveness. This finding highlights the broad variations in the clinical repercussions reported after NPD for pathological aggressiveness.

Conflict of Interests

The authors have no conflict of interests to declare.

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Abducens Nerve Schwannoma: Case Report and Literature Review

Schwannoma do nervo abducente: Relato de caso e revisão da literatura

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Abstract

The authors describe a rare case of abducens nerve schwannoma, manifested with headache and diplopia, associated to right side cerebellar syndrome. During surgery, the authors identified that the origin of the tumor was from the abducens nerve, and the histopathological diagnosis confirmed that it was a schwannoma. A gross total tumor resection was performed, and the patient recovered from her symptoms 1 month after surgery. The authors followed the Case Report guidelines (CARE) guideline and the patient authorized the authors to publish the present case report by signing an informed consent form.

Keywords

- case report
- neurilemmoma
- abducens nerve
- ocular motility disorders
- skull base neoplasm
- schwannoma

Resumo

Os autores descrevem um raro caso de Schwannoma do nervo abducente, cuja manifestação clínica foi com cefaleia e diplopia, associadas à síndrome cerebelar hemisférica direita. Durante a cirurgia, os autores identificaram que o tumor tinha sua origem junto ao nervo abducente, e o diagnóstico histopatológico confirmou schwannoma. Realizou-se uma ressecção completa do tumor e o paciente apresentou melhora total dos sintomas em um mês após a cirurgia. Os autores seguiram as diretrizes do CARE para produzir este relato e o paciente assinou o termo de consentimento livre e esclarecido, autorizando a publicação deste caso.

Palavras-chave

- relato de caso
- neurinoma
- nervo abducente
- paresia da motilidade ocular
- neoplasias da base do crânio
- schwannoma

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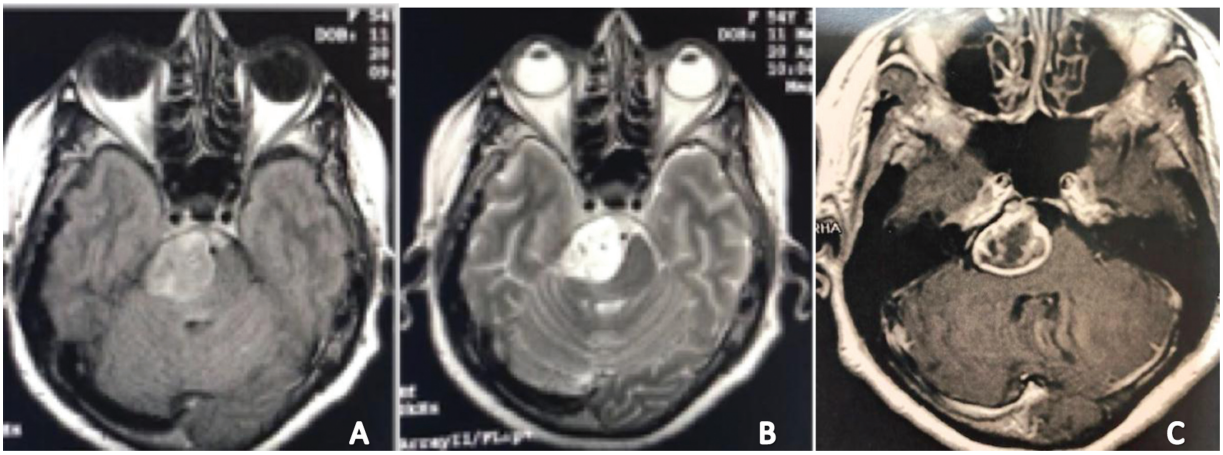

Fig. 1 Presurgical magnetic resonance imaging demonstrating a heterogenous but predominantly isointense signal on T1 images (A), hyperintense signal on T2 images (B) with a circumferential enhancement after gadolinium infusion (C).

Introduction

Schwannomas are benign slow growing tumors that arise from the Schwann cells of the neural sheath of the nerves and account for between 6 and 8% of all primary intracranial neoplasms.[1–3] Even though they can be seen in most cranial nerves (except from the optic and olfactory nerves),[3,4] they usually arise from sensory nerves (most frequently from the vestibular nerve, followed by the trigeminal nerve), with motor nerves being rarely affected.[3,5]

Schwannomas of the abducens nerve are rare. Since a schwannoma of the abducens nerve was first reported by Chen in 1981,[6] only 31 other cases had been reported worldwide by 2017.[7] The authors report a case of a patient who presented with headache and diplopia for 2 months, whose neurological exam demonstrated a right abducens nerve paresis. Investigation demonstrated an extra-axial lesion located in the prepontine cistern. During surgery, it was noticed that the tumor originated from the abducens nerve, and the histopathological diagnosis confirmed that it was a schwannoma. The patient completely recovered her ocular motricity after 1 month of follow-up.

Case Report

A 55-year-old previously healthy woman was referred to the department of oncological neurosurgery for investigation of a 2-month evolution of headache whose intensity was progressively increasing, associated with diplopia and loss of dynamic balance. The neurological exam of the patient demonstrated an inner horizontal deviation of the right eyeball secondary to paresis of the right abducens nerve. Other ocular movements were preserved. The patient presented no paresis, but coordination and delicate movements control were disturbed, since the patient presented a right sided dysdiadokokinesis, gait ataxia, and right-sided deviation of the dynamic balance. Magnetic resonance imaging (MRI) demonstrated an extra-axial lesion located in the prepontine cistern compressing the anterolateral right side of the pons. The tumor was predominantly isointense (compared with the brain parenchyma) on T1 images, with areas of hypointense signal. On T2 images, the tumor was hyperintense. After gadolinium infusion the tumor presented a heterogenous enhancement (►**Fig. 1**). The venous phase of an angioresonance demonstrated a significative right sigmoid sinus dominance. This was one of the reasons why the posterior petrosal approach was not considered a good option.

The patient was submitted to surgery by a lateral suboccipital right-sided retrosigmoid approach with complete removal of the tumor. During the surgery, it was noticed that the origin of the tumor was from rootlets of the right abducens nerve that emerged as two different roots. This duplicated origin of the nerve allowed the preservation of the main trunk in all its trajectory. A postoperative MRI scan showed gross total tumor resection (►**Fig. 2**). An anatomopathological analysis diagnosed the tumor as schwannoma, represented mostly by Antoni A areas consisting of closely apposed spindle-shaped cells in a palisading pattern (►**Fig. 3**).

During the early postoperative period, the patient persisted with right abducent palsy, but no other neurological deficits. By the 7th day of postoperative follow-up, the patient was discharged from hospital care, sustaining excellent wound healing and complete neurological recovery. Ocular motricity was completely recovered after 1 month of follow-

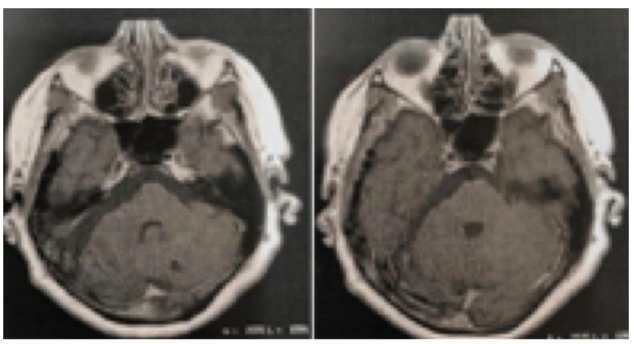

Fig. 2 Postsurgical magnetic resonance imaging demonstrating complete tumor resection

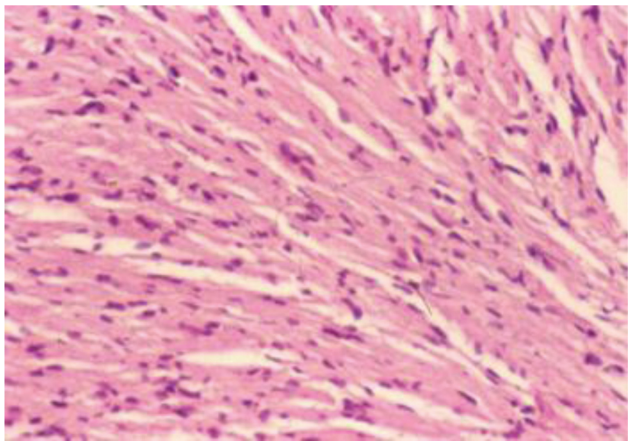

Fig. 3 Schwannoma consisting of closely apposed spindle-shaped cells in a palisading pattern (Antoni A).

up (►**Fig. 4**). The patient authorized the authors to publish the present case report by signing an informed consent form.

Discussion

The trigeminal nerve is the second most common site of schwannomas, representing ~ 0.2% of all intracranial tumors.[5] Pure motor nerves that supply the ocular muscles (IIIrd, IVth and VIth nerves) are very rarely affected by this neoplasm.[4,8,9] Unlike the more common vestibular schwannomas, those of the VIth nerve usually arise distal from the glial-Schwann sheath junction. This transitional zone of the abducens nerve represents the junction of central and peripheral myelin and lies < 1 mm from the brainstem.[8,10,11]

Abducens nerve schwannomas are more frequent in females, with a mean age of 45 years old (peak of frequency in the 5th decade of life), characteristics that were also found in our case. The youngest patient ever described was 10 years old,[12] and the oldest was 66 years old.[13] Some of the cases described in the literature were associated with neurofibromatosis type 1 (NF-1).

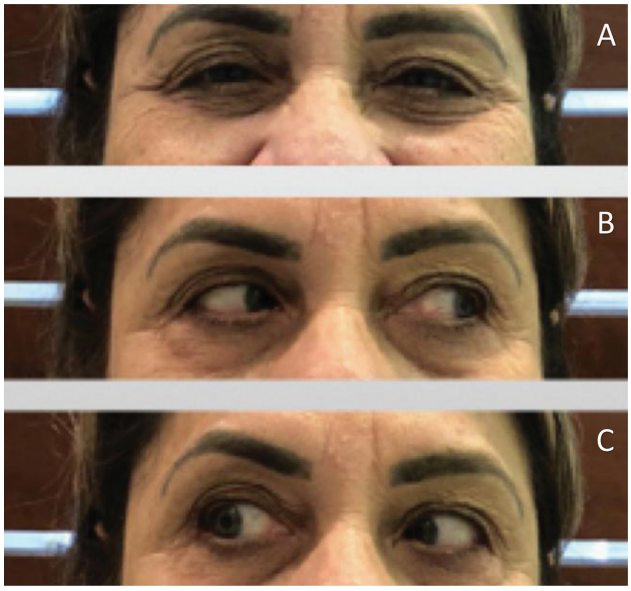

Fig. 4 Postsurgical ocular extrinsic exam demonstrating normal horizontal ocular movement. (A) Patient looking forward. (B) Patient looking to the left. (C) Patient looking to the right.

The abducens nerve emerges from the brainstem near the midline at the pontomedullary sulcus. It courses upwardly, laterally, and anteriorly in the prepontine cistern and passes underneath the Gruber ligament, entering the Dorello canal. The nerve enters in the cavernous sinus at the lower part of the posterior wall, crossing the sinus medially to the ophthalmic nerve and lateral to the internal carotid artery. Finally, the nerve enters the orbital cavity at the medial end of the superior orbital fissure.[10]

Abducens nerve schwannomas can arise from the intracranial or intraorbital portion of the nerve. Intracranial tumors can originate from the emergence of the nerve in the pontomedullary sulcus to the cavernous portion close to the superior orbital fissure. Tung et al. classified intracranial abducens schwannomas into two types depending their location: Type 1 occurs in the cavernous sinus (cavernous abducens schwannoma); and Type 2 occurs at the prepontine cistern (cisternal abducens schwannoma).[14] However, some cases involving cisternal and cavernous segments were described, named as cisternocavernous dumbbell-shaped type, and were assigned to a new category of abducens schwannomas (Type 3).[5] Based on the aforementioned classification, most abducens schwannomas arise from the cisternal portion, followed equally by the cavernous and cisternocavernous types.[8] A literature research has identified only two cases of extracranial intraorbital abducens nerve schwannomas.[4,15]

The clinical presentation differ according to the location of the tumor. Diplopia, secondary to isolated abducens nerve palsy, is the most frequent manifestation of Type 1 tumors.[3] In contrast, tumors located in the cistern may present with obstructive hydrocephalus and raised intracranial pressure, besides VIth nerve palsy.[8] Depending on the size of the cisternal tumor, other cranial nerves can be involved, such as the trigeminal, the vestibulocochlear and the facial nerves.[8,10] In such cases, patients may present with facial pain, facial numbness, hearing disturbance or oculomotor palsy.[3]

Clinical features and neuroradiologic image are frequently insufficient to reach an accurate preoperative diagnosis.[3] The diagnosis of abducens schwannoma is seldomly performed before operation and, typically, the primary suspicion is meningioma or trigeminal schwannoma.[8]

The typical MRI findings of schwannomas demonstrate an iso-to-hypointensity image in T1, hyperintensity in T2, and a heterogeneous contrast enhancement. Heterogeneous signal intensity and postcontrast enhancement are suggestive of internal hemorrhage and myxoid/cystic changes.[16] Besides, schwannomas can show degenerative changes, such as cyst formation, calcification, hemorrhage, and hyalinization,[17] characteristics that make the radiological diagnosis more difficult.

Most abducens schwannomas are solid, but a cystic variant with a ring-like enhancement is found in a significant percentage of cases.[8] Other indirect signs that highlight the

suspicion of nonvestibular Schwannomas are: normal size of the internal acoustic meatus and posterior displacement of the facial and vestibulocochlear nerve complex, which preclude the possibility of the vestibular origin.[3] A 3D-Constructive Interference in Steady State (3D-CISS) acquisition, a part of fast gradient echo sequences, can possibly define preoperatively the relationship details of the tumor and the cranial nerves adjacent to the neoplasm.[18]

A specific radiological characteristic was described in dumbbell-shaped schwannomas, which are often seen in the trigeminal nerves. But compared with the trigeminal tumors, the neoplasms arising from the abducens nerve present a different pattern. The neck constriction of dumbbell-shaped schwannomas forms an obtuse angle in trigeminal schwannomas, whereas in abducens schwannomas, it forms an acute angle.[5]

The first operated abducens schwannoma was described by Chen in 1981,[6] and, up to now, operation is the only therapy that has been reported to be successful.[8] Besides, the definite diagnosis of an abducens nerve schwannoma is established intraoperatively, when the surgeon can visualize the tumor attachment into the VIth nerve.[8]

The surgical technique and approach vary according to the location of the tumor. For schwannomas in the cavernous and parasellar regions (Type 1), the frontotemporal, subtemporal, orbitozygomatic, and anterior transpetrosal approaches have all been reported. For prepontine lesions (Type 2), the lateral suboccipital retrosigmoid, lateral suboccipital transcondylar, and anterior transpetrosal approaches have been reported.[5,8]

The surgical technique used to resect dumbbell-shaped tumors that extend both to the posterior and middle cranial fossae has not been described specifically for abducens schwannomas. The reports in the literature are for trigeminal schwannomas, in which case the anterior transpetrosal approach would be a good option.[19]

Preservation of nerve function as well as maximum tumor removal are critical in surgery for intracranial schwannomas, but abducens nerve function uncommonly recovers completely after removal of the abducens nerve schwannoma. To date, among the 32 cases of pathologically confirmed intracranial abducens nerve schwannoma reported, postoperative nerve function recovered completely in only 7 cases and partially in 3 cases.[8,9,20] Permanent or transient abducens nerve palsy occur postoperatively in most cases because the nerve was usually disturbed or sacrificed.

The reason for complete recovery of nerve function in the seven cases reported in the literature, as well as in the present case, may be the splitting of the nerve root or the existence of a separate trunk of the abducens nerve in the subarachnoid space.[8] The preservation of one of the nerve roots or the preservation of some nerve fascicles in patients with a single nerve root makes possible the recovery of ocular external gaze. This suggests that intentional subcapsular removal preserving part of the tumor capsule as a scaffold for regeneration of the nerve would potentiate functional recovery even in cases in which the course of the abducens nerve is not identified intraoperatively, as long as nerve function is preserved preoperatively.[8]

Finally, since the abducens nerve is a pure motor nerve, primary nerve repair using anastomosis would potentiate functional recovery. Direct end-to-end anastomosis after complete excision of the tumor may result in functional improvement during follow-up.[3]

Conclusion

The authors describe the 33rd case of abducens nerve schwannoma in the medical literature, but the 8th with full recovery of nerve function. Tumoral gross total removal remains the goal of the treatment, and the preservation of one the nerve roots (when multiple) or fascicles of the nerve (when single) is of paramount importance for the recovery of ocular movement.

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There was no financial support or funding for the present project.

Conflict of Interests
The authors have no conflict of interests to declare.

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Thermocoagulation Treatment of a Patient with Obsessive Compulsive Disorder and Substance Use Disorder: Case Report

Tratamento por termocoagulação de paciente com transtorno obsessivo-compulsivo e transtorno por uso de substâncias: Relato de caso

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Abstract

Obsessive compulsive disorder (OCD) is a possible cause associated with substance use disorder (SUD), a set of physical, psychological, behavioral, and cognitive phenomena related to the use of one or more chemical substances as a priority in a person's life that compromises quality of life. Since they can share the same neuronal network, this serves as a basis for neurosurgical procedures in cases refractory to conventional therapies. A 31-year-old male patient with a history of OCD and SUD refractory to conventional therapies underwent bilateral ablative stereotactic neurosurgery of the anterior limb of the internal capsule, the subgenual cingulate region, the nucleus accumbens, and the cingulate gyrus. Up to 33 months after the the procedure, the patient showed an absolute improvement in OCD and SUD and reported lack of withdrawal signs or symptoms and/or need to use drugs. In recent years, ablative neurosurgery has proven to be an alternative to OCD refractoriness, with long-term benefits. In the case analyzed, ablative stereotactic neurosurgery was effective in controlling both the signs and symptoms triggered by OCD, as well as those of anxiety and stress.

Keywords

- stereotaxic technique
- substance-related disorder
- obsessive-compulsive disorder
- neurosurgery
- psychiatry
- quality of life

Resumo

O transtorno obsessivo-compulsivo (TOC) é uma possível causa associada ao transtorno por uso de substâncias (TUS), um conjunto de fenômenos físicos, psicológicos, comportamentais e cognitivos relacionados ao uso de uma ou mais substâncias químicas como prioridade na vida de uma pessoa que compromete sua qualidade de vida. Como estes transtornos podem compartilhar a mesma rede neuronal, isto serve de base para procedimentos neurocirúrgicos em casos refratários às terapias

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Palavras-chave
- técnica estereotáxica
- transtorno relacionado ao uso de substâncias
- transtorno obsessivo-compulsivo
- neurocirurgia
- psiquiatria
- qualidade de vida

convencionais. Um paciente do sexo masculino de 31 anos com história de TOC e TUS refratários às terapias convencionais foi submetido a neurocirurgia estereotáxica ablativa bilateral do braço anterior da cápsula interna, da área subgenual, do núcleo accumbens e do giro do cíngulo. Até 33 meses após o procedimento, o paciente apresentou melhora absoluta do TOC e do TUS e relatou ausência de sinais ou sintomas de abstinência e/ou necessidade de uso de medicamentos. Nos últimos anos, a neurocirurgia ablativa tem se mostrado uma alternativa à refratariedade do TOC, com benefícios a longo prazo. No caso analisado, a neurocirurgia estereotáxica ablativa foi eficaz no controle tanto dos sinais e sintomas desencadeados pelo TOC como dos de ansiedade e estresse.

Introduction

Obsessive compulsive disorder (OCD) is characterized by obsession, defined as intrusive thoughts that may or may not be associated with compulsion, actions that alleviate the sensation of discomfort generated by them.[1] Individuals affected by OCD experience reduced ability to voluntarily control or inhibit their own behavior and tend to act repeatedly. Compulsiveness has been shown to be one of the mechanisms capable of explaining the addiction to chemical substances, via negative reinforcement in the limbic system, cognitive and behavioral inflexibility, decreased prefrontal serotonergic control, and imbalanced frontostriatal and ventral habitual responses.[2] Therefore, a dysfunction in the brain circuit may overlap the therapeutic targets of OCD and addiction.

Substance use disorder (SUD) is a complex condition that involves a set of physical, psychological, behavioral, and cognitive phenomena related to the use of one or more chemical substances as a priority in a person's life that compromises quality of life. The most severe form of SUD is often called addiction, when the users have difficulty keeping away from the substance even knowing that it will cause harm, affecting their quality of life, functionality, and interpersonal relationships.[3] Over a quarter of the world population uses drugs and, of these, ~35 million people have a SUD. Alcohol, tobacco, cannabis, opioids, amphetamines, ecstasy, and cocaine are the most used substances worldwide.[4] Drug use is still strongly associated with psychiatric comorbidities such as depression, anxiety, and OCD, mainly because they share some neuronal systems and similar risk factors.[4]

Pharmacological therapy associated with psychotherapy is the first choice to treat psychiatric conditions. However, 30 to 40% of the individuals diagnosed with OCD are refractory to this treatment, and SUD also has a high refractoriness rate.[5,6] Among the interventionist options, ablative stereotactic neurosurgery is a consolidated method in the treatment of psychiatric diseases. It is indicated for the treatment of patients who are refractory to conventional drug therapy and psychotherapy, for whom the benefits proposed are worth the risks of an invasive procedure.[7] This type of surgical procedure has been proven to be effective in up to half of the cases. Additionally, the improvements last long after the surgery, giving hope to people affected by these disorders to have a better quality of life.[8] Therefore, the present study aimed to report the case of a patient presenting with SUD and OCD who underwent thermocoagulation of the anterior limb of the internal capsule, the subgenual cingulate region, the nucleus accumbens, and the cingulate gyrus, bilaterally.

Case Report

Ethics

The present study was approved by the Ethics Committee on Human Research of the Universidade Federal de Goiás (no. 4.287.460/2020; CAAE: 33933520.5.3001.5078) and by the Ethics Committee on Human Research of the Pontifícia Universidade Católica de Goiás (no. 4.211.061/2020; CAAE: 33933520.5.0000.0037). The patient provided informed and written consent in accordance with the Declaration of Helsinki.[9]

Patient History

A single 31-year-old male agricultor sought care at our neurology service. He reported a history of drug addiction, anxiety, and OCD refractory to pharmacotherapy. He informed that SUD started when he was 15 years old, with alcohol consumption, and progressed to tobacco use at 17, cocaine at 18, cannabis at 21, followed by crack abuse, including some episodes of overdose. As a result of drug abuse, he was voluntarily admitted in 2 different rehabilitation centers, staying there for 6 and 3 months, respectively. Withdrawal symptoms included irritability, anxiety, nervousness, aggression, insomnia, agitation, and hallucinations. The neuropsychological evaluation prior to the procedure revealed severe anxiety and near-exhaustion stress and confirmed OCD refractory to treatment (►**Table 1**).

Surgical Procedure

The patient underwent a stereotactic surgical procedure in August 2018. Thermocoagulation was performed using a 244-mm long electrode with a 4-mm length and 1.5-mm diameter exposed tip at 70°C for 70 seconds guided by computed tomography (CT) and magnetic resonance

Table 1 Neuropsychological assessment

PRIOR TO THE PROCEDURE			
Symptom	**Scale**	**Score**	**Interpretation**
Depression	Beck Depression Inventory	10	Not depressed
Anxiety	Beck Anxiety Inventory	50	Severe anxiety
Stress	Lipp's Stress Symptoms Inventory for Adults	Phase 3	Near-exhaustion
Obsessive compulsive disorder	Yale-Brown Obsessive-Compulsive Scale	36	Refractory OCD
AFTER THE PROCEDURE			
Symptom	**Scale**	**Score**	**Interpretation**
Depression	Beck Depression Inventory	1	Not depressed
Anxiety	Beck Anxiety Inventory	4	Minimal level of anxiety
Stress	Lipp's Stress Symptoms Inventory for Adults	Did not reach minimum score	Not stressed
Obsessive compulsive disorder	Yale-Brown Obsessive-Compulsive Scale	1	Responded to surgical treatment (score improvement $\geq$ 35%)

Abbreviation: OCD, obsessive compulsive disorder.

imaging (MRI) fusion. Radiofrequency thermocoagulation aimed the following surgical targets: the anterior limb of the internal capsule, the subgenual cingulate region, the nucleus accumbens, and the cingulate gyrus, bilaterally. In the postoperative period, the patient was feverish until the 4th day but had no signs of meningeal involvement. On the 5th day, he was discharged from the hospital with a mild degree of mental confusion but no sensory or motor deficits.

Results

Thirty-three months after the surgical procedure, the patient reported continuous use of tobacco, but denied consumption of alcohol, cocaine, cannabis, and crack. He also affirmed that during this period he had no relapses or withdrawal signs or symptoms, and that his interpersonal relationships showed improvement, especially with his family. Currently, in addition to psychotherapy, he makes daily use of topiramate 25 mg, carbamazepine 200 mg, and chlorpromazine 25 mg. Postoperatively, the neuropsychological assessment indicated significant improvement in anxiety, stress, and OCD (►**Table 1**), showing that the proposed procedure resulted in a good response.

Discussion

In recent years, neuroablation has emerged as an alternative in cases of OCD refractory to conventional therapy (Yale-Brown Obsessive-Compulsive Scale [Y-BOCS] > 30). In 2015, a literature review that included 108 patients with refractory OCD who underwent anterior capsulotomy showed an average 51% decrease in the Y-BOCS score.[10] In a 2019 meta-analysis, 367 individuals diagnosed with treatment-resistant OCD that underwent neuroablation and 314 that underwent deep brain stimulation (DBS) were assessed. The first group had a decrease in the Y-BOCS score of 50.4%, whereas the second group had a 40.9% reduction postoperatively.[11]

A meta-analysis performed in 2020 analyzed the outcomes of 457 patients with severe and refractory OCD who underwent neuroablation and concluded that 55% of them achieved a $\geq$ 35% reduction in the Y-BOCS. These results show that ablative neurosurgeries are safe and effective for many people with OCD refractory to conventional drug therapy and psychotherapy.[6] In addition, comparing neuroablation with DBS, the literature suggests that the former is superior in individuals with refractory OCD, since it results in a higher decrease in the Y-BOCS score.[10]

On the one hand, in a literature review, the authors concluded that patients who underwent anterior capsulotomy were 9% more likely to go into remission than those treated with DBS, with no difference in the rates of adverse events between the 2 procedures.[10] On the other hand, a meta-analytic study revealed that adverse events were higher in patients treated with DBS, with an incidence of 64.6% compared with 43.6% using neuroablation.[11]

The main advantages of neuroablation over DBS are its lower cost and absence of complications for maintenance such as programming and battery change. Furthermore, it is possible to access multiple anatomical targets in the same procedure. In the present case, neuroablation resulted in greater accessibility and comfort to the patient, given that he underwent a single surgical procedure with multiple targets. However, it has the disadvantage of generating irreversible injuries, which can result in long-term adverse events, unlike DBS, which allows adjustments in stimulation parameters and even turning the device off.[8,10]

In the reported case, the patient had a 97.3% reduction in the Y-BOCS score, an instrument used to assess the severity of OCD and its response to the proposed treatment. Patients who decrease their score by $\geq$ 35% are considered responsive

to treatment.[12,13] Thus, neuroablation was effective to control the signs and symptoms triggered by OCD of our patient, as well as those of anxiety and stress, in agreement with the literature consulted.[8,10,11] Regarding SUD, after the neurosurgery, the patient stopped using all drugs, except tobacco. He has remained abstinent throughout the follow-up period of 30 months. It is worth mentioning that ablative surgeries to control SUD have an average remission rate of 58% 5 years after the procedure.[14]

The targets used in the present case play roles in the pathophysiology of both OCD and SUD, justifying the effective outcome for both. The main surgical targets with promising results in neurosurgery for the treatment of SUD are the nucleus accumbens, the anterior limb of the internal capsule, and the bed nucleus of the stria terminalis.[14–17] The anterior cingulate cortex, the cingulate fibers, the anterior limb of the internal capsule, the ventral corticostriatal tracts at the head of caudate nucleus, and the frontotalamic fibers are the major targets to control OCD.[6,8]

Only mild, transient, and controllable adverse events were observed in the present case. In a systematic review of 23 studies that included 487 patients who underwent neuroablation, most adverse events (88.4%) were also classified as mild and transient. The most common adverse events were postoperative headache (14.9%), cognitive deficits (9.1%), and behavioral problems (8.1%). Serious or permanent adverse events, not observed in our case, had and average incidence of 0.5%, and the most common ones were personality changes (2.3%), cerebral cysts or cerebral edema (1.5%), behavioral disorders (1.3%), and weight change (1.0%).[6]

Conclusion

In line with the literature, the present results point to the benefits of neuroablation to our patient, given the significant improvement in OCD, SUD, anxiety, and stress scores. It is important to emphasize that the procedure did not cause significant adverse effects to the patient and did not prevent him from performing his usual daily activities. This demonstrates the possibility of improving the quality of life of individuals with similar conditions.

Conflict of Interests

The authors have no conflict of interests to declare.

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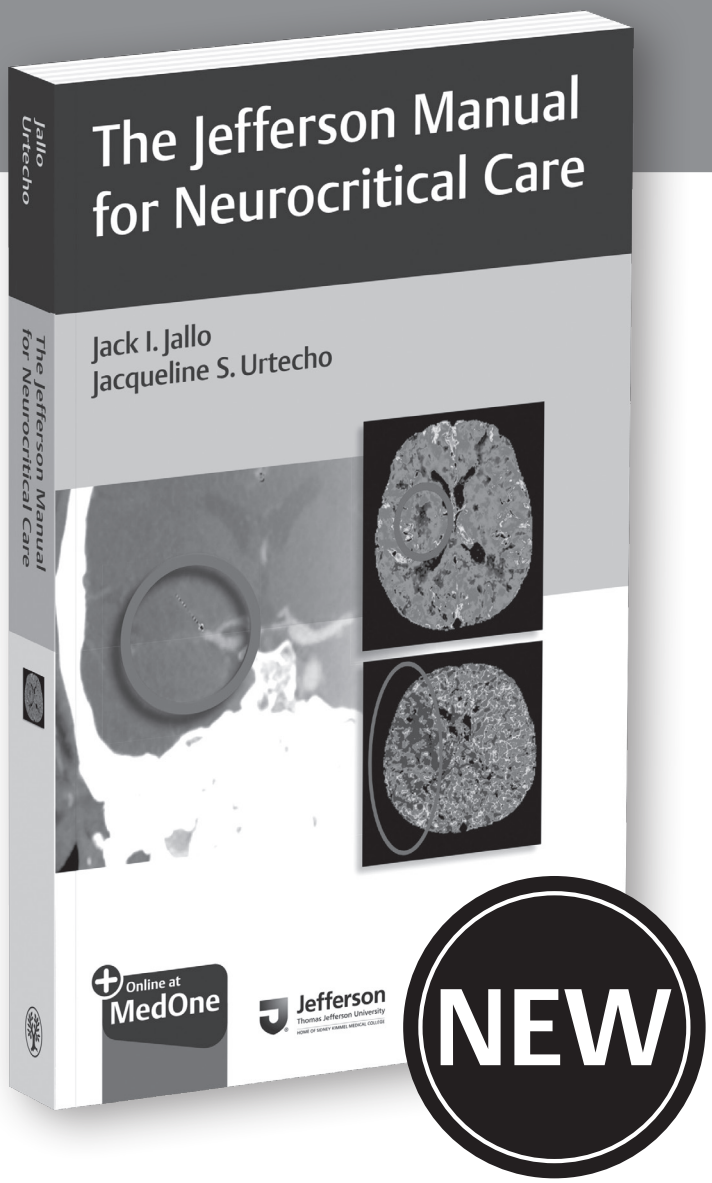

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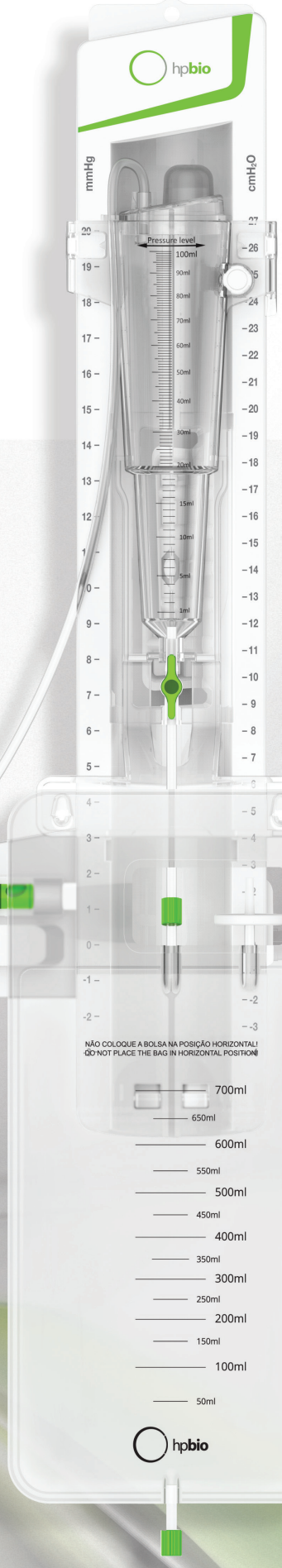

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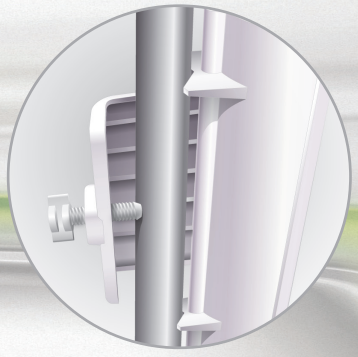

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