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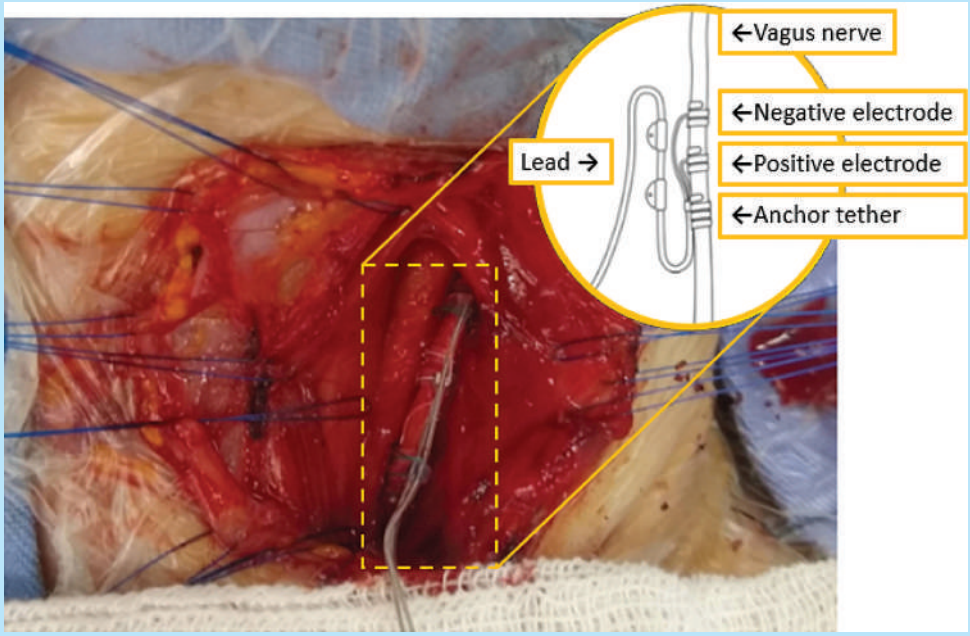

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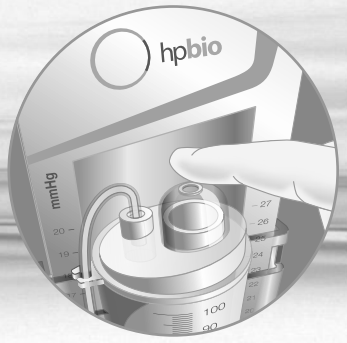

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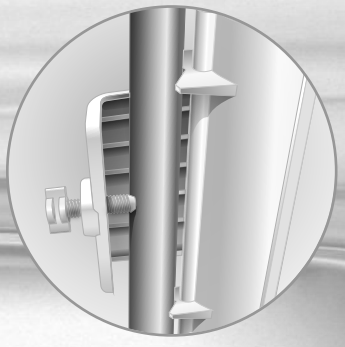

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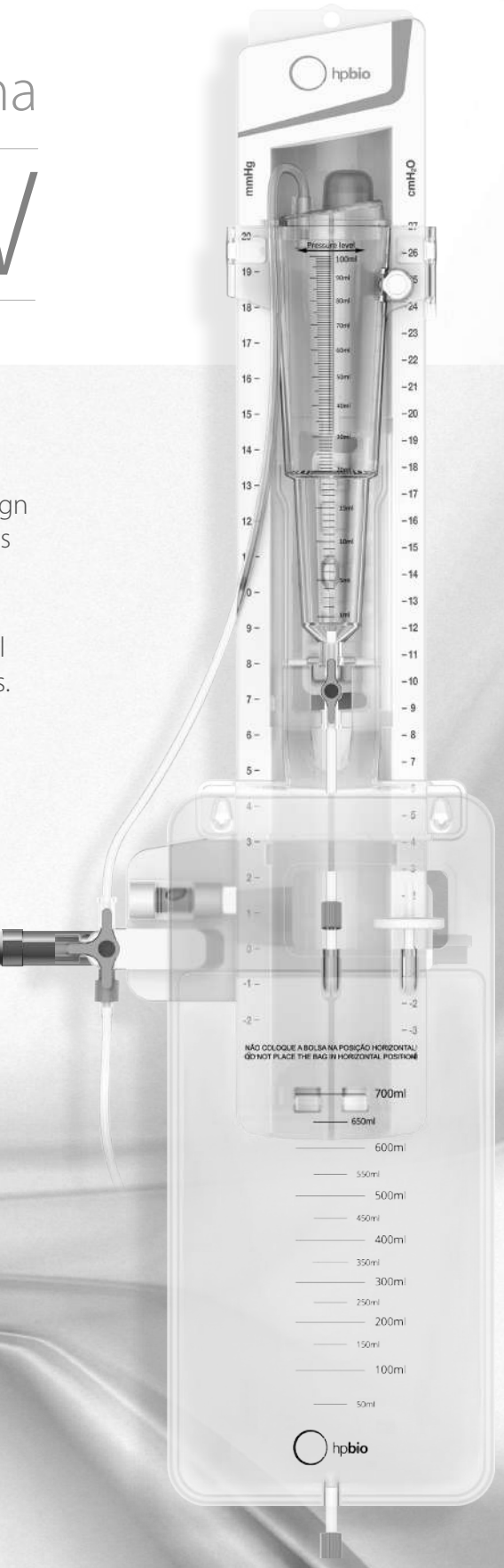

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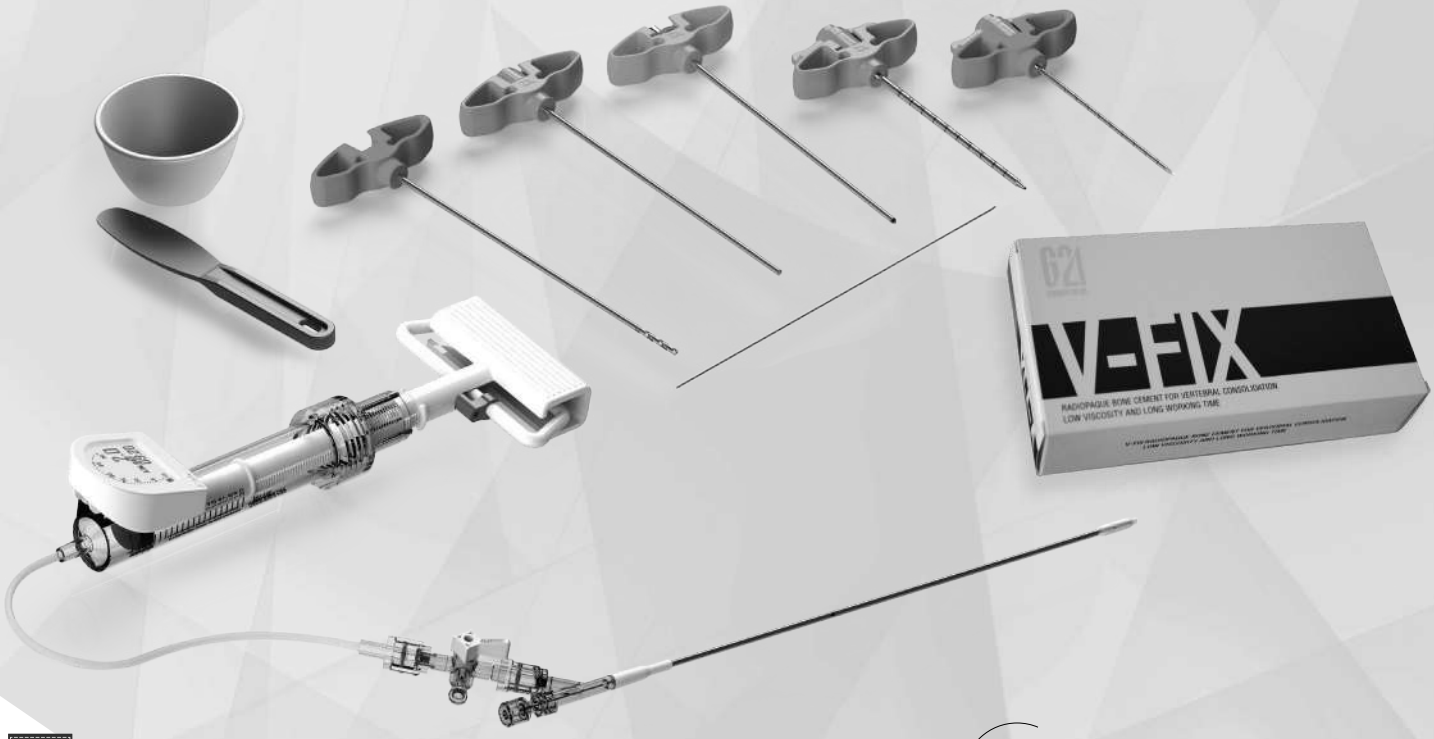

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Using the Casper Stent in Carotid Angioplasty: A Single Center Experience

O uso do stent casper na angioplastia carotídea: Experiência de único centro

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Abstract

Objectives To establish the success rate in endovascular internal carotid artery (ICA) stenosis recanalization using the double-layer stent Casper-RX (Microvention, Inc 35 Enterprise, Aliso Viejo, California, United States of America) and to identify the main comorbidities in individuals with ICA stenosis, morphological characteristics of the stenosis, diagnostic methods, intraoperative complications, as well as morbidity and mortality within 30 days of the surgical procedure.

Materials and Methods Retrospective analysis of 116 patients undergoing ICA angioplasty with a degree of stenosis $\geq$ 70% using Casper-RX stenting who underwent this procedure from April 2015 to December 2019.

Results Technical success was achieved in 99.1% of the patients. Three of them had postprocedural complications: one transient ischemic attack (TIA) and two puncture site hematomas. A cerebral protection filter was not used in only two procedures, as these consisted of dissection of the carotid. There was satisfactory recanalization and adequate accommodation of the stents in the previously stenosed arteries, with no restenosis in 99.4% of the cases.

Conclusion The endovascular treatment of extracranial carotid stenoses using the Casper-RX stent showed good applicability and efficacy. Although only two cases of thromboembolic complications occurred during the procedure, further investigation and studies on the effectiveness of this new device are needed.

Keywords
- casper stent
- double-layer stent
- carotid stenosis
- angioplasty
- stroke

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Resumo

Objetivos Identificar a taxa de sucesso na recanalização de estenose da artéria carótida interna (ACI) obtida por método endovascular quando utilizado o stent de dupla camada Casper-RX (Microvention, Inc 35 Enterprise, Aliso Viejo, California, United States of America) e identificar as principais comorbidades apresentadas pelos indivíduos com estenose de ACI, características morfológicas das estenoses, métodos utilizados para diagnósticos, ocorrência de complicações transoperatórias e a morbimortalidade nos 30 dias posteriores ao procedimento cirúrgico.

Materiais e métodos Análise retrospectiva de 116 pacientes submetidos a procedimento de angioplastia da ACI com grau de estenose $\geq$ 70%, com a utilização de stent Casper-RX, durante o período de abril de 2015 a dezembro de 2019.

Resultados O sucesso técnico foi alcançado em 99,1% dos indivíduos. Três pacientes apresentaram complicações pós procedimento, sendo um acidente encefálico transitório (AIT) e dois hematomas de sítio de punção. Em apenas dois procedimentos não se utilizou filtro de proteção cerebral devido tratar-se de dissecção carotídea. Houve satisfatória recanalização e acomodação adequada dos stents nas artérias previamente estenosadas, não havendo reestenose em 99,4% dos casos.

Conclusão O tratamento endovascular das estenoses carotídeas extracranianas com uso do stent Casper-RX demonstrou boa aplicabilidade e eficácia. Apesar de ter apresentado apenas dois casos de complicações tromboembólicas durante o procedimento, são necessárias maiores investigações e estudos sobre a eficácia deste novo dispositivo.

Palavras-chave

- stent casper
- stent de dupla camada
- estenose carotídea
- angioplastia
- AVC

Introduction

Extracranial stenosis of the internal carotid artery (ICA) accounts for between $\sim$ 10 and 15% of ischemic strokes, which is one of the main causes of death and disability in the world.[1] The advent of vascular microsurgery brought stent angioplasty as a promising alternative to ICA endarterectomy, especially for patients whose comorbidities increase their surgical risk, in cases of restenosis after procedures, and in those with previous radiation therapy of the cervical region.[2]

Stenting of the carotid artery is associated with long-term lower rates of stroke after elective treatment of individuals with significant extracranial ICA stenosis.[3] However, this technique poses a risk of intraoperative cerebral embolism due to mobilization of atherothrombotic materials after manipulation of the lesion, as well as to plaque protrusion through the expanded stent struts. For this reason, special attention has been paid to the design, material, and shape of the chosen stent.[4]

To reduce the embolic risk of the procedure, a dual-layer carotid stent model has been introduced. In addition to the self-expanding nitinol outer layer that provides support, its second micro mesh layer provides better plaque coverage while remaining flexible.[5] Short-term outcomes following the use of these devices in elective environments have proven to be promising.[6]

The Casper-RX carotid stent has the smallest area between closed cells of all carotid stents on the market. Double-layer devices have delivered greater benefits regarding atheroma plaque coverage and decreased likelihood of infarction due to the embolization of atheroma plaques.[7]

Thus, the purpose of the present article is to study carotid artery stenosis recanalization using a new model of double-layer stent, the Casper-RX, as well as to evaluate its clinical behavior in a reference center for endovascular neurosurgery in Brazil.

Methodology

Design and Sample

Retrospective study of the medical records of 116 patients undergoing angioplasty of the extracranial segment of the ICA using the Casper-RX stent from April 2015 to December 2019 in a reference center service for endovascular neurosurgery in the city of Blumenau, state of Santa Catarina, Brazil.

Inclusion and Exclusion Criteria

Symptomatic and asymptomatic patients who underwent endovascular treatment of stenosis of at least 70% of the ICA with Casper-RX stent implantation from April 2015 to December 2019 were included. Insufficient data – such as segment loss within 30 days and absence of radiological reports – were considered exclusion criteria.

Data Analysis

Categorical variables were expressed as absolute values (percentages), and quantitative variables, as means $\pm$ standard deviation (SD) or medians (interquartile range [IQR]) as appropriate. Analyses were tabulated in Microsoft Excel 2020 (Microsoft Corporation, Redmond, WA, USA) and analyzed using the SPSS Statistics for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). Device safety and therapeutic success were evaluated, as well as the rate of complications and restenosis, compared with literature data.

Variables

Epidemiological variables such as gender, age, and pre-existing comorbidities – diabetes mellitus, hypertension, dyslipidemia, smoking, and heart disease were collected. Pretreatment symptoms included headache, dizziness, ischemic stroke, and transient ischemic attack (TIA). Regarding the carotid lesion, the degree of stenosis on the affected side, laterality, treated bilaterality, presence of dissection, ulcerated plaque, and contralateral occlusion were analyzed.

Regarding the surgical procedure, the access type (femoral or axillary), immediate therapeutic success, intra- and post-operative events – from 90 days up to 6 months -, use of a cerebral protection filter, and stent diameter were studied. The overall neurological outcome of the individuals was evaluated using the 90-day modified Rankin Scale (mRS). Technical success was evaluated by carotid Doppler ultrasonography (USG) at least 6 months after the endovascular intervention. According to the degree of stenosis, patients were divided into "absent stenosis" if $< 30\%$, "residual stenosis" if the persistence was between 30 and 40%, and "late stenosis" if they presented a higher degree with onset after 6 months of follow-up. Stent occlusion was also analyzed.

The noninvasive preprocedural diagnostic methods used include magnetic resonance imaging (MRI), computed tomography (CT), magnetic resonance angiography, angiotomography, and carotid Doppler test. Regarding the invasive test, cerebral arteriography was used in all procedures during angioplasty.

Procedure

Patients undergoing endovascular intervention had atheromatous disease in the extracranial portion of the internal carotid artery, with a degree of stenosis between 70 and 99%, were symptomatic, or had been incidentally diagnosed. They were first put under sedation and total heparinization 10,000 UI, with femoral intra-arterial instillation of low osmolarity nonionic contrast through a guide catheter. Then, cerebral angiographies were performed to identify the precise site of stenosis and its degree. Brain protection filters, such as Spider FX (Medtronic, 710 Medtronic Parkway, Minneapolis, MN, United States of America), AngioGuard (Cordis 5452 Betsy Ross Dr, Santa Clara, CA, United States of America), and EmPro (Microvention, Inc 35 Enterprise, Aliso Viejo, CA, United States of America) were inserted. The filter passed through the stenosis and was then deployed. The Casper-RX stents with diameters of between 7 and 9 mm adapted to the wall, which allowed total correction of the affected arteries. After mapping and real-time radioscopy, the stents were detached. The cerebral protection filters were removed, and postoperative angiographies were performed, showing full coverage of the plaques and correct device patency. The primary endpoint was achieved with the successful placement of the device.

Antiplatelet Therapy

Double antiplatelet therapy was administered with aspirin 200 mg and clopidogrel 75 mg to all patients, from 7 days before the procedure up to 3 months after the angioplasty.

Results

Epidemiological Variables, Symptoms, and Comorbidities

The mean age of the patients was 73 (66 to 79) years old; 79% were $\geq$ 68 years old. Of the total sample, 61.2% were male. Regarding the clinical presentation, 111 (96%) were symptomatic, mainly with dizziness (59.5% of the cases), ischemic stroke (33.6%) and TIA (17.2%). The most prevalent comorbidities were arterial hypertension (90.5%), and dyslipidemia (94%) (►**Table 1**).

Table 1 Epidemiological and clinical characteristics

Characteristic	All cases $n = 116$
Age (years old) (mean [IQR])	73 (66–79)
$\geq$ 68 years old (*n* [%])	79 (68.1)
Gender (*n* [%])	
Male	71 (61.2)
Female	45 (38.8)
Clinically documented symptoms (*n* [%])	
Dizziness	69 (59.5)
Headache	7 (6)
Ischemic stroke	39 (33.6)
Transient ischemic attack	20 (17.2)
Comorbidities (*n* [%])	
Arterial hypertension	105 (90.5)
Diabetes mellitus	43 (37.1)
Current smoker	29 (25)
Dyslipidemia	109 (94)
Cardiopathy	29 (25)
Stenosis in arteriography/Doppler	
Degree (%), mean (IQR)	80 (70–92.5)
Ulceration (*n* [%])	112 (96.5)
Carotid dissection (*n* [%])	4 (3.4)
Side of occlusion (*n* [%])	
Left	62 (53.5)
Right	54 (46.5)
Contralateral internal carotid artery (*n* [%])	
Occlusion	10 (8.6)
Previous treatment	10 (8.6)
Neuroimaging before procedure (*n* [%])	
MRI	21 (18.1)
CT scan	27 (23.3)
Arteriography	116 (100)
AngioMRI	11 (9.4)
Angiotomography	50 (43.1)
Carotid Doppler	75 (64.6)

Abbreviations: CT, computed tomography; IQR, interquartile range; MRI, magnetic resonance imaging.

Preprocedural Stenosis Characteristics

Arteriography was the neuroimaging test of choice in all patients, allowing preoperative assessment of the degree of stenosis, of the presence of ulcerated plaque, and of dissecting pseudoaneurysm in the carotid arteries. Carotid Doppler test was performed in 75 individuals (64.6%). Other imaging tests used are described in ►**Table 1**. The average duration of the procedure was ~ 30 minutes.

Technical Success and Intraoperative Complications

The average diameter of the implanted devices was 8.0 mm, with no need for additional stenting for complete coverage of the plaque. The surgical access was through the femoral artery in all patients. In 114 patients (98.3%), a cerebral protection filter was used during the procedure, mostly AngioGuard (81%), EmPro (13.8%), and Spider (2.6%). There were neither intra- nor postoperative complications in the two cases performed without a cerebral protection filter; therapeutic success was achieved, as these were dissection cases.

In 113 patients (97.4%), Casper stents were successfully placed in the carotid artery. During the procedure, 1 patient (0.8%) underwent a dissection of the internal iliac artery. One patient (0.8%) had encephalic thromboembolic complications, which were promptly identified and treated with stenting and recanalization of the affected arterial segment. Another patient (0.8%), who had a critical stenosis of 99%, with calcified plaque and a kinking of the left internal carotid artery, had a rupture of the artery in the distal portion of the stent during balloon angioplasty; this was the only case of death during the procedure.

Postoperative Complications

In 97.4% of the cases, there were no complications after the surgical procedure (113/116). Among the events observed, 1 patient had TIA (0.8%) and 2 had a hematoma at the puncture site (1.6%), both treated conservatively.

There were 3 deaths, at 12, 18, and 19 days after the procedure. There was no causal relationship between these late deaths and the endovascular intervention. This outcome is attributed to the intrinsic complications of the initial ischemic stroke – infectious disorders such as aspiration pneumonia and evolution toward multiple organ failure.

Restenosis Control Follow-up and Modified Rankin Scale

Throughout the clinical follow-up, a total of 115 patients (99.1%) remained stenosis-free (< 30%) on imaging, whereas 1 patient (0.8%) had residual stenosis (between 30 and 40%). Up to the last evaluations, no patient developed carotid restenosis or device occlusion after implantation of the Casper stent.

►**Table 2** shows the mRS after 90 days of follow-up. The mean mRS value after angioplasty was 0.38, which points to the existence of reduced deficits in the functional evolution of the studied individuals.

Table 2 Outcomes and neuroimaging

Characteristic	All cases $n = 116$
Immediate procedure success (*n* [%])	115 (99.1)
Transprocedural events (*n* [%])	
None	113 (97.4)
Dissection of the internal iliac artery	1 (0.8)
Thromboembolic complication	1 (0.8)
Vascular rupture and death	1 (0.8)
Technical success (*n* [%])	
No stenosis (< 30%)	115 (99.1)
Residual stenosis (30-40%)	1 (0.8)
Late restenosis	0 (0)
Stent occlusion (*n* [%])	0 (0)
Post procedural events (*n* [%])	
None	113 (97.4)
Minor stroke	1 (0.8)
Groin hematoma at the puncture site	2 (1.6)
mRS after 3 months (mean ± SD)	0.38 ± 1.23
0 (*n* [%])	105 (90.5)
1 (*n* [%])	0 (0)
2 (*n* [%])	2 (1.7)
4 (*n* [%])	6 (5.2)
5 (*n* [%])	2 (1.7)
6 (*n* [%])	1 (0.8)
Late death (*n* [%])	3 ()

Abbreviations: mRS, modified Rankin scale; SD, Standard deviation.

Discussion

Advances in neurointerventional techniques and the emergence of new endovascular materials have made stent angioplasty a safe and effective alternative for the treatment of carotid stenosis. Factors contributing to this evolution range from greater operator experience and selection of candidates for intervention to better device design.[2] The present study reports the outcome of a case series performed in a reference center including 116 patients with asymptomatic (4%) and symptomatic (96%) carotid stenosis to evaluate the performance of the Casper-RX stent. As a primary endpoint, device placement was successfully completed in 97.4% of the cases, with no immediate intercurrences.

For a long time, arterial endarterectomy (AE) was the recommended therapy for carotid artery stenosis.[8] Currently, carotid angioplasty is increasingly indicated. Both methods achieve the same revascularization success rates, a similar incidence of complications and of stroke in the short- and long-term.[9] Patients < 70 years old, as well as the symptomatic ones with severe stenosis and comorbidities that put them at high surgical risk, seem to benefit from angioplasty treatment.[10,11] The current literature still favors

endarterectomy as being overall safer and more effective.[12] However, there is still much to learn about the feasibility and safety of stent systems used today.

A growing number of studies regarding this device supports its good performance and promising results in selected individuals. Mutzenbach et al,,[13] in a study of 138 patients who underwent angioplasty with Casper stenting, achieved full success in all cases, with no intraoperative technical failure or adverse neurological events reported within 90 days. Only 14.5% of the cases had residual stenosis (between 30 and 40%) after the procedure. In the present study, were also found a high rate of surgical success and few intraoperative complications when using Casper stents. After 90 days of follow-up, the neurological and functional outcome was favorable in most cases, with no deficits in 93.1% of the individuals assessed using the mRS scale. The rate of residual stenosis in the study population was even lower (0.8%), and no cases of late restenosis or stent occlusion were recorded, which speaks in favor of the efficacy of the implanted device. The contribution of brain protection filters and of antiplatelet therapy for these outcomes should be considered.

In another study, in a sample of 110 severe carotid stenosis patients, the implantation of Casper stents combined with a distal embolic protection device was shown to be safe and to lead to a lower rate of ischemic lesions on diffusion-weighted MRI when compared with other stents, especially the conventional single-layer ones.[14] Similarly, a reduced number of thromboembolic complications was observed in this study. During stent implantation, there was only one thromboembolic event, which was promptly reversed and did not cause any permanent neurological deficits. Throughout the follow-up of up to 6 months after the procedure, there was one case of TIA. Such an outcome may be attributed to the double nitinol layer and micro mesh, as well as to the closed-cell design, of the Casper stent.[4] The other complications – late deaths, vascular rupture, internal iliac artery dissection, and puncture site hematoma – were not related to the device itself, but rather to the inherent risk of the procedure and to the underlying diseases of the patient.

In a study with a smaller sample size, Ozpeynirci et al.[15] analyzed 29 patients who underwent ICA angioplasty using a Casper-RX stent, of whom 78.6% were male with a mean age was 71.7 years old. The authors report 6 adverse events in the perioperative period, including 1 stent occlusion (3.4%), 2 patients with type 2 parenchymal hematoma (6.8%), and 3 other patients (10.3%) with a massive cerebral infarction area not related to a worse prognosis or to stent occlusion. No thromboembolic events were observed intraoperatively.

Conclusion

The outcomes achieved in the present study corroborate the efficacy and safety of the use of Casper-RX stents to treat ICA stenosis, as previously demonstrated in the literature. In this series, technical success was achieved, with good clinical repercussion and a low complication rate, considering the sample size. However, long-term follow-up is needed to better evaluate this new device, as well as comparative studies with other closed-cell stents.

Ethics

The present study was conducted according to the Standard Item Protocol: Recommendations for Interventions (SPIRIT) and was approved by the local ethics committee under CAEE 31685320.0.0000.5370. The Informed Consent Form (ICF) was presented and made available to all individuals in the study.

Conflict of Interests

The authors have no conflict of interests to declare.

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Differential Diagnoses of Diseases Involving the Extrinsic Ocular Musculature – A Pictorial Essay*

*Diagnóstico diferencial das doenças que envolvem a musculatura ocular extrínseca – Um ensaio pictórico**

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Abstract

Introduction There are some inflammatory, infectious, and neoplastic diseases affecting the extrinsic orbital musculature (EOM) that present with pain, decreased visual acuity, and proptosis. Imaging is fundamental to the differential diagnoses of these diseases with similar clinical presentations. The present case series report has as main objective to illustrate and discuss the main pathologies that affect the orbit.

Material and Methods The present series of cases discusses the main pathologies that can affect the extraocular musculature that can be characterized by computed tomography (CT) or magnetic resonance imaging (MRI) using cases from our institution.

Results and Discussion The present study compiled several cases of ophthalmopathy from our institution to illustrate and address some of these pathologies, such as orbital lymphoma, Grave disease, metastases, periorbital cellulitis, and idiopathic orbital inflammatory syndrome. The diseases are discussed according to the presentation of clinical cases with emphasis on the main imaging findings of each pathology.

Conclusion Computed tomography and MRI can help in the diagnosis and follow-up of the diseases that affect the EOM. We must be conversant with the main characteristics of the pathologies presented in the present case series report, since such findings together with clinical data can confirm the diagnosis of these diseases or at least help to narrow the differential diagnoses.

Keywords

- graves ophthalmopathy
- orbital lymphoma
- orbital pseudotumor
- orbital cellulitis
- sarcoidosis

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Resumo

Introdução Existem algumas doenças inflamatórias, infecciosas e neoplásicas que afetam a musculatura orbitária extrínseca que se apresentam com dor, diminuição da acuidade visual e proptose. Exames de imagem são fundamentais para o diagnóstico diferencial dessas doenças com apresentações clínicas semelhantes. A presente série de casos tem como principal objetivo ilustrar e discutir as principais patologias que afetam a órbita.

Material e métodos A presente série de casos discute as principais patologias que podem afetar a musculatura extraocular passíveis de caracterização por estudo de tomografia computadorizada (TC) ou de ressonância magnética (RM) utilizando casos próprios da nossa instituição.

Resultados e discussão O presente estudo compilou diversos casos de oftalmopatia da nossa instituição para ilustrar e abordar algumas destas patologias, como linfoma orbital, doença de Grave, metástases, celulite periorbital e síndrome inflamatória orbital idiopática. As doenças são discutidas de acordo com a apresentação dos casos clínicos, dando-se ênfase nos principais achados de imagem de cada patologia.

Conclusão A TC e a RM auxiliam no diagnóstico e no acompanhamento das doenças que acometem a musculatura ocular extrínseca. Deve-se estar familiarizado com as principais características das patologias apresentadas na presente série de casos, uma vez que tais achados, juntamente com os dados clínicos, podem confirmar o diagnóstico destas doenças ou, pelo menos, ajudar a estreitar os diagnósticos diferenciais.

Palavras-chave

- orbitopatia de graves
- linfoma orbital
- pseudotumor orbital
- celulite orbital
- sarcoidose

Introduction

The extraocular muscles (EOMs) occupy the retrobulbar space and are composed of six muscles: the superior, inferior, medial, and lateral recti and the superior and inferior oblique muscles.[1,2] They may be affected in different systemic and local diseases.

Except for the superior oblique and the lateral rectus, which are innervated by the trochlear nerve and the abducens nerve respectively, the other EOMs are innervated by the oculomotor nerve; in this way, the clinical presentation of patients will depend on the muscle or nerve affected by the disease.[1,2]

Pathologies that affect the retrobulbar space may have very similar clinical presentations; for example, for orbital inflammatory syndrome (OIS), orbital lymphoid lesions, and orbital cellulitis,[3–5] both computed tomography (CT) and/or magnetic resonance imaging (MRI) are required to make a definite diagnosis or to assist in the indication and orientation of biopsies.

The present case series discusses the main pathologies that can affect the EOMs and that appear in the daily practice.

Objectives

The present series of cases aims to review the main orbital diseases that affect the extrinsic musculature of the orbit, illustrating with cases of our institution.

Material and Methods

The present study was approved by the ethics committee of the Hospital Universitário Cassiano Antônio Moraes (HUCAM, in the Portuguese acronym).

Patients with classic presentations of the main diseases that affect the extrinsic musculature of the orbit who underwent CT and/or MRI in the HUCAM imaging sector were selected.

A literature review was carried out using the PubMed and SciELO databases to elaborate the discussions of the cases.

Results and Discussion

Orbital Cellulitis

Seen more commonly in children and young adults, orbital cellulitis can be divided into five stages: type I, inflammatory edema; type II, diffuse orbital cellulitis; type III, subperiosteal abscess; type IV, orbital abscess; type V, cavernous sinus thrombosis.[5–7]

The differentiation between the infection limited to the preseptal tissue and the infection that affects the postseptal tissue is fundamental because patients with infection of the preseptal tissue alone can be treated in an outpatient setting, whereas patients with postseptal tissue involvement should be admitted for intravenous antibiotic therapy and drainage when indicated.[1,5,6,8,9]

Patients with orbital cellulitis usually present with edema and eyelid erythema, pain, proptosis, and limitation of ocular movements.[7]

In MRI, the collection of cellulite presents as isointense to EOM and hypointense to the orbital fat in T1, and hyperintense in T2, with peripheral and annular impregnation by the contrast enhancement medium (►**Fig. 1**).[3,5,10] In the presence of an abscess, diffusion restriction is observed, which may aid in its identification in the absence of contrast enhancement.[11]

In CT, the abscess presents as hypodense, with orbital fat densification and peripheral contrast enhancement.[9,10] When the etiologic agent is fungal or bacterial, the cellulite presents in a similar way in both cases on radiographic examination; in these cases, mass effect, bone erosion, and calcifications can be observed in the CT image. However, in MRI, the fungal lesion can be hypointense in T2 due to the impregnation of paramagnetic substances and free radicals released by fungi.[10]

In cases in which cavernous sinus thrombosis (type V) occurs, the "black turbinate sign" may be an early predictor of mucormycosis.[12]

Idiopathic Orbital Inflammatory Syndrome

Also known as inflammatory pseudotumor, its etiology is not yet defined, and its diagnosis is one of exclusion.[1,13–16] Unilateral presentation is most common in adults, and although rare, bilateral occurrence is more prevalent in the pediatric group.[17] Treatment is done with corticosteroid therapy.[15]

The most typical clinical presentation is acute pain, edema, and periorbital erythema, with or without reduction of visual acuity and diplopia.[14,16] It can be divided into five subgroups: lacrimal, anterior, posterior, diffuse, and myositic pseudotumor.[16,18]

It may present as a focal intraorbital lesion or with infiltrative features similar to lymphoma. In MRI, it is hypointense in T1 and T2 with contrast enhancement, evidencing inflammation of the muscles, tendons, and adjacent fat (►**Fig. 2**).[1,13,16]

Orbital myositis, one of the subtypes of idiopathic orbital inflammatory syndrome (IOIS), may involve one or two EOMs (the inferior rectus being the most affected); it is typically unilateral and affects tendinous insertions (unlike orbital involvement due to thyroid disease, which usually spares the tendinous insertions).[1,16]

One variant is the Tolosa-Hunt syndrome, an idiopathic syndrome that is characterized by inflammation of the superior orbital fissure and/or of the cavernous sinus, with consequent recurrent painful ophthalmoplegia, which responds to corticosteroid therapy.[13,19,20] In MRI, it presents as hypointense lesions in T1 and T2 in the cavernous sinus, the orbital apex, or the superior orbital fissure with impregnation by contrast enhancement medium.[13,20] Computed tomography findings are not specific but may aid in differential diagnoses. It may present asymmetric enlargement of the cavernous sinus and nodular enhancement in the prepontine cisterna, the cavernous sinus, and the orbital apex by the contrast medium.[17,19]

Several pathologies may manifest as an orbital pseudotumor, such as IgG4-related disease, idiopathic hypereosinophilic syndrome (HES), sarcoidosis, granulomatosis with polyangiitis (GPA), and Churg-Strauss syndrome. The IgG4-related orbital pseudotumor has an estimated incidence of

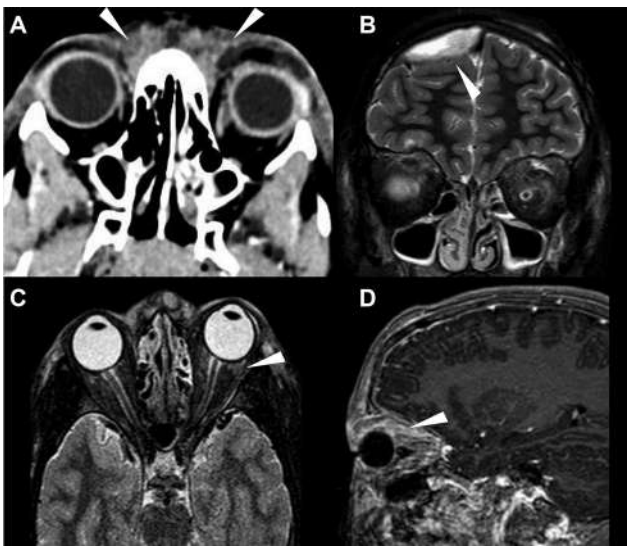

Fig. 1 Orbital cellulitis. A – Computed tomography without contrast: Thickening and heterogeneity of bilateral periorbital soft tissue with extension of the nasal and malar region (arrows). B, C and D – T2WI and T1 postcontrast show preseptal and postseptal compartments. The inflammatory process involves the orbital musculature (arrows). Extradural empyema is also noted in the right frontal convexity (arrow in b).

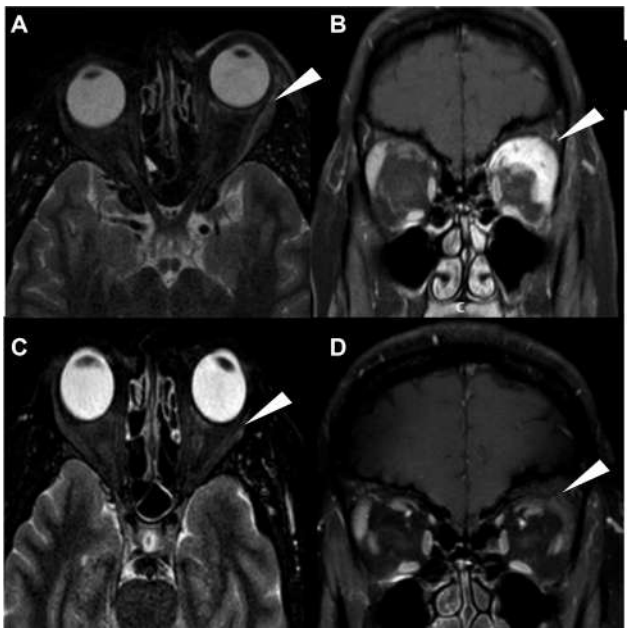

Fig. 2 Orbital inflammatory pseudotumor. A and B – T2-WI and T1 postcontrast show an extraconal expansive lesion in the superolateral aspect of the left orbit, involving the superior and lateral rectus complex surrounding the lacrimal gland, with a low T2-WI sign and with an intense homogeneous contrast enhancement (arrows). C and D – T2-WI and T1 postcontrast after 1 year showing resolution after corticoid treatment

between 5 and 20% among inflammatory orbital lesions[21] and has predilection for the lacrimal gland and nerves.[21,22] The HES is characterized by prolonged eosinophilia with no definite cause, leading to visceral damage.[23]

Orbital involvement in patients with systemic sarcoidosis is not rare. In these cases, involvement of the lacrimal gland, of the optic nerve, and of soft tissues may occur, with anterior uveitis being the most common manifestation, followed by dacryoadenitis.[24,25] Although uncommon, patients may develop strabismus due to involvement of bilateral EOMs, usually with dacryoadenitis.[26,27]

Granulomatosis with polyangiitis (GPA) typically affects the kidneys and lungs, but up to 60% of the patients may present with orbital involvement including the optic nerve, and it may be the first or only manifestation of the disease.[28] Clinically, it can manifest with pain, erythema, conjunctival injection, limited extraocular muscle movements, and vision loss.[28,29]

The imaging findings are nonspecific, presenting more commonly in CT as an infiltrative lesion of the orbit with adjacent fat obliteration and, in some cases, sclerosis and bone erosion with or without sinus pathology. In MRI, it usually presents as a hypointense lesion in T2 with contrast enhancement.[28,29]

Churg-Strauss syndrome (CSS) is a systemic vasculitis characterized by hypereosinophilia, asthma, and allergic rhinitis. Orbital manifestations are rare, but when present, may appear as an inflamed mass or inflammation of the orbital structures.[30]

Orbital Lymphoma

Orbital lymphoma corresponds to up to ~ 12% of all orbital tumor lesions and is typically non-Hodgkin lymphoma. It can occur anywhere in the orbit.[1,31]

The EOMs lymphomas affect the muscular tendons (unlike thyroid ophthalmopathies), and the most common location of involvement is the superolateral quadrant, followed by the superomedial quadrant of the orbit.[32]

Clinically, the patient may present with proptosis, palpable mass, and reduction of ocular mobility, with pain being an uncommon finding (unlike in cases of pseudotumor).[16,33]

Extraocular muscles lymphomas are hyperdense expansive lesions in CT (►**Fig. 3**) and have moderate contrast enhancement; it is difficult to differentiate them from orbital myositis. A study published in 2003 observed that lymphomas show a decrease in CT density with dual-phase contrast-enhancement protocol, whereas orbital myositis shows an increased density in the late phases.[32,33]

In MRI, lymphomas are hypointense in T1 and hypo- to isointense in T2 with a homogeneous appearance on contrast enhancement.[1,34]

Orbital Metastasis

Orbital metastasis represents 2% of all orbital lesions, with the breast being the most common primary site. The EOM is most commonly affected by orbital metastases from cutaneous melanoma.[1,31,35,36]

Generally, the symptoms are related to mass effect. A great majority is unilateral[1,36,37] and can range from well-defined focal lesions to infiltrative lesions.[36]

In the case of an already established metastatic cancer, biopsy of the orbital lesion is often not indicated.[36]

Breast metastases often present with diffuse and irregular growth along the rectus muscles and fascial planes.[38]

Computed tomography assists mainly in the diagnosis of prostatic metastases due to its predilection for bone with development of osteoblastic orbital metastases (►**Fig. 4**).[37]

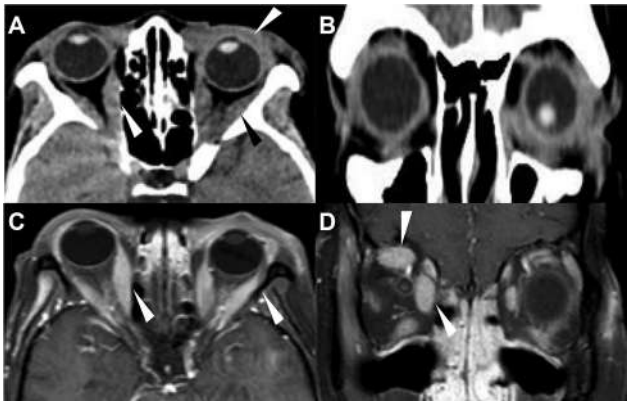

Fig. 3 Orbital lymphoma. A and B – Computed tomography without contrast shows left eyelid involvement with thickening of the bilateral extrinsic musculature (arrows). C and D – T1 postcontrast shows intense homogeneous contrast enhancement of the bilateral extrinsic musculature (arrows).

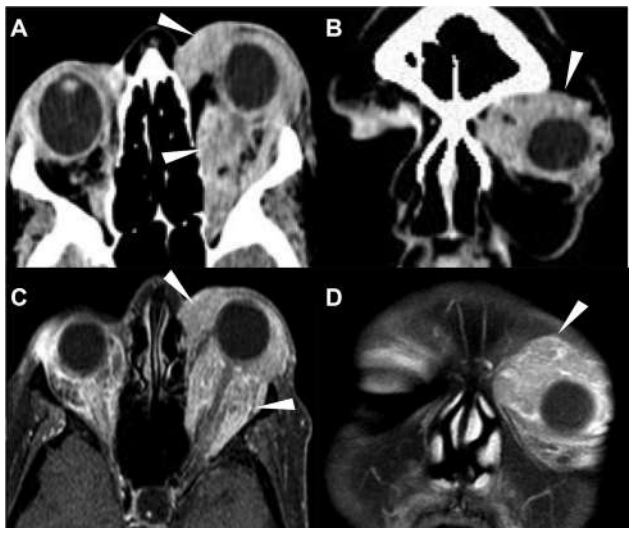

Fig. 4 Orbital metastasis in computed tomography. A and B – Computed tomography without contrast shows thickening and densification of the periorbital soft tissues in the left orbit, with extension to the intraconal fat (arrows). C and D – Mass with left orbital infiltrative aspect showing intense enhancement after contrast, with intra- and extraconal components infiltrating the extrinsic musculature and involving the greasy planes and optic nerve, determining reduction of the caliber of the same and proptosis (arrows).

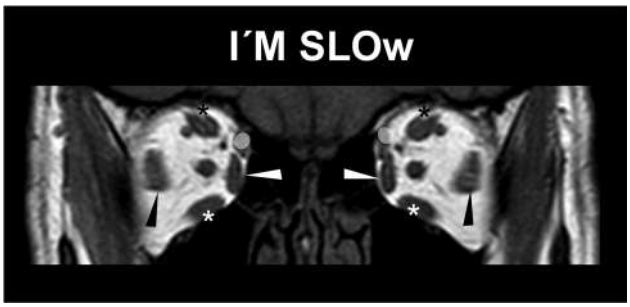

Fig. 5 Mnemonic "I'M SLOW" Magnetic resonance imaging showing the inferior rectus (white asterisk), the medial rectus (white arrow), the superior rectus (black asterisk), the superior oblique (circle), and the lateral rectus (black arrow).

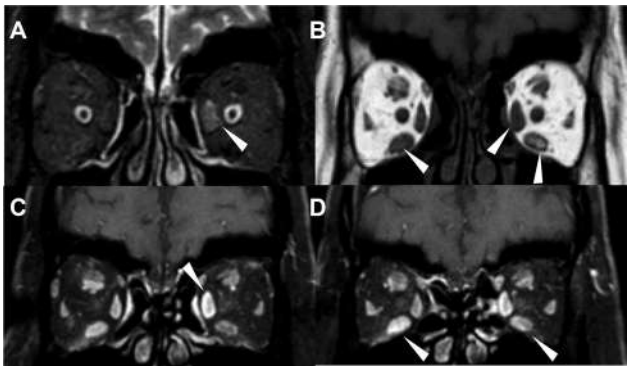

Fig. 6 Thyroid ophthalmopathy. A and B – T2-WI and T1-WI show thickening of the extrinsic ocular musculature, especially of the inferior and medial recti, associated with an increase in the fat component (arrows). C and D – T1 postcontrast shows an intense homogeneous contrast enhancement (arrows).

Signal intensity in MRI exhibits some degree of contrast enhancement and varies depending on the primary site of metastasis.[39]

Thyroid Ophthalmopathy

Graves ophthalmopathy is the main cause of proptosis in adults. It is usually bilateral and with symmetrical involvement of EOMs. The muscle most commonly involved is the inferior rectus, followed by the medial, superior, and lateral recti, usually known by the mnemonic "I'M SLOW" (►**Fig. 5**).[1,32]

It is more commonly seen in patients with hyperthyroidism but can also be found in patients with hypothyroidism or normal thyroid function.[1,40]

Computed tomography and MRI examinations evidenced thickening of the EOMs with relative preservation of the tendon insertions, increase of retro-ocular orbital fat, and may present contrast enhancement. Muscle bellies are typically hypodense in CT and hyperintense in T2 (►**Fig. 6**).[1,40,41]

Miscellaneous

Less common diseases, such as Crohn disease, Behçet disease, rheumatoid arthritis, Lyme disease, and systemic lupus erythematosus can also affect the extrinsic ocular musculature.

Patients with Crohn disease may exhibit ocular manifestations, mainly episcleritis and uveitis and, less commonly, orbital myositis.[42]

The ocular involvement in Behçet disease is already well established in the literature and is usually considered when uveitis and vasculitis occur simultaneously. Patients with Behçet disease may also present with orbital myositis, although there are few reports on its occurrence.[43]

Rheumatoid arthritis, systemic lupus erythematosus, and Lyme disease may also manifest with orbital myositis.[44–46] ►**Table 1** summarizes the main imaging features of the pathologies mentioned in this iconographic essay.

Table 1 Main imaging features

	Clinics	Computed tomography	Magnetic resonance imaging
Cellulitis	Edema, pain, and proptosis	Abscess presents as hypodense with orbital fat densification, and peripheral impregnation	T1-isointense T2- hyperintense peripheral and annular impregnation
IOIS	Acute pain, edema, and erythema	Focal or infiltrative with tendon thickening	T1- hypointense T2- hypointense Contrast enhancement - muscle, tendons and fat.
Lymphoma	Proptosis, palpable mass	Moderate contrast enhancement	T1-hypointense T2- hypo/isointense homogeneous enhancement
Metastasis	Symptoms related to mass effect	Varies	T1-varies T2-varies some degree of contrast enhancement
Thyroid ophthalmopathy	Bilateral, symmetrical involvement of EOM	Thickening of the EOM with relative preservation of the tendon insertions. Muscle bellies are hypodense.	T2- Muscle bellies are hyperintense.

Abbreviations: EOM, extrinsic orbital musculature.

Conclusion

Computed tomography and MRI help in the diagnosis and follow-up of the diseases that affect the EOMs. We must be conversant with the main characteristics of the pathologies presented in the present case series since such findings together with clinical data can confirm the diagnosis of these diseases or at least help to narrow the differential diagnoses.

Ethics Approval and Consent to Participate

Ethical approval was provided by the HUCAM Institutional Review Board (CAAE - 08119819.8.0000.5071), Brazil.

Availability of Data and Materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request. All data generated or analyzed during the present study are included in the present published article (and its supplementary information files).

Contributions of the Authors

Santana L. M. and Rosa-Junior M analyzed and interpreted the patient data regarding CT and MRI and were major contributors in the writing of the manuscript. Martins L. A. analyzed and interpreted the patient data regarding CT and MRI and made the figure slides. All authors read and approved the final manuscript.

Conflict of Interests

The authors have no conflict of interests to declare.

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Epidemiological Profile of 96 Intracranial Tumors Treated in a Single Reference Center

Perfil epidemiológico de 96 tumores intracranianos tratados em um único centro de referência

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Abstract

Objectives The present study aims to categorize the prevalence of intracranial tumors surgically treated at the neurosurgery service of Hospital Universitário Evangélico Mackenzie (HUEM) between 2016 and 2018.

Material and Methods This survey included patients surgically treated due to primary or metastatic intracranial neoplasia between 2016 and 2018 at a referral center in the city of Curitiba. These patients were analyzed for epidemiological, histopathological, and topographic data, and they underwent an assessment of the outcome at the time of hospital discharge.

Results A total of 96 patients met the inclusion criteria. The most prevalent tumor was the glioma, with 39.6% of the sample, with glioblastoma being the most prevalent histological type. Brain metastases and meningiomas represented, respectively, 21.9% and 18.8% of the total. There was a predominance of supratentorial and intra-axial tumors in our sample.

Conclusion Glioma was the most commonly found tumor, directly associated with high morbidity and mortality. The development of new and more effective drugs with action directed at the molecular level of intracranial tumors may be the path to a longer survival and improvement in the quality of life of these patients.

Keywords
- brain neoplasm
- primary brain neoplasms
- epidemiology
- brain metastasis

Resumo

Objetivos O presente estudo tem como objetivo levantar a prevalência dos tumores intracranianos abordados cirurgicamente pelo Serviço de Neurocirurgia do Hospital Universitário Evangélico Mackenzie (HUEM) entre 2016 e 2018.

Material e Métodos Foram selecionados pacientes com diagnóstico de neoplasia intracraniana primária ou metastática no intervalo de 2016 a 2018 tratados cirurgicamente em um centro de referência na cidade de Curitiba. Esses pacientes foram analisados quanto a dados epidemiológicos, histopatológicos, e topográficos e foram ainda submetidos a uma avaliação do desfecho no momento da alta hospitalar.

Palavras-chave
- tumor cerebral
- tumor cerebral primário
- epidemiologia
- metástase cerebral

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Resultados O total de 96 pacientes preencheram os critérios de inclusão. O tumor mais prevalente foi o glioma, com 39,6% da amostra, sendo o glioblastoma o tipo histológico mais prevalente. As metástases cerebrais e os meningiomas representaram, respectivamente, 21,9% e 18,8% do total de pacientes. Houve um predomínio de tumores supratentotoriais e intra-axiais em nossa amostra.

Conclusão O glioma foi o tumor mais encontrado, associado à elevada morbimortalidade. O desenvolvimento de fármacos novos e mais efetivos com ação direcionada ao nível molecular dos tumores intracranianos pode ser o caminho para uma maior sobrevida e melhora da qualidade de vida desses pacientes.

Introduction

Tumors of the central nervous system (CNS) represent ~ 2% of all tumors that affect adults and 2.4% of all cancer deaths annually.[1,2] The incidence rate of primary brain tumors is 10.8 per 100,000 person-years,[3] while the incidence of brain metastases is estimated at 11 in every 100,000 individuals in the population.[2] They are a significant cause of cancer morbidity and mortality, especially in children and young adults, in whom they respectively account for ~ 30% and 20% of cancer deaths.[4] An increase in the incidence of CNS tumors has been observed in recent decades, especially among most advanced age groups. This is due to several causal factors, especially the improvement in diagnostic imaging techniques.[5]

As proposed by the World Health Organization (WHO), CNS tumors are divided into grade I to grade IV, in view of the histology and architectural pattern of primary lesions. There are other forms of classification that evaluate tumors using immunohistochemistry, cytogenetics, and molecular biology techniques.[6] The determining factors in the prognosis of brain tumors are the type of the tumor, its histological grade, location, age of the patient, and status of Karnofsky performance. In the case of metastases, the primary tumor location, sensitivity to therapy, and the number of lesions in the CNS are added.[7]

According to the Central Brain Tumor Registry of the United States (CBTRUS), from tumors diagnosed between 2007 and 2011, meningiomas were the most frequently reported ones and the most common brain tumors in adults (36%).[8] The incidence of meningioma increases with age and is twice as common in women as in men. The majority of meningiomas are benign (grade I), followed by 5 to 20% atypical (grade II), and 1 to 3% malignant type (grade III). Gliomas are the second most frequent tumor (28%), and approximately half of them (45.6%) are glioblastomas. Grade I glioma (pilocytic astrocytoma) is more common in children and young adults while grade II (oligodendroglioma) glioma has a peak incidence between the 3rd and 4th decade of life, and the incidence of glioma malignancy increases with age. Pituitary tumors, on the other hand, are the third most common type of tumor in adults, observed mainly in women, with an increase in age-related incidence (peak 7th decade), and the majority being benign adenomas, usually asymptomatic and diagnosed incidentally. Meningiomas are also tumors that can be discovered in a asymptomatic presentation as well.

Approximately 1 in 2,000 children are diagnosed with a brain tumor by the age of 14 in the United States according to the CBTRUS. Brain tumors are the most common solid tumors, and they are responsible for the most cancer deaths in children.[9] Approximately half of pediatric tumors are gliomas, mostly pilocytic astrocytoma.

Compared with other cancers, brain tumor has a lower incidence but a huge oncological and neurosurgical standing due to its high rates of morbidity and mortality, complications, and the presence of metastases. There is also a disproportionate number of deaths and sequelae compared with other types of cancer, which makes intracranial tumors an important public health problem.

Objectives

The present study aimed to conduct a survey of intracranial neoplasms surgically treated at a referral center over a period of 3 years (2016–2018) at a University Hospital located in Brazil's south that serves predominantly the Unified Health System to raise the epidemiological profile of these tumors. The secondary objective is to describe the functional outcome of these patients after the surgical treatment.

Material and Methods

The ethics committee of Faculdade Evangélica Mackenzie do Paraná authorized the research under protocol number 17991119.1.0000.0103. This present study consists on a retrospective cohort which included all patients surgically treated in a 3-year interval (2016–2018) at the neurosurgery service of Hospital Universitário Evangélico Mackenzie (HUEM) with initial diagnosis of primary or metastatic intracranial tumor. Patients whose medical records were lacking anatomopathological data were transferred to other services, denied surgery or had no operative treatment were excluded from this series.

The analyzed patients' data were epidemiological criteria were sex and age, histopathological and topographic placement of the tumor. The patients outcome was analyzed throught the patients work capacity and autonomy. Those evalutions were performed at the hospital discharge.

Results

A total of 96 patients were included in this study, 46 men (48%) and 50 women (52%).

►**Table 1** shows the distribution of patients' gender and the histopathological types of intracranial tumors. There was an equal number of men and women treated for gliomas, meningiomas, and miscellany tumors (chordomas, craniopharyngiomas, glomus jugulare, medulloblastomas, neuroblastoma and paragangliomas) in this series.

Gliomas were the most prevalent type of tumor, totalizing 38 (39.6%) out of the 96 patients. Glioblastoma was the most found glioma, identified in 27 patients (71%), followed by diffuse astrocytoma, anaplastic astrocytoma, and oligodendroglioma with 6 (15.7%), 3 (7.9%), and 2 cases (5.4%), respectively.

When analyzing the topography of gliomas, supratentorial tumors were the most frequent, with 12 located in the temporal lobe (31.6%), 11 in the parietal lobe (28.9%), 10 in the frontal lobe (26.3%), 2 in the basal ganglia (5.3%), and 2 in the frontotemporal region (5.3%). Only 1 glioma was in the posterior fossa (2.6%).

Brain metastases were second in terms of the prevalence of tumors in the CNS in our study (21.9%), presenting more often in women (61.9%) in this series. Breast cancer metastasis accounted for ⅓ of the total of metastases, and representing the most frequent primary location of cancer with

Table 1 Epidemiological and histopathological analysis of the tumors

Gliomas	Number of patients (n)	Men (n)	Woman (n)	Age average (years) ± SD	Most prevalent location
Glioblastoma	27	15	12	59.7 ± 10.92	Temporo-parietal
Diffuse astrocytoma	6	3	3	54 ± 10.75	Frontal
Anaplastic astrocytoma	3	0	3	62.3 ± 2.88	Temporal
Oligodendroglioma	2	1	1	50.5 ± 2.12	Frontal
Metastasis source					
Breast	7	0	7	54.42 ± 10.96	Frontal
Lung	5	3	2	61.8 ± 12.67	Parietal
Melanoma	4	1	3	46 ± 21	Posterior fossa
Unknown	3	2	1	60.66 ± 13.50	Frontal
Colon	1	0	1	59 ± 0	Temporal
Kidney	1	1	0	77 ± 0	Parietal
Meningiomas (location)					
Convexity	9	4	5	48.3 ± 17.10	–
Parafalcine	3	2	1	64 ± 1.42	–
Olfactory groove	2	1	1	47.5 ± 4.94	–
Sphenoid wing	2	1	1	63 ± 14.14	–
Parasselar	1	0	1	51 ± 0	–
Petroclival	1	1	0	44 ± 0	–
Central nervous system glands					
Pituitary macroadenoma	4	2	2	65 ± 8.97	Sella turcica
Pituitary microadenoma	2	1	1	54.5 ± 10.60	Sella turcica
Pineal disgerminoma	1	1	0	24 ± 0	Pineal region
Miscellany					
Neuroblastoma	3	3	0	37 ± 21.93	Frontal
Glomus jugulare	3	0	3	36.67 ± 13.05	Jugular foramen
Craniopharyngioma	2	1	1	36.5 ± 13.5	Sella turcica
Chordoma	1	1	0	51 ± 0	Clivus
Medulloblastoma	1	1	0	31 ± 0	4th ventricle
Paraganglioma	1	1	0	27 ± 0	Jugular foramen
Osteoid osteoma	1	0	1	18 ± 0	Parietal
Total	96	46	50		

Abbreviation: SD, standard deviation.

metastasis to the CNS, followed by lung cancer (23.8%), and melanoma (19%). The supratentorial compartment was the most affected by brain metastasis.

Out of the 96 patients, 6 had a pituitary adenoma (⅔were microadenomas and were treated due to hormonal production), and one was a pineal disgerminoma.

Miscellany tumors grouped 12 tumors which included neuroblastomas, glomus jugulare, craniopharyngiomas, choromas, medulloblastomas, paragangliomas, and an osteoid osteoma. The most frequent tumors in this group were the glomus jugulare and neuroblastomas—with three tumors each. Two craniopharyngiomas were treated in this period, while only one chordoma, medulloblastoma, and paranganglioma.

The meningiomas represented 18.8% of the 96 intracranial tumors, totalizing 18 tumors. The most frequent location was the hemisphere convexity, representing 50%. There were three cases of parafalcine meningioma, and two cases of sphenoid wing and two cases of olfactory groove. Only one case of petroclival meningioma and parasellar meningioma were reported in this series.

►**Table 2** evidences that brain metastasis had the worst outcomes, followed by the gliomas. The meningiomas patients who passed away died due to cerebrospinal fluid (CSF) leak followed by meningitis, an usual postoperatative complication of skull base meningiomas.

Discussion

The most common pediatric intracranial tumors are usually represented by posterior fossa tumors and low-grade gliomas. The CNS represents the most frequent solid neoplasm location in this group. In this sample, the youngest patient was 18 years-old and was treated for an osteoid osteoma.

Although CNS tumors are not common, they are an important cause of cancer morbidity and mortality, especially in children and young adults, being responsible for ~ 30% and 20% of cancer deaths, respectively.[4] In epidemiological study at the University of New York, in 2016, it was found that women over 35 years-old present greater occurrence of meningioma, constituting the most common histological type among intracranial tumors in adults, which differ from the findings of the present study, in which gliomas were more prevalent (39.6%) equally in both genders.[4,10]

Meningiomas are the most common primary intracranial tumors. They are usually slow growing, circumscribed (non-infiltrating), benign lesions that arise from the arachnoid cap cells.. Histologically malignant (incidence is 1.7% of meningiomas) and/or rapidly growing varieties are also described. There may be multiple meningiomas in up to 8% of cases, and they may occur in any area where arachnoid cells are found (between brain and skull, within ventricles, and along spinal cord).[11]

The most frequent meningioma location is the parasagittal region, due to the high number of arachnoid granulations. In the present sample, the most common location was the hemisphere convexity. The meningioma prevalence in woman/men in this series differs from the literature because it represents a small piece and universe of patients.

In addition, it is estimated that in the United States of America, 6 to 14% of newly diagnosed cancers will metastasize to the CNS. In these cases, the most common primary tumor sites/types are the lung (45%), breast (15%), melanoma (10%), and colorectal (5%).[11] These findings differed from those of the present study, in which the most common primary tumor site was the breast (33.3%) followed by lung (23.8%).

The most frequent primary tumors that metastasize to the CNS are the breast, lung, and melanoma. We found that the average age of women who presented with breast cancer was middle age. These tumors are more aggressive and tend to resist conventional chemo and radiotherapy, usually the triple-negative tumors (no hormonal receptors). Those tumors frequently send metastasis to the brain and present in woman in their 40 to 50's with a positive family history.

In the past, lung cancer was a men's disease, but after smoking became a trend also among women, the number of lung cancer cases in this group has increased a lot and so did metastatic brain cancer. In our sample, we had three men and two women being surgically treated for metastatic lung cancer.

As for CNS gland tumors, pituitary microadenomas are the most prevalent when compared with macroadenomas or tumors of the pineal gland, which is in line with the findings of the present study. If these tumors are functional, immediate drug treatment is indicated. The goal of the treatment is to decompress the optical pathways and cure any endocrinological disorder the tumor may be causing.[12]

When medication fails or when patients have an important impairment due to tumor compression or hormonal

Table 2 Outcome analysis after surgery

Tumor	Death	Severe deficit	Mild deficit	Palliative care	Following	Total
Gliomas	18	3	1	12	4	38
Metastasis	15	1	1	3	1	21
Meningiomas	2	1	4	3	8	18
Central nervous system glands	1	2	0	0	4	7
Miscellany	4	1	5	0	2	12
Total	**40**	**8**	**11**	**18**	**19**	**96**

production, a skull base approach from the sphenoidal sinus is used to reach the sella turca. The pineal disgerminoma usually presents as headache associated with nausea, diplopia, and hydrocephalus. One possible surgical pathway for this topography is the supracerebellar infratentorial approach.

A severe deficit is defined by an impairment that leads to disabilities and deteriorates the quality of life, while a mild deficit produces loss of production and capacity, but the patient is still functional in the society. Depending on the lesion topography and tumor behavior, surgery is also deleterious to the patient and the risk of complications are high (CSF leak, infections, multiple surgeries, and long intensive care unit length of stay). The patients' conditions are also a challenge in terms of surgical management for the surgeon, anesthesiologist, and intensive care unit staff.[13]

The most frequent intracranial tumors are the meningiomas, and the most common brain tumor are brain metastases.[11] The difference between the results in literature and those of our sample may be due to the fact that HUEM is a skull base and oncology reference center. Most patients who were treated for brain metastasis were being followed by the clinical oncology group of the hospital. The number of patients can be considered low to infer the results numbers to a bigger population and is more likely to only represent a strict reality of a hospital in the south of Brazil. It may represent a locoregional reality and the tendencies from this 3-year period (2016–2018).

Conclusion

Intracranial tumors account for an important share of neurosurgery wards, and the epidemiological knowledge may guide research to develop drugs and treatments to diminish brain cancer mortality. This sample showed a predominance of intra-axial tumors.

Gliomas and metastases represent the most life-threatening events in neuro-oncology and are also linked to high morbidity. There was a slightly predominance for females in our sample, and an odd finding of an equal number of men and woman being treated for meningioma.

Conflict of Interests

The authors have no conflict of interests to declare.

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Reducing VNS stimulation parameters: Is it safe?

É seguro reduzir parâmetros de estimulação do VNS?

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Abstract

Introduction Vagal nerve stimulation (VNS) is an adjuvant therapy used in the treatment of patients with refractory epilepsy who are not candidates for resective surgery or who have limited results after surgical procedures. Currently, there is enough evidence to support its use in patients with various types of epilepsy. Therefore, the present study was conducted to explore the possibility of optimizing therapy by reducing the consumption of the system's battery.

Methods The prospective and double-blind analysis consisted in the evaluation of 6 patients submitted to VNS implantation for 3 months, followed by adjustment of the stimulation settings and continuity of follow-up for another month. The standard protocol was replaced by another with a frequency value of 20 Hz instead of 30 Hz to increase battery life. The safety of this procedure was evaluated through the assessment of two main variables: seizures and side effects.

Results The stimulation at 20 Hz showed 68% reduction in the incidence of seizures ($p = 0.054$) as well as low incidence of side effects.

Conclusion The present study suggests that the reduction of the stimulation frequency from 30 to 20 Hz is a safe procedure, and it does not compromise the effectiveness of therapy.

Keywords
- vagus nerve stimulation
- vagal stimulation
- VNS
- refractory epilepsy

Resumo

Introdução A estimulação do nervo vagal (VNS, na sigla em inglês) é uma terapia adjuvante usada no tratamento de pacientes com epilepsia refratária que não são candidatos à cirurgia de ressecção ou que apresentam resultados limitados após procedimentos cirúrgicos. Atualmente, há evidências suficientes para apoiar seu uso em pacientes com vários tipos de epilepsia. Portanto, este estudo foi realizado para explorar a possibilidade de otimizar a terapia reduzindo o consumo da bateria do sistema.

Métodos A análise prospectiva e duplo-cega consistiu na avaliação de 6 pacientes submetidos ao implante de VNS por 3 meses, seguido de ajuste das configurações de

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Palavras-chave
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- estimulação elétrica
- nervo vago
- epilepsia resistente à medicamentos

estimulação e continuidade do seguimento por mais 1 mês. O protocolo padrão foi substituído por outro com um valor de frequência de 20 Hz em vez de 30 Hz para aumentar a vida útil da bateria. A segurança desse procedimento foi avaliada através da avaliação de duas variáveis principais: crises convulsivas e efeitos colaterais.

Resultados A estimulação em 20 Hz apresentou redução de 68% na incidência de convulsões ($p = 0{,}054$), bem como baixa incidência de efeitos colaterais.

Conclusão Este estudo sugere que a redução da frequência de estimulação de 30 para 20 Hz é um procedimento seguro e não compromete a eficácia da terapia.

Introduction

One of the techniques used in the treatment of patients with refractory epilepsy that are not candidates for resective surgery is vagus nerve electrical stimulation (VNS).[1,2] This technique consists of implanting a bipolar electrode in the vagus nerve in the cervical region and a generator in the infraclavicular region. The left side is the chosen one for this procedure due to the cardiac fibers that originate from the right vagus nerve. Although the mechanism of action by which it operates has not yet been fully elucidated, it is believed to involve diffuse effects on brain metabolism from both cortical and subcortical regions, through modulation of the activity of the *locus ceruleus*, nucleus of the solitary tract and reticular formation of the brain stem.[3] Results show that this therapy is effective not only in reducing the frequency and duration of epileptic seizures,[4–6] but also in promoting a better quality of life for these patients.[7]

Mechanism of Action

It is postulated that the cortical modulation exerted by VNS is manifested through the modulation of the noradrenergic and serotonergic systems, especially due to stimulation of the *locus ceruleus* and the dorsal raphe nuclei, which was confirmed through measurement of monoamines in cerebrospinal fluid (CSF).[8] It is known that the increase of the activity of the *locus ceruleus* after electrical stimulation of the vagus nerve, demonstrated by an increase in c-fos, can cause both release of norepinephrine in the limbic circuit as well as activation of the dorsal raphe nuclei, which send diffuse serotonergic projections to the telencephalon and diencephalon.[9]

Anatomy

The vagus (X) nerve is a mixed cranial nerve with ~ 80% of sensitive fibers. Efferent fibers innervate the larynx and promote parasympathetic control of the heart, lungs, and abdominal viscera. It exits the brainstem at the posterolateral sulcus of the medulla with the glossopharyngeal (IX) and accessory (XI) nerves.[10] The right vagus nerve innervates the sinoatrial node while the left innervates the atrioventricular node. The ideal nerve location for VNS implantation is the cervical region, where it travels in the carotid sheath, between the carotid artery and the jugular vein. A segment of ~ 3 cm is commonly needed for implantation and, when feasible, it should be performed as distal as possible in case a new electrode is needed in the future.

Surgical Procedure

As described earlier, the device is preferentially implanted on the left side of the patient to avoid the cardiac fibers of the right vagus nerve. The electrode and generator are tested before the procedure. The first surgeon is at the patient's left in the cervical region. The patient lies supine on the surgical table with the head supported by a cushion and slightly extended; a pad is placed under the shoulder for assistance.

A 5-cm longitudinal incision is made at the level of the cricothyroid interval from the midline to the anterior border of the sternocleidomastoid muscle (►**Fig. 1**). The platysma muscle is divided in the direction of the fibers, and the deep cervical fascia is opened. The sternocleidomastoid muscle is folded laterally to expose the neurovascular bundle through blunt dissection. The carotid sheath is opened to expose the carotid artery and the jugular vein, which is retracted laterally to reveal the vagus nerve trunk deep in between structures (►**Fig. 2**). After careful dissection, the lead's spirals are wrapped around the nerve from the proximal to the distal contact (►**Fig. 3**). It is of great importance to maintain the adequate position of spirals (the anchor tether

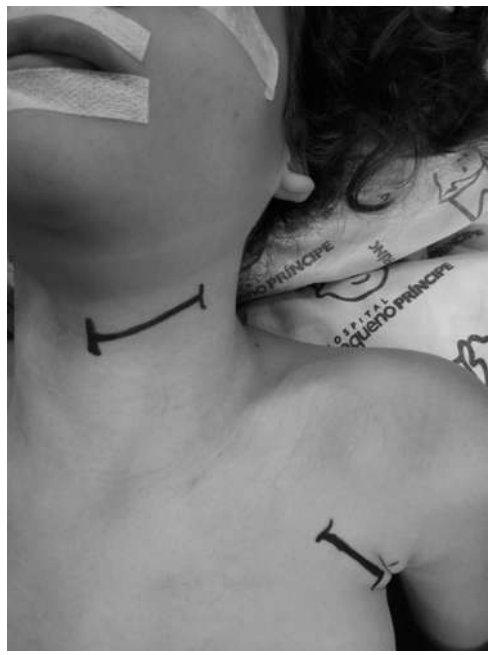


Fig. 1 A 5cm longitudinal incision is made at the level of the cricothyroid interval from the midline to the anterior border of the sternocleidomastoid muscle

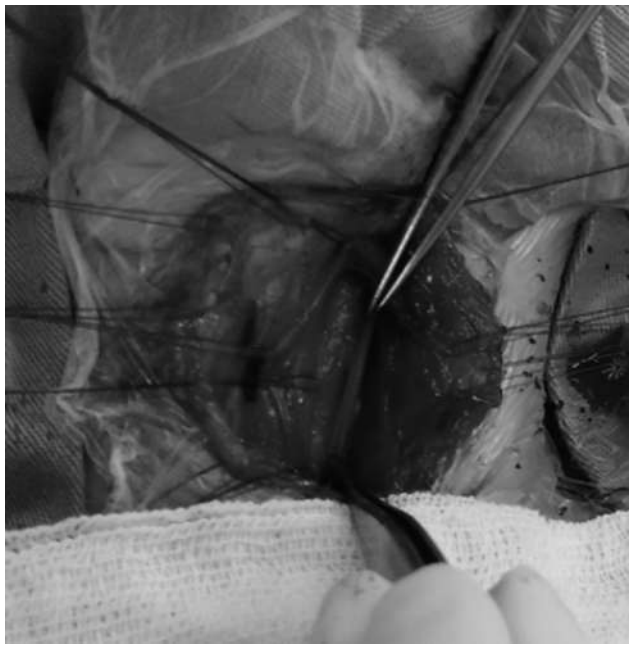


Fig. 2 The carotid sheath is opened to expose the carotid artery and the jugular vein, which is retracted laterally to reveal the vagus nerve trunk deep in between structures

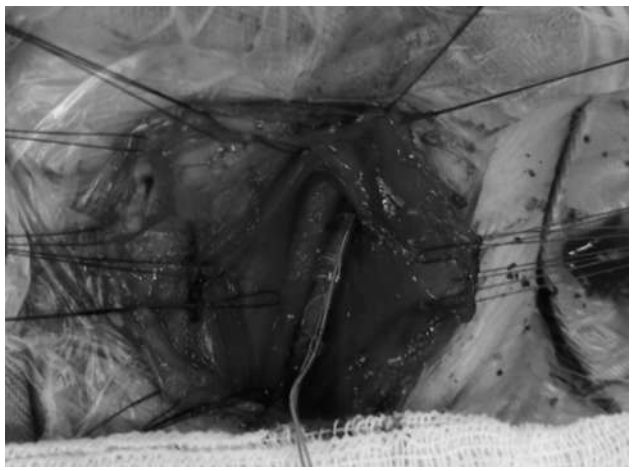


Fig. 3 After careful dissection, the lead's spirals are wrapped around the nerve from the proximal to the distal contact

is placed inferiorly; the positive contact in between; and the negative contact superiorly, as demonstrated in ►**Fig. 4**) to stimulate afferent and non-efferent fibers.

To place the generator on the anterior chest wall inferior to the clavicle, an incision is made at the level of the anterior axillary line to create a subcutaneous pouch under the pectoral fascia, large enough to accommodate the device (►**Fig. 1**). The electrode is then carefully tunneled from the neck to the chest, above the sternocleidomastoid muscle and the clavicle, and connected to the generator. The intraoperative test is performed to confirm adequate system functioning through impedance testing. If the implanted generator supports closed-loop stimulation, it is also necessary to verify the system's capability of correctly identifying the heart rate. At our center, stimulation is initiated immediately after the

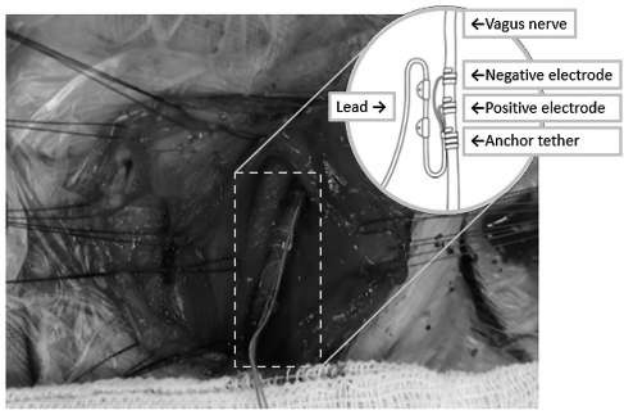


Fig. 4 Adequate position of spirals (anchor tether is placed inferiorly, positive contact, in between, and negative contact, superiorly)

procedure with the following settings: 0.25 to 0.5 mA, 30 Hz, 500 micros, 30 seconds ON, and 5 minutes OFF.

Rationale

The device employed for the electrical stimulation of the vagus nerve allows adjustment of several parameters, as current, frequency, pulse width, ON and OFF time. Although the current stimulation protocol was initially based on animal studies[11–13] and, subsequently, on humans (mainly in EOS 1–5 studies), it has not yet been thoroughly elucidated and individual variations are quite frequent,[14] mainly due to the lack of conclusive randomized trials objectively comparing different values of frequency, amplitude, and pulse width. Therefore, the present study intends to demonstrate the safety of reducing the stimulation frequency from 30 to 20 Hz.

Methods

The current study consisted in a double-blind prospective analysis of patients with refractory epilepsy previously submitted to VNS implantation who underwent reduction of frequency stimulation (from 30–20 Hz) and were followed up for evaluation of changes in frequency and/or duration of epileptic seizures and emergence of side effects.

The eligibility criteria included individuals of both genders from 2 to 18 years of age, with refractory epilepsy of focal or generalized origin, already submitted to VNS implantation at Hospital Pequeno Príncipe by the same surgeon (T. O.), that demonstrated interest in participating voluntarily. The exclusion criteria, in turn, consisted of age group outside the previously mentioned range or lack of interest in participating in the research. The project was approved by the ethics committee of Hospital Pequeno Príncipe and did not generated expenses for the participants. All individuals who agreed to participate in the survey signed the informed consent. It was clarified that there could be a reduction in the number of surgical procedures for generator replacement due to increase in battery survival. All changes in stimulation parameters were performed in the hospital, and the patient remained in place long enough for at least two cycles of stimulation to occur to early diagnose any immediate side

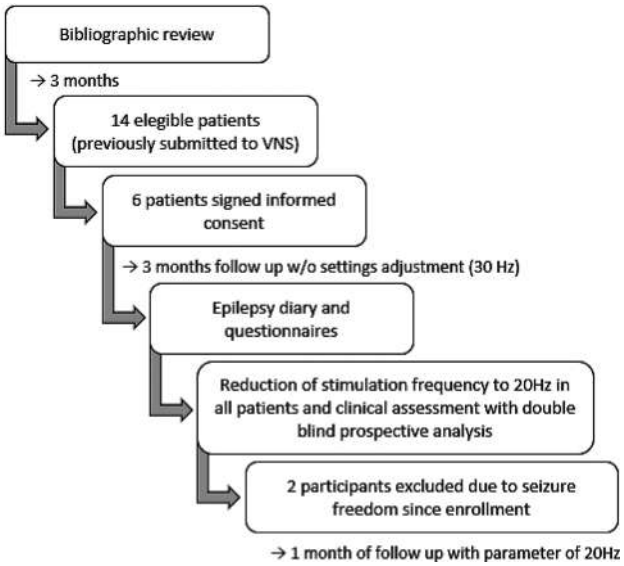


Fig. 5 Methods' flowchart

effects. It should be noted that the researcher responsible for setting adjustments was not the same who evaluated the results. The participants and their families were extensively instructed on the double-blind nature of the project and the need for randomization to reduce placebo effect.

Six patients stimulated with 30 Hz were initially followed up for 3 months with a questionnaire and a seizure diary. Due to lack of participant compliance, the authors opted for collecting data through online diaries, telephone contacts or office visits. After baseline evaluation, the frequency stimulation was reduced to 20 Hz, and the patients were followed up for another month. Because of the small sample size, adjustments were performed for all patients, which composed the control group. However, to maintain the double-blind approach, the participants, and the author responsible for evaluating the results were unaware of this information (►**Fig. 5**).

In addition to a comparative statistical analysis performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), the data were processed through the *t*-paired analysis in the Minitab program (Minitab, LLC., State College, PA, USA) to compare the two stimulation groups (20 and 30 Hz). To test the normality of the distribution of the 30 Hz and 20 Hz samples according to the multiple variables, the Anderson-Darling and Ryan-Joiner were used. The H0 hypothesis, rejected if $p < 0.05$ for 95% confidence intervals, considered that the sample distribution followed a normal distribution.

Results

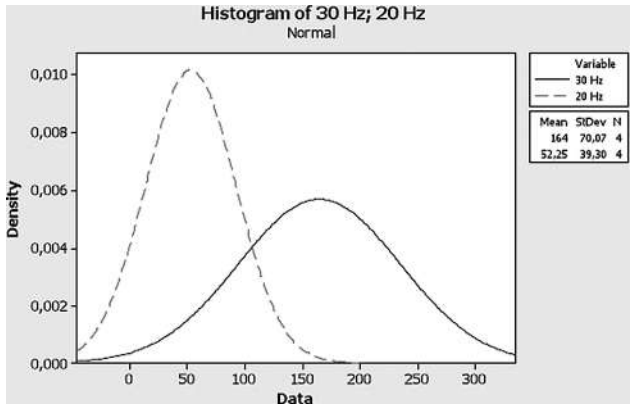
Of the 14 patients selected for the research, only 6 demonstrated interest in participating and signed the informed consent. The mean age of the sample analyzed was 10 years (8–18 years) and half of the participants was female. In the baseline evaluation, two patients had already presented with complete seizure remission. An average of 109 seizures per week per patient was observed, with 90.7% being partial, ~ 9% drop-attack, and 0.3% being tonic-clonic. All patients who were still seizing obtained some reduction in seizure duration, and 75% were considered responsive (achieved more than 50% reduction in seizure frequency). Likewise, three of four patients reported less intense events, while one remained unchanged.

With the inclusion of all patients in the group of 20 Hz, however, it was not possible to exclude the possibility that the data did not follow a normal distribution. This probably occurred due to the presence of two outliers that no longer had seizures since the baseline evaluation and stayed that way after reducing the frequency to 20 Hz. To approach normality, it was decided to exclude these two participants and perform all the analysis with only the data of the four remaining ones.

Two patients reported side effects after frequency reduction to 20 Hz: one had transient dysphonia while the second evolved with permanent dysphagia and dysphonia. Nonetheless, it is crucial to mention the latter had clinical deterioration due to hospitalization, which could have contributed to the complaints.

Contrarily to expectations, in the month following settings adjustment, there was a 68% reduction in seizures ($p = 0.054$). Moreover, in the 75% of patients who were still seizing, a reduction in both intensity and duration of the episodes was noticed. It is necessary to emphasize that, in the two patients who had no seizures, there was no clinical worsening after reducing the frequency to 20 Hz.

After comparing the mean of the total number of seizures during stimulation at 30 Hz and at 20 Hz, there was no statistically significant difference ($p = 0.054$), despite a tendency of seizure reduction with 20 Hz stimulation. This fact can be explained by the presence of overlap data in the histogram of the two distributions, even though the means of total seizure number with stimulation at 30 Hz and at 20 Hz were distinct (**Graph 1**). When applying the paired *t*-test, it was not possible to state with 95% confidence that the averages of the total seizure number with stimulation at 30 Hz or 20 Hz were different since the confidence interval included 0 (- 4.0; 227.5), as demonstrated in ►**Table 1**. However, when changing the interval (26.1; 197.4), it became evident that the averages differed with 90% certainty (►**Table 2**). This should be carefully interpreted, however, as the resultant seizure reduction could be simply a



Graph 1 Histogram of the total number of seizures during stimulation at 30Hz and at 20Hz

Table 1 Paired *t*-test of the total number of seizures with stimulation at 30 and 20 Hz

	N	Mean	Standard deviation	Standard error
30 Hz	4	164	70.1	35
20 Hz	4	52.3	39.3	19.6
Difference	4	111.8	72.7	36.4

95% confidence interval for the mean difference: (- 4.0; 227.5).
T-test of difference from mean = 0 (versus no = 0); *t*-value = 3.07; *p*-value = 0.054.

Table 2 Paired *t*-test of the total number of seizures with stimulation at 30 and 20 Hz

	N	Mean	Standard deviation	Standard error
30 Hz	4	164	70.1	35
20 Hz	4	52.3	39.3	19.6
Difference	4	111.8	72.7	36.4

90% confidence interval for the mean difference: (26.1; 197.4).
T-test of difference from mean = 0 (versus no = 0); *t*-value = 3.07; *p*-value = 0.054.

consequence of the stimulation of the vagus nerve itself and could appear months after the initiation of therapy.

Discussion

The VNS system allows for changes in almost all settings, and most of the patients are stimulated with the standard protocol of 30 Hz, 500 µs, 30 seconds ON, 5 minutes OFF, and amplitudes that vary from 0.25 to 2.25 mA.

Frequency values range from 20 to 30 Hz, because it has been demonstrated that frequencies greater than 50 Hz could cause irreversible nerve damage.[15] A recent study in rats, however, suggested that frequencies between 130 Hz to 180 Hz as recommended in brain, spinal cord, and trigeminal stimulation, could lead to greater seizure attenuation than 30 Hz stimulation.[16] Nonetheless, these results have not yet been demonstrated in humans. Low frequency electrical stimulation (1 Hz), in turn, has not been as effective as high frequency (30 Hz) in seizure control.[17]

Diversely, pulse width ranges from 250 to 500 µs, and current amplitude from 0.0 up to 3.5 mA. The amplitude chosen for initial stimulation, however, varies from 0.25 to 0.5 mA and is gradually increased to 1.75/2 mA in months. Most patients do not benefit from further increases as the vast majority of fibers are already stimulated with values close to 1.5 to 2.25 mA.[18] Although it has been shown that clinical response with a reduction in epileptic seizures in the first 3 months after implantation was quite similar in groups that used current amplitudes lower or higher than 1 mA,[19] it should be noted that in the non-responsive group there was greater improvement after increasing the amplitude. This fact could be explained not only by settings adjustment, but also by the stimulation time itself,[9] since clinical response may be delayed on account of the cumulative effect of stimulation. Furthermore, as children tolerate increases in amplitude better than adults because of fewer side effects, a need for higher current or pulse width values in these patients may be noticed.[20]

It is noteworthy that stimulation does not occur continuously, but rather in cycles. Although the initial stimulation is generally started with cycles of 30 seconds ON and 5 minutes OFF, the system allows for cycles of 7 to 60 seconds ON and 0.2 to 10 minutes OFF. In a retrospective analysis of the parameters of electrical stimulation in 154 patients in the XE5 study, it was not possible to correlate seizure control with changes in current amplitude, frequency, and pulse width between 3 and 12 months of follow-up. In one group, however, it was observed that reducing the OFF time to $\leq$ 1.1 minute led to better control with the reduction in seizures being improved from 21 to 39%.[21] Although some authors advocate rapid electrical stimulation (7 seconds ON and 30 seconds OFF), it has not yet been possible to demonstrate statistical difference with this protocol.[4]

Moreover, it should be considered that increases in electrical stimulation parameters will generate higher battery consumption and a consequent reduction in battery life,[18] in addition to increases in surgical procedures to replace the generator. For example, computational models have already demonstrated that, although there are less stimulated fibers with pulse width reduction from 500 to 250 µs, the required increase in amplitude to maintain the same electrical stimulation consumes less energy than with 500 µs pulse width stimulation and lower amplitudes.[18] Lower values of pulse width (250 µs) and frequency (20 Hz) can be used on patients according to the manufacturer's manual (Cyberonics, 2015, VNS Therapy®, Cyberonics Inc. Houston TX, USA), with the main objective of reducing side effects. A projection of battery life according to the various current values, pulse width, and frequency can be seen in ►**Fig. 6**.

The reduction from 30 to 20 Hz in the present study showed a reduction of 68% in the incidence of seizures ($p = 0.054$) as well as low incidence of permanent side effects (only 1 out of 6 patients). However, it is necessary to interpret these data with caution since most of the participants were the ones who responded to therapy. Moreover, this improvement could also result from the time patients had been treated, as vagus nerve electrical stimulation response may not be immediate, and its effectiveness may progressively increase over time.

Limitations

The main limitations of our study are the small sample size and the use of the same patient as his own control group. The next step in the investigation of vagus nerve electrical stimulation at 20 Hz frequency would be the development of a randomized study, with a group of stimulation at 20 Hz and a control group at 30 Hz with crossover after a follow-up period.

Parameters at 3kOhms (M103/104)			Time from BOL* to IFI			Time from IFI to N EOS			Time from N EOS to EOS		
			10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle	10% Duty Cycle	33% Duty Cycle	50% Duty Cycle
mA	Hz	µS	Years	Years	Years	Years	Years	Years	Years	Years	Years
0.5	10	130	>10	>10	>10	2.8	2.5	2.4	2.2.	2.0	1.9
0.5	15	130	>10	>10	>10	2.7	2.2	1.9	2.1	1.7	1.5
0.5	20	130	>10	>10	>10	2.5	1.9	1.7	2.0	1.5	1.3
0.5	25	130	>10	>10	>10	2.4	1.7	1.4	1.9	1.4	1.2
0.5	30	130	>10	>10	9.5	2.3	1.6	1.3	1.8	1.3	1.1
0.5	10	250	>10	>10	>10	2.7	2.3	2.0	2.1	1.8	1.6
0.5	15	250	>10	>10	>10	2.5	1.9	1.6	2.0	1.5	1.3
0.5	20	250	>10	>10	>10	2.4	1.7	1.4	1.9	1.3	1.1
0.5	25	250	>10	>10	8.7	2.3	1.5	1.2	1.8	1.2	0.9
0.5	30	250	>10	9.8	7.6	2.1	1.3	1.0	1.7	1.0	0.8
0.5	10	500	>10	>10	>10	2.5	1.9	1.6	1.9	1.5	1.2
0.5	15	500	>10	>10	8.9	2.3	1.5	1.2	1.8	1.2	0.9
0.5	20	500	>10	9.3	7.2	2.1	1.2	1.0	1.6	1.0	0.8
0.5	25	500	>10	8.1	6.1	1.9	1.1	0.8	1.5	0.9	0.6
0.5	30	500	>10	7.1	5.2	1.8	0.9	0.7	1.4	0.8	0.6
0.5	10	750	>10	>10	9.4	2.3	1.6	1.3	1.8	1.2	1.0
0.5	15	750	>10	9.1	7.0	2.1	1.2	0.9	1.6	1.0	0.7
0.5	20	750	>10	7.5	5.6	1.9	1.0	0.7	1.5	0.8	0.6
0.5	25	750	>10	6.4	4.7	1.7	0.9	0.6	1.3	0.7	0.5
0.5	30	750	>10	5.5	4.0	1.5	0.7	0.5	1.2	0.6	0.4
0.5	10	1000	>10	>10	7.9	2.2	1.4	1.1	1.7	1.1	0.8
0.5	15	1000	>10	7.7	5.8	1.9	1.0	0.8	1.5	0.8	0.6
0.5	20	1000	>10	6.3	4.5	1.7	0.8	0.6	1.3	0.7	0.5

Fig. 6 Projection of battery life according to the various current values, pulse width, and frequency

Conclusions

When considering the significant reduction in the frequency of epileptic seizures and the improvement in the quality of life of implanted patients, along with the low incidence of irreversible or debilitating side effects, it is possible to recognize that electrical stimulation of the vagus nerve is a safe therapy in the treatment of pediatric and adult patients with refractory epilepsy who are not candidates for resective surgery. Although this was a pilot study with a small sample size, it demonstrated that, in the short term, it is apparently safe to reduce the stimulation frequency to 20 Hz without compromising the effectiveness of therapy. The subsequent increase in battery lifetime would, consequently, reduce the need of surgical replacements of the generator.

Conflict of Interests

The authors have no conflict of interests to declare.

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Preoperative Endovascular Embolization of Glomus Jugulare Tumors: A Retrospective Case Series of 22 Embolizations in 20 Patients and Literature Review

Embolização endovascular pré-operatória de tumores de glômus jugular: Uma série de casos retrospectiva de 22 embolizações em 20 pacientes e revisão da literatura

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Abstract

Objective Glomus jugulare tumors, or tympanojugular paragangliomas, are rare, highly vascularized skull base tumors originated from paraganglion cells of the neural crest. With nonabsorbable embolic agents, embolization combined with surgery has become the norm. The authors assess the profile and outcomes of patients submitted to preoperative embolization in a Brazilian tertiary care hospital.

Methods The present study is a single-center, retrospective analysis; between January 2008 and December 2019, 22 embolizations were performed in 20 patients in a preoperative character, and their medical records were analyzed for the present case series.

Results Hearing loss was the most common symptom, present in 50% of the patients, while 40% had tinnitus, 30% had dysphagia, 25% had facial paralysis, 20% had hoarseness, and 10% had diplopia. In 7 out of 22 embolization procedures (31%) more than a single embolic agent was used; Gelfoam (Pfizer, New York, NY, USA) was used in 18 procedures (81%), in 12 of which as the single agent, followed by Embosphere (Merit Medical, South Jordan, UT, USA) (31%), Onyx (Medtronic, Minneapolis, MN, USA) (9%), and polyvynil

Keywords
- endovascular procedures
- glomus jugulare
- therapeutic embolization

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alcohol (PVA) and Bead Block (Boston Scientific, Marlborough, MA, USA) in 4,5% each. The most common vessel involved was the ascending pharyngeal artery, involved in 90% of the patients, followed by the posterior auricular artery in 15%, the internal maxillary artery or the occipital artery in 10% each, and the superficial temporal or the lingual arteries, with 6% each. Only one patient had involvement of the internal carotid artery. No complications from embolization were recorded.

Conclusions Preoperative embolization of glomus tumors is safe and reduces surgical time and complications, due to the decrease in size and bleeding.

Resumo

Objetivo Tumores de glômus jugular, ou paragangliomas timpanojugulares, são tumores de base de crânio raros, altamente vascularizados, originados das células paragangliônicas da crista neural. Com agentes embólicos não-absorvíveis, embolização combinada com cirurgia se tornou a norma. Os autores avaliam os perfis e desfechos de pacientes submetidos a embolização pré-operatória em um hospital terciário brasileiro.

Métodos O presente estudo é uma análise retrospectiva realizada em centro único; entre janeiro de 2008 e dezembro de 2019, 22 embolizações foram realizadas em 20 pacientes em caráter pré-operatório. Seus registros médicos foram analisados para a presente série de casos.

Resultados Hipoacusia foi o sintoma mais comum, presente em 50% dos pacientes, enquanto 40% tinham tinnitus, 30% tinham disfagia, 25% tinham paralisia facial, 20% tinham rouquidão e 10% tinham diplopia. Em 7 das 22 embolizações (31%), mais de 1 agente embólico foi utilizado; Gelfoam (Pfizer, Nova York, NY, EUA) foi usado em 18 procedimentos (81%), em 12 dos quais como agente único, seguido de Embosphere (Merit Medical, South Jordan, UT, EUA) (31%), Onyx (Medtronic, Minneapolis, MN, USA) (9%), e polyvynil alcohol (PVA) e Bead Block (Boston Scientific, Marlborough, MA, EUA) (4,5% cada). Os vasos mais comumente acometidos foram a artéria faríngea ascendente (90% dos pacientes), seguida da artéria auricular posterior (15%), a artéria maxilar interna e a artéria occipital (10% cada) e as artérias temporal superficial e lingual (6% cada). Apenas um paciente teve acometimento da artéria carótida interna. Não houve complicação secundária a embolização.

Conclusão Embolização pré-operatória de glômus jugular é segura e reduz tempo e complicações cirúrgicas, pela redução em tamanho e sangramento.

Palavras-chave
- procedimentos endovasculares
- gomo jugular
- embolização terapêutica

Introduction

Glomus jugulare tumors, more recently described as tympanojugular paragangliomas, are rare, highly vascularized though slow-growing skull base tumors that originate from paraganglion cells of the neural crest.[1] Even though their histological substrate is benign, they often present as aggressive lesions, invading the temporal bone, the upper neck, the middle ear, and the jugular foramen itself.[2] The approach for these lesions remains controversial: while radiosurgery, radiotherapy, and gamma knife radiosurgery as primary treatments showed high rates of growth afterwards, they had low morbidity[3–7]; meanwhile, neurosurgeons are often faced with challenges due to the rich vascularization of the lesions as well as to the intimate relationship with neural and vascular structures.[1,2,8,9] To minimize the risks for the patient and ensure total resection, a combined approach involving neurosurgeon, interventional radiologist, and ear, nose, and throat (ENT) surgeon is ideal.[10] After the introduction of modern, nonabsorbable embolic agents, embolization combined with surgery after at least 2 days has become the norm. Since 2008, the authors have treated 20 patients with this combined approach; in the present series, we present the results of a retrospective analysis of this group.

Patients and Methods

Between January 2008 and December 2019, 22 paraganglioma embolizations were performed in 20 patients in a preoperative character in the Neurological Institute of Curitiba (INC, in the Portuguese acronym), a tertiary reference center in Southern Brazil. There were 11 women (55%) and 9 men (45%), with a mean age of 51.25 ± 16.3 years old (range: 23 to 87 years old). A total of 50% of the lesions were on the

right side. All patients with glomus jugulare who presented to our service underwent both embolization and surgery afterwards. Every single patient is still alive and in regular follow-up with the team.

The present study is a retrospective analysis of a series of cases treated by the same team (neurosurgeons and interventional neuroradiologists); the procedures were performed in either a Siemens AXIOM system (Siemens, Munich, Germany) (before 2013) or a Philips Allura Xper FD20 system (Philips, Amsterdam, Netherlands) (since 2013). Given the retrospective nature of the present case series, institutional approval was obtained from the Committee of Ethics in Research of our institution (approval protocol 4.211.396) but the need to obtain a consent form was waived.

As previously reported by the group, embolization of glomus jugulare tumors was performed through super selective catheterization of feeder arteries between 3 to 5 days prior the surgical procedure; feeders from the external carotid artery (ECA [ascending pharyngeal, internal, maxillary, and occipital arteries, for instance]) and internal carotid artery (ICA [through carotid tympanic branches]) were embolized with gelatin foam (Gelfoam; Pfizer, New York, NY, USA), polyvinyl alcohol foam, or polyvynil alcohol (PVA) (Ivalon; Nycomed, Paris, France) particles, embolic spheres (Embosphere; Merit Medical, South Jordan, UT, USA), Bead Block (Boston Scientific, Marlborough, MA, EUA), and ethylene-vinyl alcohol copolymer, or EVOH (Onyx; Medtronic, Minneapolis, MN); the choice of the materials was subject to medical indication as well as to authorization by the health insurance provider of each patient. The aim of the treatment was radical and complete tumor removal in one surgical procedure with preservation of the cranial nerves.[10]

Results

Of the 20 patients who presented to our department for evaluation, 11 (55%) had already been submitted to previous neurosurgical procedures (►**Table 1**). Hearing loss was the most common symptom, present in 10 patients (50%), while 8 (40%) had tinnitus, 6 (30%) had dysphagia, 5 (25%) had facial paralysis (classified as House-Brackmann [HB] 2 in 2 patients, HB 3 in 1 patient, and HB 4 in 2 patients), 4 (20%) had hoarseness, and 2 (10%) had diplopia. While 11 patients (55%) reported no previous medical condition, hypertension was found in 6 patients (30%), diabetes and dyslipidemia were found in 2 patients each (10%), clinically-diagnosed generalized anxiety, tabagism, and atrial fibrillation were reported in 1 patient each (5%).

In 7 out of 22 embolization procedures (31%) more than a single embolic agent was used; Gelfoam was used in 18 procedures (81%), in 12 of which as the single agent, followed by Embosphere in 7 procedures (31%), Onyx in 2 procedures (9%), and PVA and Bead Block in 1 each (4,5%).

Concerning the arterial feeder, 5 patients (25%) had multiple arteries involved; the most common vessel was the ascending pharyngeal branch of the external carotid artery, involved in 18 patients (90%), followed by the posterior auricular artery in 3 cases (15%), the internal maxillary artery and the occipital artery in 2 cases each (10%), and the superficial temporal and the lingual arteries, with 1 case each (5%). Only 1 patient (5%) had involvement of the ICA; she was submitted to 3 procedures, and after the 1st the ICA supply was terminated; later, she underwent direct lesion injection of Onyx as well, our sole procedure with direct percutaneous injection of any agent.

The embolization was deemed total by the interventionist in 13 procedures (59%), partial in 4 procedures (18%), and was not reported in the remaining 5 (►**Table 2**). No complications were reported after the embolizations. Surgical resection, on the other hand, was considered total in 12 (60%) of the patients and partial in 8 (40%). Further microsurgery was indicated in 2 patients (10%), and stereotactic radiosurgery (Leksell Gamma Knife Perfexion; Stockholm, Sweden), in 4 patients (20%).

Postoperative symptoms included dysphagia in 4 patients (20%), worsening of hearing loss in 3 patients (15%), cerebrospinal fluid (CSF) leak in 2 patients (10%), and worsening of facial paralysis or surgical site granuloma in 1 patient each (5%), with tracheal laceration, necrosis of skin graft, and bone exposition in a specific patient. All patients are alive to this date; ►**Figs. 1** and **2** provide clinical examples.

Discussion

While rare, slow-growing and histologically benign, glomus jugulare tumors are considered aggressive lesions; invasion of temporal bone, of the middle ear, of the neck, and of vascular structures is common. Their most defining aspect is their hypervascularization, which directly influences both imaging and treatment.[1,2]

Concerning imaging features, preoperative digital subtraction angiogram (DSA) is still a vital component of both a correct diagnosis of glomus jugulare tumors, allowing for differential diagnosis with schwannomas, for instance, as well as of the dynamic evaluation of the lesion, identifying a hypervascular mass with rapid arterial blushing, the feeder arteries, which are often hypertrophied, as well as a possible involvement of the internal carotid artery, and venous drainage, often enlarged, possible compression or enlargement of the jugular vein, not to mention size and possible occlusion of the jugular bulb or involvement of the middle ear.[10,11] Magnetic resonance imaging (MRI) with gadolinium injection displays the characteristics, size, and extension of the lesion, as well as its relationship with neighboring structures.[12,13] Glomus jugulare tumors appear as well vascularized lesions, with heterogeneous gadolinium enhancement on T1WI in the typical "salt and pepper" pattern, representing dark vascular flow voids and intense contrast enhancement; on T2WI, the tumors are heterogeneous with dark flow voids.[11,14] Computed tomography (CT) may be useful for analysis of neighboring bone structures and possible invasion[11]; a noncontrast CT typically shows a poorly defined soft tissue mass along with a destructive bony aspect within the jugular foramen.[12,15,16]

Concerning the treatment rationale, tumor embolization is a centenary idea; Dawbarn first described in 1904 a

Table 1 Baseline characteristics of the patients

Patient	Age (years old)	Sex	Previous diseases	Clinical features	Lesion laterality	Arterial supply	Previous surgery
1	87	Female	Arterial hypertension, dyslipidemia	Hearing loss, vertigo, facial paralysis (House-Brackmann 3), hoarseness, cough, dysphagia	Right	Ascending pharyngeal artery, posterior auricular artery	Yes
2	49	Male	Arterial hypertension, tabagism	Hearing loss, dysphagia	Right	Posterior auricular artery	Yes
3	63	Female	Not reported	Not reported	Left	Ascending pharyngeal artery, occipital artery	Not reported
4	37	Male	Not reported	Not reported	Right	Superficial temporal artery	Not reported
5	65	Female	Arterial hypertension	Tinnitus	Right	Ascending pharyngeal artery	No
6	51	Female	None	Hoarseness	Left	Ascending pharyngeal artery	No
7	70	Female	None	Hearing loss, tinnitus, facial paralysis (House-Brackmann 2)	Right	Ascending pharyngeal artery	Yes
8	41	Male	None	Asymptomatic (incidental finding)	Right	Ascending pharyngeal artery	Yes
9	60	Female	None	Dysphagia, diplopia	Right	Ascending pharyngeal artery	Yes
10	32	Female	None	Hearing loss, hoarseness	Left	Ascending pharyngeal artery	No
11	36	Male	None	Hearing loss, facial paralysis (House-Brackmann 2), diplopia	Left	Ascending pharyngeal artery	Yes
12	40	Male	Arterial hypertension	Tinnitus	Right	Ascending pharyngeal artery	Yes
13	81	Female	Arterial hypertension, type 2 diabetes	Facial paralysis (House-Brackmann 4), hearing loss	Left	Ascending pharyngeal artery, maxillary artery	Yes
14	55	Male	Generalized anxiety	Dysphagia, hoarseness	Left	Ascending pharyngeal artery	Yes
15	55	Female	None	Tinnitus, dysphagia, facial paralysis (House-Brackmann 4), hearing loss, lesion extrusion through external acoustic meatus	Right	Ascending pharyngeal artery, maxillary artery, internal carotid artery	Yes
16	23	Male	None	Hearing loss, tinnitus	Right	Ascending pharyngeal artery	No
17	44	Male	None	Hearing loss	Left	Ascending pharyngeal artery, lingual artery	Yes
18	60	Female	Arterial hypertension, atrial fibrillation, type 2 diabetes, dyslipidemia, interatrial communication	Tinnitus, auricular discomfort	Left	Ascending pharyngeal artery, posterior auricular artery	No
19	43	Female	None	Tinnitus, hearing loss, facial paresthesia	Left	Ascending pharyngeal artery, occipital artery	No
20	33	Male	None	Tinnitus, dysphagia	Left	Ascending pharyngeal artery	No

Table 2 Embolization and microsurgical characteristics of the patients

Patient	Embolic agent	Complete embolization?	Complications from embolization	Complications from surgical resection	Outcome	Necessity of new surgical approach
1	Gelfoam	Yes	None	None	Complete resection	None
2	PVA	Yes	None	Complete hearing loss	Complete resection	None
3	Embosphere and Gelfoam	Yes	None	None	Complete resection	None
4	Gelfoam	Yes	None	None	Complete resection	None
5	Embosphere and Gelfoam	Yes	None	Local granuloma	Incomplete resection	Open surgery
6	Embosphere	Yes	None	None	Incomplete resection	Gamma Knife radiosurgery
7	Embosphere and Gelfoam	Not described	None	Not reported	Complete resection	None
8	Embosphere and Gelfoam	Not described	None	None	Incomplete resection	Open surgery
9	Embosphere and Gelfoam	Not described	None	Cerebrospinal fluid leak	Incomplete resection	Gamma Knife radiosurgery
10	Gelfoam	Not described	None	None	Complete resection	None
11	Embosphere and Gelfoam	Partial	None	None	Complete resection	None
12	Gelfoam	Yes	None	None	Complete resection	None
13	Gelfoam	Yes	None	Worsening of facial paralysis (House-Brackmann 5)	Incomplete resection	Gamma Knife radiosurgery
14	Gelfoam	Not described	None	Worsening of dysphagia	Complete resection	None
15	Gelfoam - first embolization	Partial	None	Tracheal laceration, necrosis of skin graft, bone exposition	Incomplete resection	None
	Gelfoam - second embolization	Partial	None			
	Onyx - third embolization (intralesional)	Partial	None			
16	Gelfoam	Yes	None	Cerebrospinal fluid leak, worsening of hearing loss, dysphagia, and tinnitus	Incomplete resection	Gamma Knife radiosurgery
17	Gelfoam, Onyx, Bead Block	Yes	None	None	Incomplete resection	None
18	Gelfoam	Yes	None	None	Complete resection	None
19	Gelfoam	Yes	None	Dysphagia	Complete resection	None
20	Gelfoam	Yes	None	Worsening of dysphagia	Complete resection	None

Abbreviation: PVA: polyvynil alcohol.

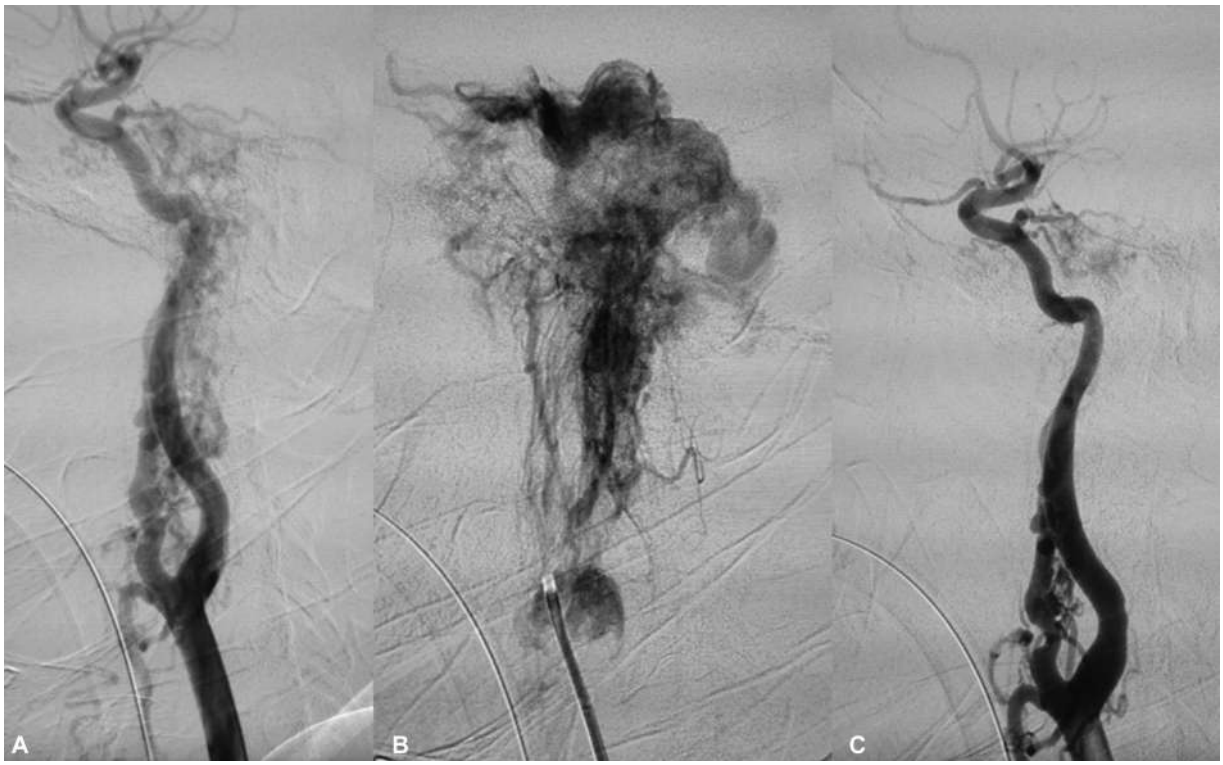

Fig. 1 A 36-year-old male who first presented with hypoacusia, with later development of HB 2 facial paralysis, had been previously operated without embolization. He had no known comorbidities. He was evaluated at our institution and was submitted to embolization of glomus jugulare tumor with Gelfoam and Embosphere by selective catheterization of the left ascending pharyngeal artery, which was shown by angiography to be the main feeder. The patient had no complications from the procedure and underwent surgery without complications as well, achieving complete resection and needing no further treatment. All images are lateral DSA acquisitions during embolization. A: early arterial phase of vast left side hypervascularized, invasive tumor fed by the ascending pharyngeal artery. B: late arterial phase after selective catheterization of the ascending pharyngeal artery. C: control early arterial acquisition showing significant decrease of the lesional blood supply.

"starvation plan" for facial sarcomas and carcinomas[17]; after surgical access, the ECA would be cannulized and liquid paraffin would be injected. In 1930, Brooks reported the use of autologous muscle to close a post-traumatic carotid-cavernous fistula.[18] Cerebral angiography, as we know it, also had a long history, since the days of Egas Moniz and his studies on surgically exposed cervical carotid arteries,[19,20] passing through the technical advances of Seldinger in 1953, creator of the modern percutaneous arterial access,[21] and Djindjian, who first described superselective catheterization of branches of the ECA.[22]

The first reported case of glomus jugulare tumor embolization was in 1973, by Hekster,[23] with autologous muscle; the first uses of Gelfoam, Silastic (American Heyer Schulte, Goleta, CA, USA) spheres, and adhesives through ECA branches was published by Hilal in 1975.[24] Since then, the use of the technique spread and allowed for experiences with different materials. The first use of PVA was in a carotid body tumor in 1980, by Schick.[25] Since then, the use of the technique spread and allowed for experiences with different materials. In 1994, George et al. documented the first direct, intralesional injection of n-butyl-cyanoacrylate (NBCA) in paragangliomas,[26] followed by the description by Jacobs of combined arterial and venous preoperative embolization[27]; in our series, we had only one case of direct intralesional injection, and no case of combined arterial and venous approach.

Paragangliomas are often fed by branches of the ECA, especially the ascending pharyngeal artery, the occipital artery, and the posterior auricular artery; intracranial invading tissue may be supplied by the clival meningeal branches of the ICA and the meningeal branches of the vertebral artery. In case of intradural extension to the posterior fossa, both the posterior and the anterior inferior cerebellar arteries may be involved.[1,28,29]

It has been long known that embolization of glomus jugulare tumors are most successful when combined with other therapeutic modalities, due to high rates of revascularization,[1,29–32] as well as the multitude of feeding arteries and pedicles originating from eloquent branches[30,33]; preoperative embolization is vital in decreasing blood loss during surgical resection, allowing for safer surgeries.[29] It also may reduce surgical exposure time, spare a patient from thermocoagulation trauma, and prevent sinus-packing procedures.[30]

While generally safe,[29] preoperative embolization is not risk-free. Low cranial nerve palsy, presumably due to embolic ischemia of the *vasa nervorum* or tumor embolic infarction with swelling and nerve compression, stroke, due to reflux or withdraw-induced embolism, or dramatic hypotension, after embolization of a large catecholamine-secreting tumor, have all been described, even if their incidence is extremely low.[26,34–36] In our series, we had no complications arising from the embolization per se.

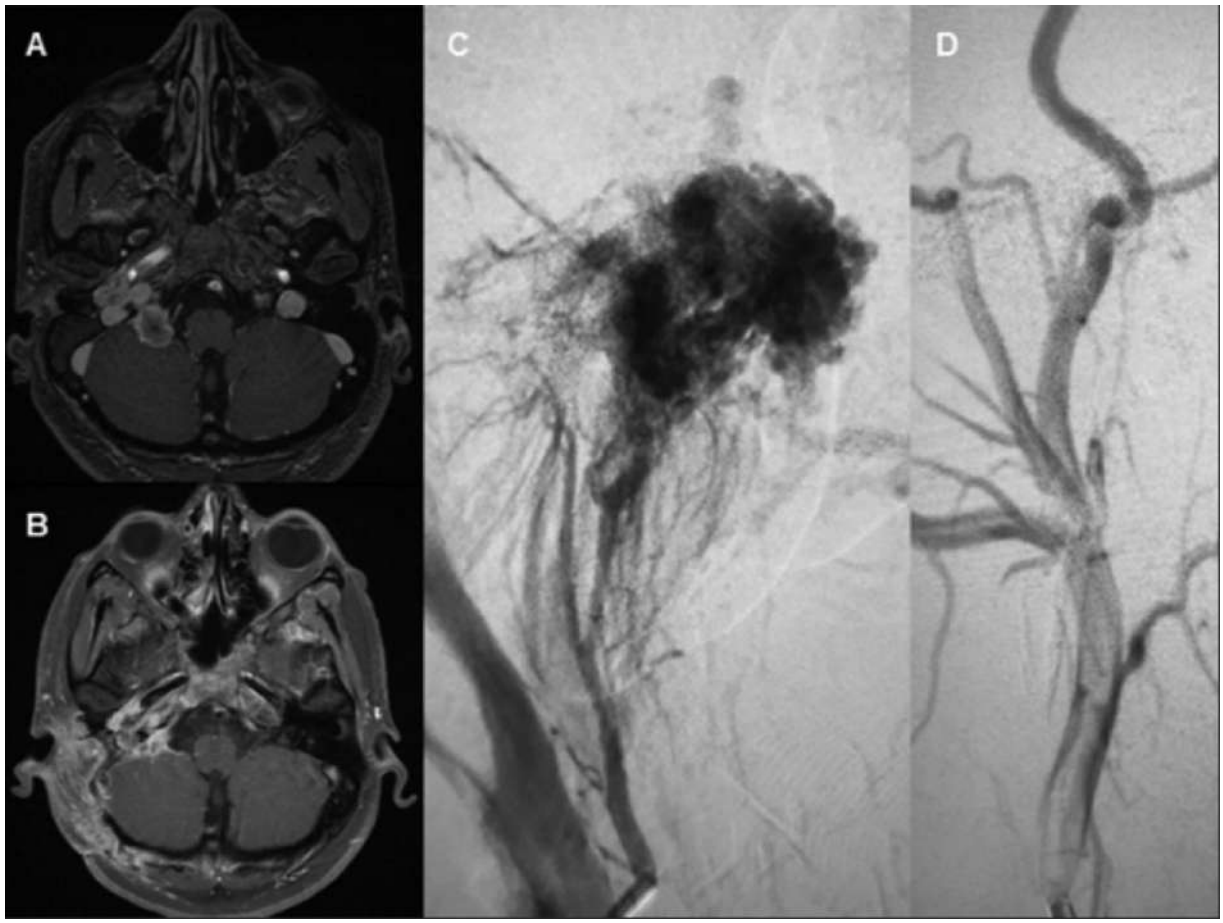

Fig. 2 A 21-year-old male complained of right side pulsatile tinnitus and hypoacusia for 10 months, as well as intermittent ipsilateral cervical pain, before admission to our hospital. ENT examinations elsewhere were without imaging, and he only performed CT and MRI examinations after our evaluation. Both revealed a large, invasive tumor in the jugulare foramen; DSA revealed the tumor was completely supplied by the ascending pharyngeal artery. The patient underwent a total embolization with Gelfoam and the tumor was resected in the same week, using a right craniocervical access. Afterwards, the patient developed CSF leak, later corrected. Due to extensive involvement of glossopharyngeal and accessory nerves, the patient underwent Gamma Knife radiosurgery (25 Gy, 50% isodose) as adjuvant treatment. A and B: axial, postgadolinium injection T1W1 images showing right side hypervascularized lesion in the foramen jugulare, before and after surgery. C: lateral DSA acquisition after selective catheterization of the ascending pharyngeal artery showing the hypervascularized glomus jugulare. D: control lateral DSA acquisition with catheterization of the external carotid artery after embolization with Gelfoam.

Many techniques have been described thus far, ranging from transarterial embolization with PVA particles to direct, percutaneous embolization with NBCA or Onyx.[30,36,37] It must be noted that not only does embolization provide better surgical outcomes but it also has positive impact in clinical manifestations such as tinnitus and vertigo.[38] Even though use of embolization as sole treatment is not advised, it may provide radiological stabilization as well.[39,40]

The following surgery should ideally be performed on the 3rd and on the 14th day after embolization, giving time for decrease of the edema generated by the embolization but before possible vessel reopening and recruiting of other arterial feeders. It is worth noting that paragangliomas may be highly compartmentalized, with independent segments fed by different branches. In our series, total embolization was achieved in 47% of the cases.

Embolization is typically done through one or more of three techniques: transarterially, injecting the embolic agent through superselective catheterization; direct percutaneous intratumoral puncture, which may close arterial supply, capillary bed, and venous drainage, but is harder to adequately gauge; and a transvenous injection, including occlusion of the inferior petrous sinus.[26,27,30]

Agents available for arterial use include autologous muscle, NBCA glue, Ethylene Vynil Alcohol Copolymer (EVOH) (Medtronic, Minneapolis, MN, USA), ethanol, hydrogel, microcoils, microspheres, Gelfoam gelatin sponge, PVA, and microfibrilar collagen, which may be used independently or in association with one another. Both permanent ICA ballooning and carotid stenting may be warranted in selected cases, including cases in which the tumor is extensively supplied by the ICA.[29,41,42] Factors that may influence the choice of embolic agent include, but are not limited to, the experience of the neurointerventionalist with each substance, the time lapse until the surgery, and the possibility of total occlusion. For instance, while the use of microspheres may allow for deeper penetration within the lesion and later open surgery, less experienced

neurointerventionalists may underestimate the diffusion of the substance, especially those with smaller diameters, and inadvertently generate distal venous embolization. In our case, we preferred the larger Gelfoam due to standard procedure of scheduling surgeries in the following days after the embolization and better prevention of venous emboli. This reasoning finds exception when concerning direct injection, either with Onyx, Precipitating Hydrophobic Injectable Liquid (PHIL) (Microvention, Tustin, CA, USA) or NCBA,[26,43] in which preoccupations such as incomplete embolization are also due to care to not inject into the arterial circulation.

We note that our series is one of the largest to date, with few having more patients when specifically concerning glomus jugulare lesions and not all skull base tumors. However, our case series is not without limitations, which include the single-center, retrospective nature of the analysis, the lack of a control group with nonembolized tumors, and the aforementioned bias toward the use of Gelfoam in detriment of other embolic agents.

Conclusion

Glomus jugulare tumors are complex lesions that demand a multidisciplinary approach to ensure satisfactory resection with preservation of lower cranial nerves, especially in case of intracranial extension. Preoperative embolization is essential to ensure one-stage operation of such hypervascularized lesions; there is a wide variety of techniques and material available for the interventional neuroradiologist. Complications from embolization, though rare, cannot be overlooked.

Authors Contributions

Pedro MKF: manuscript research and composition
Leal AG: manuscript research and composition
Ramina R: manuscript revision
Meneses MS: manuscript revision

Conflict of Interests

The authors have no conflict of interests to declare.

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Extending the Indications of 5-Aminolevulinic Acid for Fluorescence-Guided Surgery for Different Central Nervous System Tumors: A Series of 255 Cases in Latin America

Ampliando as indicações de ácido 5-aminolevulínico em cirugia guiada por fluorescência para diferentes tumores do sistema nervoso central: Uma série de 255 casos na América Latina

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Abstract

Introduction Fluorescence guidance with 5-aminolevulinic acid (5-ALA) is a safe and reliable tool in total gross resection of intracranial tumors, especially malignant gliomas and cases of metastasis. In the present retrospective study, we have analyzed 5-ALA-induced fluorescence findings in different central nervous system (CNS) lesions to expand the indications of its use in differential diagnoses.

Objectives To describe the indications and results of 5-ALA fluorescence in a series of 255 cases.

Methods In 255 consecutive cases, we recorded age, gender, intraoperative 5-ALA fluorescence tumor response, and 5-ALA postresection status, as well the complications related to the method. Postresection was classified as '5-ALA free' or '5-ALA residual'. The diagnosis of histopathological tumor was established according to the current classification of the World Health Organization (WHO).

Results There were 195 (76.4%) 5-ALA positive cases, 124 (63.5%) of whom underwent the '5-ALA free' resection. The findings in the positive cases were: 135 gliomas of all grades; 19 meningiomas; 4 hemangioblastomas; 1 solitary fibrous tumor; 27 metastases; 2 diffuse large B cell lymphomas; 2 cases of radionecrosis; 1 inflammatory disease; 2 cases of gliosis; 1 cysticercosis; and 1 immunoglobulin G4-related disease.

Keywords
- 5-aminolevulinic acid
- brain cancer
- extent of resection

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Conclusion Fluorescence with 5-ALA can be observed in lesions other than malignant gliomas or metastases, including meningiomas, hemangioblastomas, pilocytic astrocytomas, and lymphomas. Although there is need for further evidence for the use of 5-ALA beyond high-grade gliomas, it may be a safe and reliable tool to improve resection in positive tumors or to guide the histopathologic analysis in biopsies.

Resumo

Introdução A fluorescência com ácido 5-aminolevulínico (5-ALA) é uma ferramenta segura e confiável para a ressecção total de tumores intracranianos, especialmente gliomas malignos e casos de metástase. Neste estudo retrospectivo, analisamos os achados de fluorescência induzida por 5-ALA em diferentes lesões do sistema nervoso central (SNC), visando ampliar as indicações de seu uso no diagnóstico diferencial.

Objetivos Descrever as indicações e resultados da fluorescência com 5-ALA em uma série de 255 casos.

Métodos Em 255 casos consecutivos, registramos idade, sexo, resposta tumoral de fluorescência intraoperatória com 5-ALA, e *status* de 5-ALA pós-ressecção, bem como as complicações relacionadas ao método. A pós-ressecção foi graduada como "5-ALA livre" ou "5-ALA residual". O diagnóstico histopatológico foi estabelecido de acordo com a classificação atual da Organização Mundial de Saúde (OMS).

Resultados Houve 195 (76.4%) casos 5-ALA positivos, 124 (63,5%) dos quais foram submetidos a ressecção "5-ALA livre". Os achados nos casos positivos foram: 135 gliomas; 19 meningiomas; 4 hemangioblastomas; 1 tumor fibroso solitário; 27 metástases; 2 linfomas difusos de grandes células B; 2 radionecroses; 1 doença inflamatória; 2 glioses; 1 cisticercose; e 1 doença relacionada à imunoglobulina G4.

Conclusões Fluorescência com 5-ALA pode ser observada em outras lesões além de gliomas malignos ou metástases, incluindo meningiomas, hemangioblastomas, astrocitomas pilocíticos, e linfomas. Embora haja necessidade de mais evidências para o uso de 5-ALA que não em casos de gliomas de alto grau, sua aplicação pode ser segura e confiável para melhorar a ressecção de tumores positivos ou orientar a análise histopatológica em biópsias.

Palavras-chave
- ácido 5-aminolevulínico
- câncer no cérebro
- extensão de ressecção

Introduction

5-aminolevulinic acid (5-ALA) is the sole precursor of the non-protein heme constituent of hemoglobin. Once biosynthesized, it is transformed in cytosol until it gets converted to protoporphyrin IX (PpIX) inside the mitochondria. The accumulation of PpIX in certain lesions helps to distinguish neoplastic from normal tissue under blue light filter for photodynamic detection.[1]

Neurosurgical microscopes coupled with a switchable white and violet-blue light source excite the PpIX, enabling the visualization of tumor fluorescence, in red, and normal tissue, non-fluorescent, in blue.[2] Applications of 5-ALA in brain tumor surgery have been described in the last two decades, and have been stimulated by increasing resection areas with better progression-free survival (PFS), especially in malignant intracranial lesions, such as glioblastomas and metastases.[3–5] These promising results evolved to distinct applications in recent laboratory and translational studies.[6–11] Over the years, 5-ALA has also been introduced in the treatment of other intracranial tumors,[6–11] especially in cases of metastases[6–8] and meningiomas.[9–11]

Routinely used in Europe, Asia and Australia, 5-ALA was approved by the United States Food and Drug Administration (FDA) in 2017.[12–16] In Brazil, it is approved by the Brazilian Patent Office and National Sanitary Vigilance Agency (Agência Nacional de Vigilância Sanitária, ANVISA, in Portuguese) under registry number 80046190162.[17]

Since 2015, a few articles[18–20] have reported the initial Latin America experience with 5-ALA fluorescence brain surgery. This emerging tool has become standard to maximize brain tumor removal, enabling real-time guidance through the tissue with surgeon's constant interrogation about what is normal tissue and what is infiltrated brain. With other concomitant intraoperative tools, such as neuronavigation, intraoperative magnetic resonance imaging (MRI), awake surgery, and electrophysiological monitoring, 5-ALA optimized the surgical treatment in neuro-oncology, providing safer and better outcomes.

The purpose of the present article is to describe the application of 5-ALA fluorescence-guided surgery to expand its indications beyond malignant gliomas and metastases.

Methods

Between November 2015 and May 2020, at our institution, there were 255 consecutive cases of central nervous system tumors in which the patients underwent 5-ALA fluorescence-guided surgery. All patients had a preoperative Karnofsky Performance Scale (KPS) > 70% at the time of the procedure. 5- aminolevulinic acid was administered in selected suspected cases of gliomas, metastases and meningiomas. The present study complies with ethical standards, and informed consent was obtained from patients or their relatives.

Preoperative Care

Every patient underwent an imaging evaluation with magnetic resonance imaging (MRI), spectroscopy, and perfusion. The indications for advanced MRI varied according to tumor location and diagnostic hypothesis. Tractography and functional MRI were performed for tumors in eloquent regions. Three hours prior surgery, 5-ALA was administered orally, amounting to a dose of 20 mg/kg dissolved in 50 mL of drinking water.

Intraoperative Care

Patient care (anesthesia induction, positioning etc.) was as routine. Intraoperative pathology were performed for every case. Image guidance with neuronavigation was used in all intracranial tumors. Electrophysiological stimulation and monitoring or awake surgery were also performed for tumors in eloquent areas. The OPMI PENTERO 800 (Carl Zeiss Meditec AG, Jena, Germany) was the neurosurgical microscope used in the present series.

During the corticotomy, switching from white to blue excitation light showed cortical and/or subcortical tumor infiltration and the limits of the 5-ALA positiveness. In cases of 5-ALA-negative tumors, intraoperative MRI (iMRI) was available. Fluorescence intraoperative findings were classified in three zones: non-fluorescent tissue – usually normal brain, necrosis, or 5-ALA negative tumors, in blue; strong 5-ALA fluorescence – in red, showing positive solid tumors; and poor 5-ALA fluorescence – in pink, showing infiltrating tissue. Intraoperative pathology examinations were performed in each fluorescent zone.

At the end of surgery, the cases in which all tissue with visible strong and poor fluorescence were classified as '5-ALA free'. Cases of residual tumors were classified as '5-ALA residual', and the decision was based on the risks of postoperative deficits. The final diagnosis was established according to the 2016 World Health Organization (WHO) criteria.

Postoperative Care

All patients underwent postoperative MRI scans in the first 24 hours. The imaging findings were evaluated by the neuroradiology team.

Results

There were 255 cases in 236 patients ranging from 3 to 90 years of age who underwent 5-ALA fluorescence-guided surgery. The sample was composed of 99 women and 137 men. A total of 19 patients with high-grade gliomas underwent surgery in two different occasions. ►**Table 1** summarizes the results based on the final diagnosis and the 5-ALA removal status. ►**Figs. 1** to **7** show illustrative cases of specific diseases.

Complications due to 5-ALA administration: one male patient with history of drug addiction presented cardiac arrhythmia two hours after the administration of 5-ALA, prior to anesthetic induction. Surgery was suspended and performed a week later, without additional administrations of 5-ALA. This case was excluded from the 5-ALA response results. No other complication associated with 5-ALA was found in the present series.

5-ALA response: there were 195 (76.4%) 5-ALA positive and 60 (23.6%) 5-ALA negative cases.

5-ALA removal status: 124 (63.5%) of the 195 positive cases underwent complete removal based on fluorescence ('5-ALA free'); in 57 (29.2%) cases, the patients underwent '5-ALA residual' resection; and there were 14 cases (7.3%) of biopsies with 5-ALA positivity.

Astrocytic and oligodendroglial tumors: there were 4 pilocytic astrocytomas: 2 (50%) negative and 2 (50%) positive for 5-ALA. Regarding diffuse tumors, there were 24 grade-II astrocytomas: 6 (25%) 5-ALA positive, 4 of which with heterogeneous fluorescence varying between poor and strong, and 18 (75%) 5-ALA negative; 7 oligodendrogliomas: 6 (85.7%) negative and 1 (14.3%) 5-ALA homogenously positive. As for anaplastic tumors, there were 6 grade-III astrocytomas: 3 (50%) positive (in 2 of these cases, fluorescence was found in an anaplastic isle), and 3 (50%) negative; 10 anaplastic oligodendrogliomas: 9 (90%) positive (3 with heterogeneous fluorescence varying between poor and strong), and 1 (10%) negative. There were 108 glioblastomas: 4 (3.8%) negative, and 104 (96.2%) positive, 18 of which cases had heterogeneous fluorescence due to necrosis (negative) and positivity variation between poor and strong. Moreover, three (2.8%) cases 5-ALA positive glioblastomas were giant-cell variants.

Ependymal tumors: there were 3 grade-I subependymomas: 2 (66.6%) negative cases and 1 (33.4%) positive case; 8 grade-II ependymomas: 3 (37.5%) negative, and 5 (62.5%) positive (1 of which with heterogeneous fluorescence due to a subependymal component [poor] mixed with an ependymal [strong] component). There was one case of an anaplastic ependymoma that was positive.

Meningiomas: there wer 17 cases of grade-I and 2 cases grade-II meningioma, all of them (100%) positive. In 2 (10.5%) of the cases, there was heterogenous fluorescence due to calcification zones (pink).

Mesenchymal non-meningothelial tumors: there were 4 hemangioblastomas and 1 solitary fibrous tumor, all of them positive.

Metastases: there were 35 cases, 8 (22.8%) negative, and 27 (77.2%) positive. There were 24 adenocarcinomas (10 in the lungs, 12 in the breasts, 1 in the thyroid, and 1 in the colon): 4 (16.6%) negative, and 20 (83.4%) positive; 5 melanomas: 3 (60%) negative, and 2 (40%) positive. There were 6

Table 1 Tumors classified by types, 5-aminolevulinic acid (5-ALA) response, and removal status

Diagnosis	Total	5-ALA positive	5-ALA removal
Astrocytic and oligodendroglial			
Pilocytic astrocytoma, grade I	4	2	2 5-ALA free
Difuse astrocytoma, grade II	24	6	4 5-ALA free
Oligodendroglioma, grade II	7	1	1 5-ALA free
Anaplastic astrocytoma, grade III	6	3	1 5-ALA free
Anaplastic oligodendroglioma, grade III	10	9	7 5-ALA free
Glioblastoma, grade IV	108	104	59 5-ALA free, 7 biopsies
Astroblastoma	1	1	1 5-ALA free
Diffuse midline glioma	1	1	1 biopsy
Ependymal			
Subependymoma, grade I	3	1	1 5-ALA free
Ependymoma, grade II	8	5	3 5-ALA free
Anaplastic ependymoma, grade III	1	1	1 5-ALA free
Mixed neuronal-glial			
Ganglioglioma	4	0	–
Rosette-forming glioneuronal tumor	1	0	–
Dysplastic cerebellar gangliocytoma	1	0	–
Meningiomas			
Meningioma, grade I	17	17	16 5-ALA free
Atypical Meningioma, grade II	2	2	2 5-ALA free
Mesenchymal non-meningothelial			
Hemangioblastoma	4	4	4 5-ALA free
Solitary fibrous tumor	1	1	1 5-ALA free
Metastatic			
Adenocarcinoma, breast	10	6	4 5-ALA free
Adenocarcinoma, lung	12	12	7 5-ALA free/2 biopsies
Melanoma	5	2	2 5-ALA free
Small cells, kidney	2	1	1 5-ALA free
Adenocarcinoma, colon	1	1	1 5-ALA free
Adenocarcinoma, thyroid	1	1	1 5-ALA free
Adenoneuroendocrine carcinoma	3	3	1 5-ALA free/1 biopsy
Carcinoid tumor, lung	1	1	1 5-ALA free
Other tumors			
Diffuse large B-cell lymphoma	3	2	1 5-ALA free, 1 biopsy
Schwannoma	1	0	–
Non-neoplastic			
Radionecrosis	2	2	2 5-ALA residual
Inflammatory	2	1	1 5-ALA free
Gliosis	6	2	2 5-ALA residual, 1 biopsy
Cysticercosis	1	1	1 5-ALA free
Demyelinating disease	2	1	1 biopsy

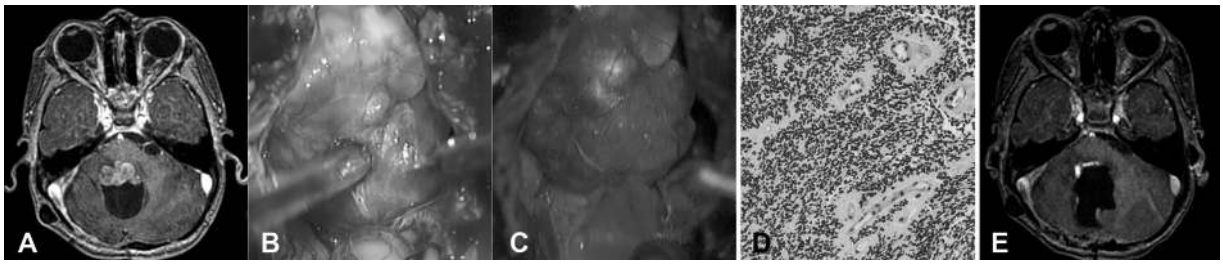

Fig. 1 Illustrative case of a grade-II ependymoma: (**A**) preoperative magnetic resonance imaging (MRI) scan. (**B**) intraoperative finding; (**C**) positivity for 5-aminolevulinic acid (5-ALA); (**D**) histopathological finding; (**E**) postoperative MRI.

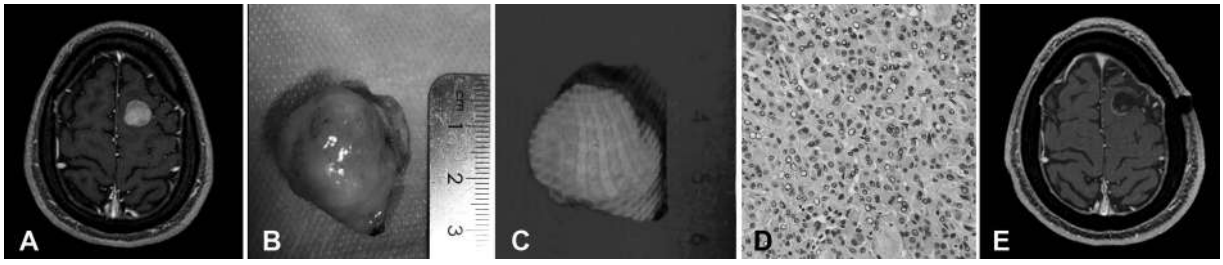

Fig. 2 Illustrative case of a grade-I meningioma: (A) preoperative MRI; (**B**) intraoperative finding; (**C**) 5-ALA positivity; (**D**) histopathological finding; (**E**) postoperative MRI.

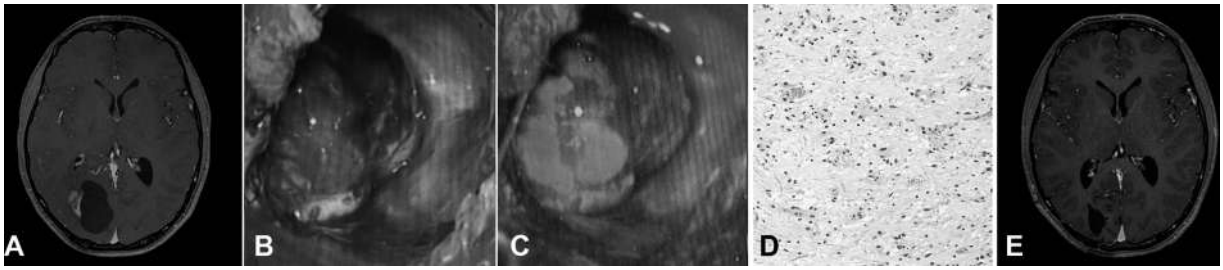

Fig. 3 Illustrative case of a pilocytic astrocytoma: (**A**) preoperative MRI; (**B**) intraoperative finding; (**C**) 5-ALA positivity; (**D**) histopathological finding; (**E**) postoperative MRI.

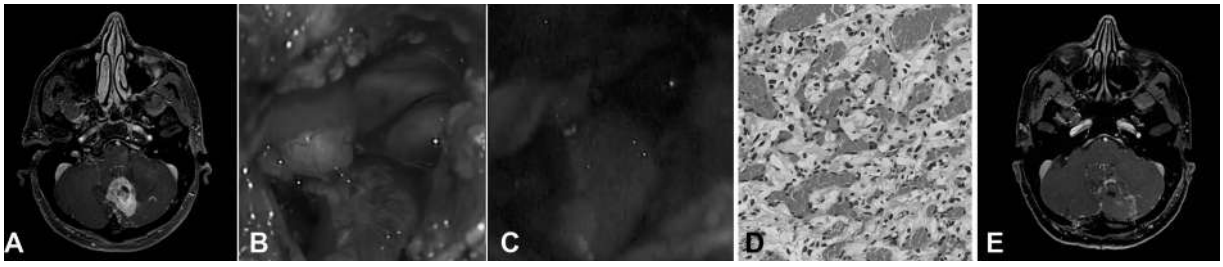

Fig. 4 Illustrative case of a hemangioblastoma: (**A**) preoperative MRI; (**B**) intraoperative finding; (**C**) 5-ALA positivity; (**D**) histopathological finding; (**E**) postoperative MRI.

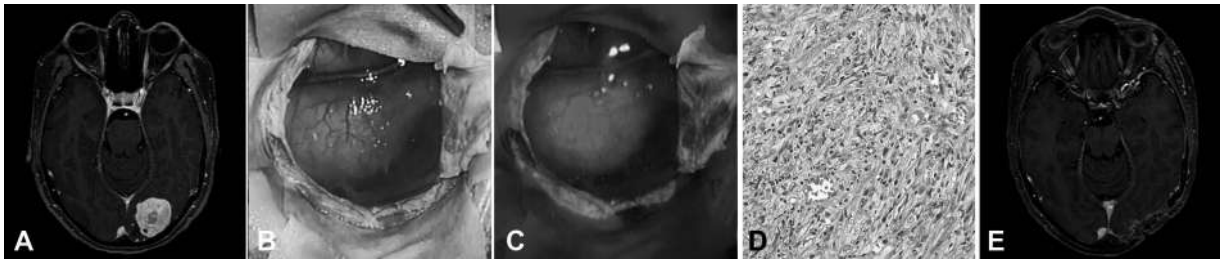

Fig. 5 Illustrative case of Solitary fibrous tumor: (**A**) preoperative MRI; (**B**) intraoperative finding; (**C**) 5-ALA positivity; (**D**) histopathological finding; (**E**) postoperative MRI.

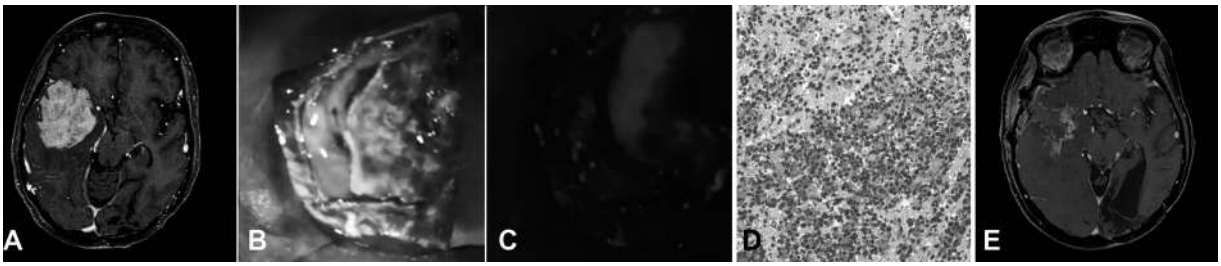

Fig. 6 Illustrative case of a diffuse large B-cell lymphoma: (**A**) preoperative MRI; (**B**) intraoperative finding; (**C**) 5-ALA positivity; (**D**) histopathological finding; (**E**) postoperative MRI.

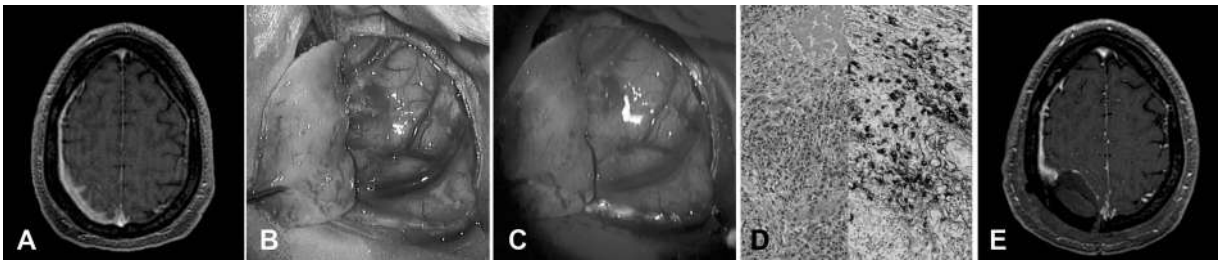

Fig. 7 Illustrative case of immunoglobulin G4-related disease: (**A**) preoperative MRI; (**B**) intraoperative finding; (**C**) 5-ALA positivity; (**D**) histopathological finding (left) with immunochemistry (right); (**E**) postoperative MRI.

other cases, which included 2 cases of small-cell carcinoma of the kidney (1 positive case and 1 negative), 1 carcinoid lung tumor, and 3 cases of mixed adeno-neuroendocrine carcinoma (all of them positive). Heterogeneous fluorescence varying from 'red to pink' was found in three (15%) adenocarcinomas.

Diffuse large B-cell lymphomas: 2 (66.7%) out of the 3 cases were positive, 1 of which had heterogeneous fluorescence varying between poor and strong.

Non-neoplastic diseases: there were 7 cases of unusual lesions; they were all positive, and included radionecrosis (2 cases with heterogenous fluorescence), unspecific inflammatory disease (1 case), gliosis (2 cases with heterogeneous fluorescence), cysticercosis (1 case) and immunoglobulin G4-related disease (1 case, with pink fluorescence).

Discussion

A natural compound, 5-ALA is metabolized via the heme biosynthetic pathway to produce PpIX. Under fluorescent blue light, the PpIX stored in malignant lesions is distinguishable from normal brain tissue and enhances the intraoperative guidance for tumor removal. The intensity of the fluorescence predicts the degree of tumor cellularity.[3–5] The optimal safe fluorescence was produced with 20 mg/kg by oral administration 4 to 6 hours prior to tumor removal. No fluorescence can be visualized with a dose of 0.2 mg/kg, and doses higher than 20 mg/kg do not enhance fluorescence.[21]

In 1998, Stummer et al.[1,2] reported the first series of 270 cases of 5-ALA fluorescence-guided surgery for glioblastoma. In 2006, a randomized phase-III study confirmed 5-ALA as a reliable adjuvant tool to achieve gross total removal of high-grade gliomas, with acomplete resection in 65% of 5-ALA cases versus 36% of the patients who underent conventional microsurgery;[22] consequently, PFS was higher in the 5-ALA group.[23] In 2007, the European Medicines Agency (EMA) approved 5-ALA, but it was only approved by the FDA in 2017 for use as an intraoperative optical imaging agent in patients with suspected high-grade gliomas.[12] The delayed FDA approval was due to the conceptualization of 5-ALA as a therapeutic tool, not as an intraoperative imaging tool. Curiously, in 2004, Brazil's ANVISA approved 5-ALA as a dye to be applied on human subjects under registry number 80046190162.[17]

The first cases of 5-ALA fluorescence-guided surgery for intracranial tumors in Latin America were reported in 2018.[18,19] Before that, neuronavigation, intraoperative MRI, and serial biopsy were the tools available to aid in maximal safe resections.[24] These techniques remain extremely relevant in cases in which fluorescence is negative.

Although the use of 5-ALA in the surgical resection of high-grade gliomas and cases of metastasis has been widely documented in the literature,[6–11] consistent findings of fluorescence have been reported regarding other tumors, including benign and non-neoplastic lesions.[3,4] There are few available articles[29,33,37] describing the use of 5-ALA fluorescence in those differential diagnoses.

For suspected low-grade gliomas or intra-axial tumors without contrast enhancement, the indicarion of 5-ALA fluorescence can be based on preoperative images suggesting anaplastic 'hot areas' on MRI perfusion. These anaplastic foci may be identified during resection by the accumulation of fluorescence and by a separate histopathological analysis. A shorter period may be expected for malignant transformation in patients with fluorescent low-grade gliomas.[25,26] In the present article, 6 (25%) of the 24 confirmed cases of grade-II

astrocytoma, and 1 (14.2%) of the 7 cases of oligodendroglioma, were 5-ALA positive. These patients had a minimum follow-up of 2 years, and showed no signs of disease progression or differentiation until now. In contrast, of the 12 cases of 5-ALA positive grade-III astrocytic (3 cases) and oligodendroglial (9 cases) lesions, 2 (16.6%) had their final had their final diagnosis due to the finding of an anaplastic focus positive for 5-ALA. In both cases, there were preoperative images without contrast enhancement with hot spots on perfusion. The use of 5-ALA optimized tissue sampling for the histopathological evaluation. In the present series, the isocitrate dehydrogenase 1 (IDH1) status showed no relationship with 5-ALA positivity, corroborating the literature findings.[26]

In high-grade gliomas, especially glioblastomas, 5-ALA fluorescence appears to be > 80% positive, with high sensitivity and positive predictive value.[13,27] High-grade gliomas are the main and major indication for use of this method. In the present series, of 124 high-grade gliomas, 116 (93.6%) were 5-ALA positive, with 96.3% of glioblastomas and 75% of anaplastic gliomas. There were 42 (36.2%) cases cases high-grade glioma that were '5-ALA residual' due to infiltration of eloquent areas. Previous adjuvant treatments, such as radiation and chemotherapy, in recurrent malignant tumors seem to not decrease the fluorescence response, although false-positive fluorescence can be observed more frequently.[15] Of 19 cases submitted to reoperation with 5-ALA fluorescence, 2 (10.5%) presented presented radionecrosis despite heterogeneous positivity, ranging from negative to strongly positive zones.

There are few descriptions of 5-ALA fluorescence for pilocytic astrocytomas in pediatric patients, showing positiveness in 53% of the cases.[28,29] In the present series, 2 (50%) of 4 cases were 5-ALA positive, both appearing as a cystic mass with a mural nodule. Fluorescence was especially helpful in the final inspection for residual lesions.

Schwake et al.[29] described 71% and 80% of 5-ALA positivity in grade-III and -II ependymomas respectively. In the present study, out of 9 cases, 6 (66.7%) were positive, 1 of which was grade III. There was also 1 (33.3%) case in 3 of a 5-ALA positive subependymoma. Several articles[30–32] evaluated the utility of 5-ALA-guided removal of spinal lesions, finding positive fluorescence to be reliable especially in ependymomas and meningiomas.

In intracranial meningiomas, 5-ALA positive fluorescence may range from 77% to 96%,[9,11] with intratumoral fluorescence homogeneity higher than 75%. In the present series, 100% of the 19 cases of meningioma were 5-ALA positive, with no apparent correlation with the histopathological grade. The method was useful to visualize dural and osseous infiltrations not visible under the white light of the microscope, previously described with 100% specificity and 89% sensitivity.[10] This reinforces a possible benefit of 5-ALA in optimizing the resection result in conjunction with the Simpson removal classification. The long term follow-up of these patients will be the object of further studies.

Like pilocytic astrocytomas, hemangioblastomas can also show positive fluorescence in mural nodules.[33] 100% of the 4 cases cases described in the present article were 5-ALA positive, and the method helped achieve complete removal.

Large series[6,7] of intracranial metastases show 5-ALA positivity ranging between 28% and 81.8%. In the present article, 77.2% of the cases were 5-ALA positive, with higher response in adenocarcinomas (83.3%) than in melanomas (40%). Fluorescence was useful to help define the possible cortical and subcortical limits of resection, although not necessarily containing metastatic infiltration.[4] Heterogeneous positivity was found in 10 (28.5%) of the 5-ALA positive metastases, ranging from poor to strong fluorescent zones. Although expected in cases with previous adjuvant treatment such as chemotherapy and irradiation,[6] we found no relationship in the present series. The use of 5-ALA was particularly efficient in cases in which 'en bloc' removal – in opposition to 'piecemeal resection' – was possible, given the possibility of safe oncological margins.

Due to the expected difficulty in the differential radiological diagnosis between high-grade glioma and primary central nervous system lymphoma, 5-ALA seems to be a useful tool in stereotaxic biopsies, optimizing tumor sampling based in positivity.[34,35] In a series of 41 biopsies, Yamamoto et al.[36] observed 82.9% of 5-ALA positivity in Ppimary central nervous system lymphomas. Evers et al.[37] reported 8 of 11 patients (73%) with strong homogenous fluorescence as well. In the present series, there were 14 5-ALA positive biopsies that aided in the intraoperative analysis. Samples were collected from both positive and negative areas. Intraoperative histopathology confirmed anomalous tissue in all positive fragments. It was especially helpful in non-neoplastic lesions, such as a case of immunoglobulin G4-related disease and an intracranial cysticercoid cyst.

In our experience, the use of 5-ALA has been safely extended to any contrast-enhanced tumor of the central nervous system, except for schwannomas. Its application to benign lesions such as pilocytic astrocytomas, hemangioblastomas, and meningiomas may have relevance in the final inspection of the surgical cavity, avoiding any residual fluorescence. Also, 5-ALA fluorescence seems to be especially interesting in atypical or challenging diagnoses, reinforcing its high sensitivity. These cases should be the subject of future studies.

Conclusion

Although more evidence is needed, the indications for 5-ALA fluorescence-guided surgery may be safely expanded based on the expected positive fluorescence. Its applications include tumors with potentially positive fluorescence other than malignant gliomas or metastases, optimizing removal and the histopathologic diagnosis.

Conflict of Interests

The authors have no conflict of interests to declare.

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Analysis of Serum Cholesterol, Statins and Atherosclerotic Plaque in Ruptured and Unruptured Intracranial Aneurysm

Análise de colesterol sérico, estatina e placa aterosclerótica em aneurisma intracraniano roto e não roto

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Abstract

Introduction Intracranial aneurysm (IA) is a major healthcare concern. The use of statin to reduce serum cholesterol has shown evidence to reduce cardiovascular risk in various diseases, but the impact on IA has not been described. This study aims to determine whether statin use, and serum cholesterol levels interfere with outcomes after IA event.

Methods A cohort of patients with IA was analyzed. Patients social and demographics data were collected. Modified Rankin scale (mRS) score after 6 months of follow-up was the endpoint. The data regarding statins use, presence or not of atherosclerotic plaque in radiological images and serum cholesterol of 35 patients were included in our study. Linear regression models were used to determine the influence of those 6 variables in the clinical outcome.

Results The prevalence of atherosclerotic plaque, high cholesterol and use of statins was 34.3%, 48.5%, and 14.2%, respectively. Statins and serum cholesterol did not impact the overall outcome, measured by mRS after 6 months ($p > 0.05$), but did show different tendencies when separated by IA rupture status. Serum cholesterol shows an important association with rupture of aneurysm ($p = 0.0382$). High cholesterol and use of statins show a tendency for worse outcome with ruptured aneurysm, and the opposite is true for unruptured aneurysm. The presence of atherosclerotic plaques was not related with worse outcomes.

Keywords
- cholesterol
- statins
- plaques
- outcomes for IA

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Conclusions Multiple and opposite mechanisms might be involved in the pathophysiology of IA. Ruptured aneurysms are associated with higher levels of serum cholesterol. Serum cholesterol and statins use were not correlated with worse outcomes, but further studies are important to clarify these relationships.

Resumo

Introdução Aneurisma intracranial (AI) é uma grande preocupação para a saúde. Evidências apontam que o uso de estatina para reduzir o colesterol sérico diminui o risco cardiovascular em diversas doenças, mas o impacto em AI ainda não foi descrito. Este estudo almeja determinar se o uso de estatina e o nível sérico de colesterol interferem no desfecho clínico após a ocorrência de AIs.

Métodos Uma coorte de pacientes com AI foi analisada. Os dados sociodemográficos dos pacientes foram coletados. Ao final de 6 meses de acompanhamento, aplicou-se a escala modificada de Rankin (mRS). Os dados sobre uso de estatina, existência de placa aterosclerótica em imagens radiológicas, e colesterol sérico de 35 pacientes foram incluídos no estudo. Modelos de regressão linear foram usados para determinar a influência dessas 6 variáveis nos desfechos clínicos.

Resultados A prevalência de placa aterosclerótica, colesterol elevado, e uso de estatina foram respectivamente 34,3%, 48,5% e 14,2%. Estatina e colesterol sérico não impactaram nos desfechos medidos pela mRS em 6 meses ($p > 0,05$), mas mostraram diferentes tendências quando separados pelo estado de ruptura do AI. Colesterol sérico apresenta uma importante associação com ruptura de aneurisma ($p = 0,0382$). Colesterol elevado e uso de estatinas representam uma tendência a piores desfechos para aneurismas rompidos, e o oposto é verdade para os não rompidos. A presença de placa aterosclerótica não está relacionada com piores resultados.

Conclusões Mecanismos múltiplos e opostos podem estar envolvidos na patofisiologia do AI. Aneurismas rompidos estão associados com maiores níveis de colesterol sérico. Colesterol sérico e estatinas não foram correlacionados com piores desfechos, mas mais estudos são importantes para clarificar a relação entre esses fatores.

Palavras-chave
- colesterol
- estatinas
- placa
- desfechos para AI

Introduction

Intracranial aneurysm (IA) is a major healthcare concern. It is defined as a dilation of a cerebral blood vessel. Aneurysms are considered as the consequence of an abnormal blood flow. Increased hemodynamic stress leads to vessel damage and subsequent inflammation.[1] The inflammatory process can be harmful to the vessel, leading to apoptosis of its smooth muscle cells and to progressive weakening of the vessel, as they are the primary matrix-synthesizing cells in the vessel.[1]

The lesions are widely spread in the adult population. Some studies suggest that the prevalence of IA among this group can reach up to 5%.[2] Clinical prognosis can vary widely depending on the size of the lesion.[3,4] Subarachnoid hemorrhage (SAH) is a major complication, occurring in about 6 to 7 persons annually, 85% of which can be directly attributed to aneurysm rupture.[5] Almost 2/3 of patients end up with a poor outcome such as death, or permanent disabilities.[6] The case fatality after SAH can reach up to 50% and even though it is more likely to happen in older people, half of the patients are under 55 years.[5]

Many attempts have been made to predict patient outcome after SAH with mixed results. Most studies use a combination of methods, including versions of the modified Rankin scale (mRS)[7] and Glasgow outcome scale (GOS),[8] as well as variables such as the patient's gender, age, history and aneurysm size and location.[7] The lack of consistency and precision in the methods used casts doubt on their ability to predict outcomes reliably.[9] A prime concern among patients with IA is arterial embolism; thromboembolisms occur when atherosclerotic plaques have their lipidic core exposed to the bloodstream.[9] Large thrombotic occlusions can happen either in the anterior or posterior intracranial circulation, resulting in cortical symptoms, as well as medullary and pontine infarction syndromes, respectively.[10] Atherosclerotic lesions are relatively common in patients with IA, with one study finding some visible atherosclerotic alterations in 37% of the patients during operations.[11]

The formation and progression of atherosclerotic plaques is a multifactorial process, but one key contributor to it is the low-density lipoprotein cholesterol (LDL). When deposited in the vessel's wall, LDL oxidizes, attracting monocyte-derived

cells to the lesion's site. Those cells penetrate the vessel wall due to its reduced integrity, reaching the sub endothelial space where they will differentiate into mature macrophages. Those macrophages will eventually internalize the lipoproteins to form the foam cells and the plaque.[12,13] Therefore, it stands to reason that the inhibition of LDL synthesis could prove to be an effective way of preventing strokes. Some of the major drugs capable of affecting LDL synthesis are statins, competitive inhibitors of HMG-CoA reductase that end up inhibiting overall lipoprotein synthesis in the liver and, consequentially, LDL production.[14] Additionally, it has been found that statin increases the high-density lipoproteins (HDL),[15] which have been linked with atherosclerotic plaque regression.[16]

Cholesterol levels have also shown association with other vascular diseases;[17] and while lower levels of LDL and higher levels of HDL are associated with the prevention of atherosclerotic plaque formation, the opposite is true regarding the prevention of SAH,[18] making the role of statin in IA even more unclear.

As there is evidence to support the efficacy of statin in the prevention of strokes,[19] this study aims to investigate the possible correlation between statins, serum cholesterol levels and outcome for IAs after 6 months.

Methods

Study Design

This is a prospective single-center cohort study with patients who were admitted in the hospital due to SAH, between January 2018 and November 2019. All patients were treated with either microsurgery or embolization. Social and demographic data were acquired from charts of patients from the department of neurosurgery of the Hospital das Clínicas (HCFMUSP) database. It was also collected information about statins use, high cholesterol levels, presence of atherosclerotic plaques with radiological image, and aneurysm intracranial rupture status upon admission. The mRS scores were collected prospectively at 6 months of follow-up.

Population Data

The study recruited 401 patients (adult men and women) from the Department of Neurological Surgery of the Hospital das Clínicas da FMUSP (HCFMUSP). After admission, the patients were divided in two groups: the first included patients with SAH and ruptured aneurysm (244), and the second included patients with unruptured aneurysms undergoing elective surgery (177).

Data from 401 patients were analyzed, and 35 were included in this study (►**Fig. 1**). All 35 patients with data for serum cholesterol, use of statins, and presence or not of atherosclerotic plaque were followed for 6 months for outcome evaluation.

A questionnaire concerning previous risk factors to aneurysmatic disease was performed, which included hypertension, smoking, alcoholism, drug abuse, family history, previous SAH and date of the last event. Besides that, a socioeconomic evaluation of the participants was performed, assessing: educational level, family income, occupation, and marital status. Patients were followed for 6 months. At the end of the study, mRS and GOS were used to measure outcome after SAH.

Exclusion Criteria

Patients with missing cholesterol and statins use data, radiological images for atherosclerotic plaques status, or who stopped attending the follow-up appointments in less than 6 months were excluded from the study.

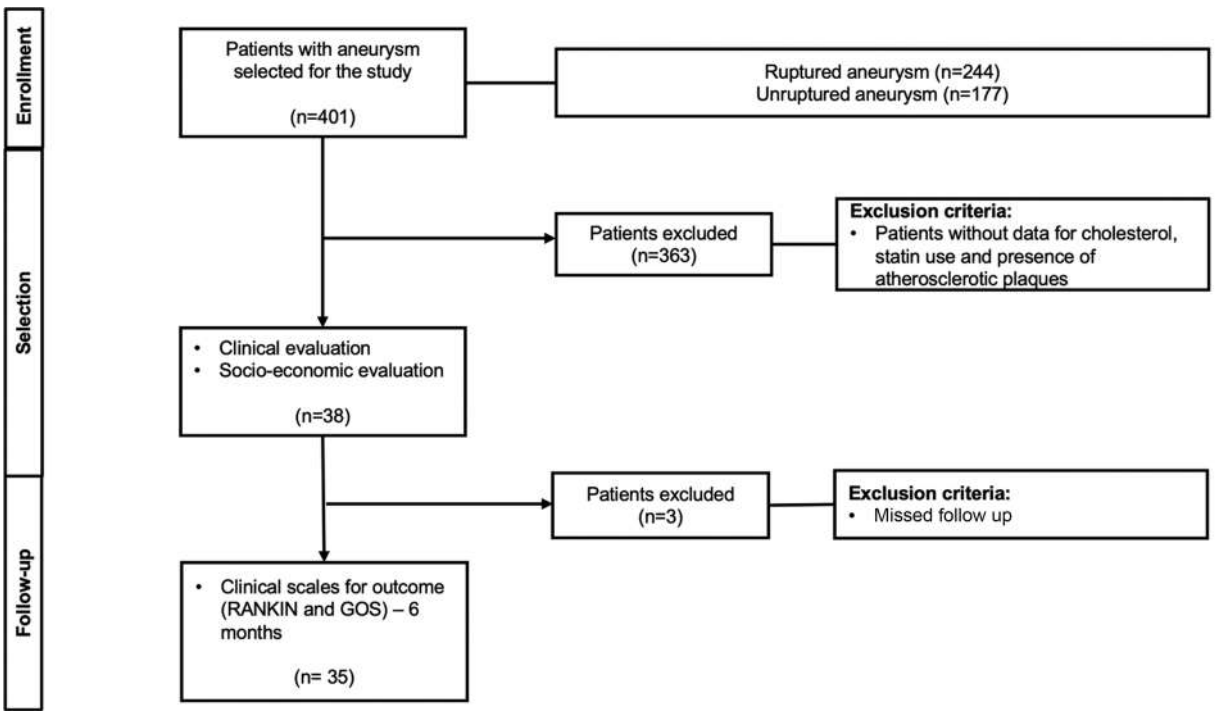

Fig. 1 Population data and selection process based on inclusion and exclusion criteria. Thirty-five patients were included in this study.

Inclusion Criteria

All patients were included, regardless of gender and age, with ruptured and unruptured brain aneurysms who were admitted to HCFMUSP between January 2018 and November 2019. Patients with high-grade SAH, rated 4 or 5 in the Hunt Hess scale, were not included.

Statistical Analysis

We used univariate linear and logistic regressions with statin use, presence of atherosclerotic plaques, and high cholesterol as independent and dichotomous variables. High cholesterol was defined as a serum cholesterol higher than 200 mg/dl. Serum cholesterol at admission was also used as an independent and continuous variable. The outcome was mRS at 6-months. Significance level was established as 0.05. For the logistic regression, unfavorable outcome was defined as mRS score greater than 2.

Patients were also divided in ruptured and unruptured aneurysm groups. The prevalence of statin use between the groups was analyzed with Fisher exact test for categorical data. A significance level of 0.05 was used.

Results

Epidemiology and Comorbidities

Among the 35 patients included in the study, the average age was 57.71 ± 9.79 years, and 91.4% were male. Hypertension was present in 62.9% of the patients, 22.9% had previous diabetes mellitus, 37.1% were smokers, 14.3% were heavy alcohol drinkers and 42.9% patients had ruptured aneurysm. (►**Table 1**). Regarding treatment, 6% were treated with embolization and 93% with microsurgery. No patients had previous history of ruptured aneurysms.

Serum Cholesterol and Outcome

The median Glasgow coma scale (GCS) at admission in the hospital was 14.

The mean value of serum cholesterol in the group with unruptured aneurysm was 195.2, and in the ruptured aneurysm group was 211.6. This difference was not statistically significant ($p > 0.05$). The mRS score at 6 months was on average 1.4 ± 0.91. The mean serum cholesterol upon admission was 202.25 ± 46.28 (►**Fig. 2**). A total of 17 patients had cholesterol levels higher than 200 mg/dl, with 52,9% being in the ruptured aneurysm group.

The linear regression using cholesterol as a predictor and the mRS score at 6 months shows that cholesterol does not have a statistically significant influence in the outcome measured by the mRS ($p > 0.05$). However, adding an interaction term for serum cholesterol and rupture of aneurysm, the linear regression model shows that these two variables are influenced by one another ($p = 0.0382$).

Despite the fact serum cholesterol itself does not show a significant influence, high cholesterol shows a tendency for

Table 1 Patient characteristics

Intracranial aneurysm		Unruptured (20)	Ruptured (15)	*p*-value
Epidemiology				
	Age (years)	60.8 (8.14)	53.73 (10.61)	**0.04**
	Gender (male)	18 (90%)	14 (93.3%)	1.00
	Hypertension	12 (60%)	10 (66.7%)	0.74
	Diabetes mellitus	4 (20%)	4 (26.7%)	0.70
	Smoking	5 (25%)	8 (53.3%)	0.16
	Alcoholism	2 (10%)	3 (20%)	0.63
	Previous SAH	0	0	–
	Multiple aneurysm	7 (100%)	5 (35.7%)	**0.01**
Clinical Scales				
	Hunt Hess - admission	–	2.5 (1.23)	–
	WFNS - admission	–	2 (1.29)	–
	GSC - admission	–	13 (3.06)	–
	GOS - 6 months	4.75 (0.64)	4.8 (0.41)	0.78
	mRS - 6 months	1.4 (1.0)	1.4 (0.83)	1.00
Variables				
	Serum cholesterol (mg/dL)	195.2 (40.2)	211.6 (53.2)	0.33
	Atherosclerotic plaque	7 (35%)	5 (33.3%)	1.00
	Statins	4 (20%)	1 (6.7%)	0.37

Abbreviations: GOS, Glasgow outcome scale; GCS, Glasgow coma scale; mRS, modified Rankin scale; SAH, subarachnoid hemorrhage. Data is presented as mean (SD) for continuous variables, and count (%) for categorical variables. Patients were divided in ruptured and unruptured aneurysm. *P*-value shows comparison between groups.

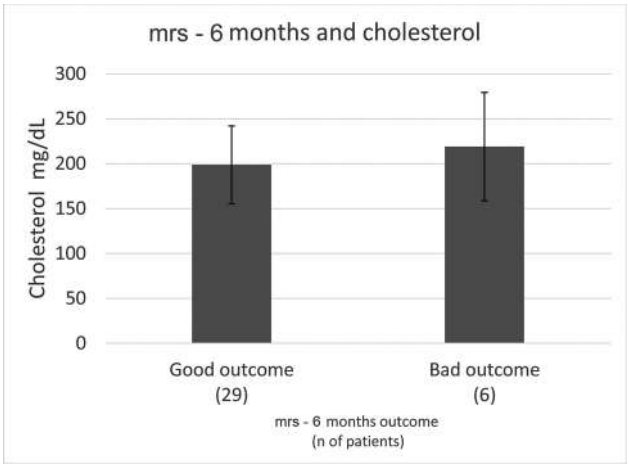

Fig. 2 Patients' admission cholesterol and mRS scale at 6 months. Unfavorable outcome was defined as mRS score greater than 2. Favorable outcome was defined as a score lower or equal to 2.

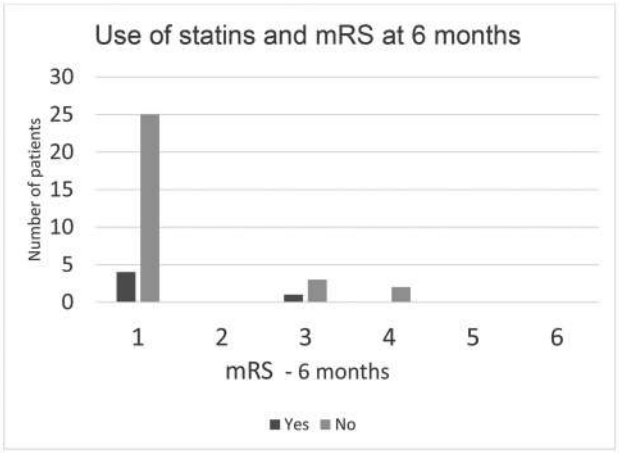

Fig. 3 Distribution of mRS – 6 months for outcome evaluation based on statins use.

worse outcomes in the ruptured aneurysm group (0.76 increase in mRS score for every 100 mg/dl increase in serum cholesterol [-0.05; 1.57], $p = 0.064$), but a tendency for better outcomes in the unruptured aneurysm group (-0.705 mRS score decrease for every 100 mg/dl increase in serum cholesterol [-1.87; 0.46], $p = 0.223$).

Statin and Outcome

In the unruptured aneurysm group, 20% were using statins. In the ruptured aneurysm group, only 6.7% were using this medication. This difference was not statistically significant ($p > 0.05$) (►**Fig. 3**).

The linear regression with "use of statins" as a predictor and the mRS scale score at 6-months shows that statins does not have a statistically significant influence in the outcome measured by the mRS ($p > 0.05$).

The sub analyses with ruptured and unruptured aneurysm show no difference in either group ($p > 0.05$). However, while patients using statins had a tendency for worse outcomes in unruptured aneurysm (0.125 increase in the mRS at 6 months [-1.07; 1.32]), statin use was correlated with better outcomes in ruptured aneurysm (-0.429 decrease in the mRS at 6 months [-2.33; 147.]) (►**Table 2**).

Atherosclerotic Plaques and Outcome

In the unruptured aneurysm group, 35.0% had atherosclerotic plaques. In the ruptured aneurysm group, only 33.3% presented atherosclerotic plaques. This difference was not statistically significant ($p > 0.05$).

All atherosclerotic plaques were directly correlated with the aneurysm's site, with 11 cases (32.3%) being in the posterior communicating artery, 10 (29.4%) in the middle cerebral artery, 6 (17.6%) in the anterior communicating artery, 5 (14.7%) in the internal carotid artery and 2 (5.8%) cases in the anterior cerebral artery.

Table 2 Linear regression model for prediction of outcome 6 months after intracranial aneurysm event

Simple linear regression				
Coefficients for univariate analyses:	**Ruptured**		**Unruptured**	
	Estimate	***p*-value**	**Estimate**	***p*-value**
Atherosclerotic plaques	0.0	1.0	−0.176	0.717
Cholesterol	0.760	0.064	−0.705	0.223
Statins	−0.429	0.635	0.125	0.829
Multiple linear regression				
Coefficients for multivariate analyses:	**Estimate**		***p*-value**	
Intercept	2.785		–	
Atherosclerotic plaques	−0.031		0.927	
Cholesterol	−0.700		0.194	
Statins	−0.041		0.930	
Rupture	−2.982		0.051	
Interaction (rupture: cholesterol)	0.015		0.047 *	

Serum cholesterol, use of statins, and presence of atherosclerotic plaque were used as independent variables. Multiple linear regression scale measured at 6 months was defined as outcome.

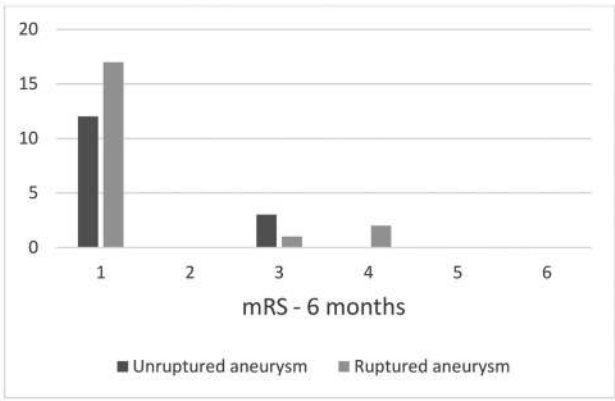

Fig. 4 Distribution of ruptured and unruptured aneurysm based on outcome measured by mRS scale – 6 months.

The linear regression with "presence of atherosclerotic plaque" as a predictor and the mRS score at 6-months shows that atherosclerotic plaques do not have a statistically significant influence in the outcome measured by the mRS ($p > 0.05$).

The sub analyses with ruptured and unruptured aneurysm show no differences in either group ($p > 0.05$). There was also no statistically significant difference in the distribution of ruptured and unruptured aneurysm based on the mRS at 6 months ($p > 0.05$) (►**Fig. 4**).

Discussion

There are many ways already used to predict IA outcome. The World Federation of Neurological Surgeons' (WFNS) Grading System for Subarachnoid Hemorrhage scale correlates lack of ruptured aneurysm and higher levels of consciousness with better outcomes.[20,21] Further research seems to indicate that advanced age and larger aneurysms contribute to worse outcomes.[22] Notably, cholesterol levels and the presence of atherosclerotic plaques are absent from these scales, despite being so intertwined with the disease's pathophysiology that it would not be unreasonable to think they may have some impact in its outcome.

The serum cholesterol level may be absent from most outcome predictors, but we can find it somewhat indirectly in statin research. The role of statins as a preventive factor in IA remains ambiguous in the literature. In some animal models it has been found that they could either halt[23] or promote[24] IA progression. In clinical studies however, no correlation was found between statin use and IA prevention,[25] aligning with our findings.

Even though the biochemical role of statins in reducing the inflammatory processes in the vessels walls is largely understood, it doesn't seem to correlate with actual clinical studies when it comes to IA prevention. The inflammatory process in the vessel where macrophages turn into foam cells and form plaques can be attributed to LDL, as its oxidized form is incorporated into these cells.[26] The oxidized LDL induces the vessel's endothelium to express certain molecules that allow monocytes to adhere and infiltrate the vessel.[27] Because statins reduce LDL[15] and oxidized LDL[28] levels, the logical conclusion would be that they should be beneficial to prevent intracranial aneurysms. Since this assertion is not verified by clinical trials, inflammation does not fully explain the underlying causes of IAs, and other factors are probably at play.

Despite the lack of statistical significance in our study regarding the tendency of higher levels of cholesterol to correlate with worse outcomes, other studies could verify this relation.[28,29] Measuring cholesterol as a whole might be problematic when it comes to outcome. Systematic reviews and meta analyses[18] show that even though hemorrhagic strokes are negatively correlated with total cholesterol levels, only a higher level of HDL is positively associated with hemorrhagic strokes, LDL being the opposite.[18]

One possible reason for this phenomenon would be that low levels of cholesterol could promote necrosis in the arterial medial layer's smooth muscle cells,[30,31] making the vessel more likely to suffer microaneurysms.[32] Another theory claims that low cholesterol may reduce platelet aggregability, thus making hemorrhage more likely.[30,33] This might explain why we couldn't find a correlation between statin use and better outcomes, as it primarily reduces LDL levels and the increased likelihood for hemorrhagic stroke may mitigate their benefits. It is important to note that statin therapy was not associated with increased risks of hemorrhage.[34–38]

It has already been established that atherosclerosis is the underlying pathological basis of strokes, coronary artery disease, peripheral artery disease, and hipertension.[39–42] However, being the cause of the disease does not necessarily mean that the maintenance of cholesterol levels are the main contributors to negative outcomes. As a matter of fact, high cholesterol is only the sixth risk factor regarding attributable deaths in heart attacks and strokes.[42] Furthermore, literature is scarce when it comes to IA specifically, making it hard to determine if the maintenance of cholesterol levels is as important in intracranial aneurysms as it is in other cardiovascular diseases.[43,44] Despite the fact that our results could not establish any significant change regarding presence or not of atherosclerotic plaques and clinical outcomes, more research is required in the subject.

The relatively small number of patients with concomitant data for statin use, serum cholesterol level and presence of atherosclerotic plaque, might explain the lack of statistical significance for some variables in our study. Moreover, a clinical trial with randomization of treatment with statins and a longitudinal control of serum cholesterol levels is also necessary for a definitive answer. Other limitations include the lack of a model with more variables that affect IA outcomes, and data for use of different types of statin and their dose, which may interfere with results.

Patients with major complications of IA have notably poor outcomes,[45,46] making accurate prediction a valuable tool in the decision making process of the treatment.[47] Current prediction methods can be helpful to define probable outcome, but they are not always accurate nor widely used.[45–48] Even though we could not find a correlation between

cholesterol levels and outcome, the investigation of other pathophysiological components of IA may prove helpful in determining a more accurate outcome.

Conclusion

Intracranial aneurysm is an important healthcare problem, and understating the factors that might have an influence in the outcome of IA is the key for an adequate treatment. Our results show that there is no statistical significance to prove that use of statins, serum cholesterol and the presence of atherosclerotic plaque correlate with worse outcomes, even though ruptured aneurysms were associated with higher levels of serum cholesterol. Multiple and opposite mechanisms might be involved in the circumstance of IA and further studies are needed to describe and understand the pathophysiology specific for IA.

Ethical Standards

This research project was approved by the Ethics and Research Committee of the Hospital das Clínicas of the FMUSP. Online registration CAPPesq: 15226. Approved 06/20/2016. Approved on the Brazilian platform CAAE, number: 61719416.6.0000.0068

Conflict of Interests

The authors have no conflict of interests to declare.

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Nasosinusal Endoscopic Anatomy and Physiology

Anatomia e fisiologia da endoscópica nasossinusal

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Abstract

The present article focuses on the analysis of the nasal cavity's anatomy succinctly and descriptively. This essay was carried out through a bibliographic review, directed to the detailed anatomy of the nasal cavity, and the structures that form its sinuses. We have identified the need for more studies directed to the related anatomical area so that the improved knowledge of this region ensures a nasoendoscopic treatment with better effectiveness and no complications.

Keywords
- anatomy
- nasal cavity
- nasoendoscopy
- neurosurgery

Resumo

O presente artigo foca na análise da anatomia da cavidade nasal de forma sucinta e descritiva. Esse trabalho foi realizado através de uma revisão bibliográfica, direcionada à anatomia detalhada da cavidade nasal, e às estruturas que formam seus seios. Constatamos a necessidade de mais estudos direcionados à área anatômica relacionada para que o conhecimento aprimorado desta região possa garantir um tratamento nasoendoscópico de melhor efetividade e sem complicações.

Palavras-chave
- anatomia
- cavidade nasal
- nasoendoscopia
- neurocirurgia

Introduction

In the areas of otorhinolaryngology and neurosurgery, endoscopic surgery has evolved significantly in the last decades. This happened due to improvements in endoscopy, such as the development of instruments for endonasal use, bipolar coagulation, and neuronavigation by image, which enabled better visualization of the nasosinusal region anatomy and the skull base.[1]

Tumors of the nasal cavity and paranasal sinus tend to be diagnosed at a late stage since their symptoms are usually attributed to more common etiologies. Nasal lesions include sinonasal papilloma, hemangioma, malignant fibrous histiocytoma, fibromatosis, leiomyoma, ameloblastoma, myxoma, hemangiopericytoma, fibroma, bone and bone-fibrous lesions, such as fibrous dysplasia, ossifying fibroma, and osteoma. Intracranial tissues can extend to the nasal area and present as encephaloceles, meningoceles, and pituitary tumors.[2]

Currently, transnasal, and especially transsphenoidal, approaches have been performed jointly by neurosurgeons and otorhinolaryngologists, which allowed a better transsphenoidal endonasal access to the skull base, avoiding extensive and traumatic dissections of the nose and, possibly, the oral region. These approaches, performed with the

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use of a rigid nasal endoscope, provide excellent visualization, allowing the surgeon to perform a precise and meticulous dissection with greater nose anatomy and function. These characteristics represent a great advance, especially for the sphenoid sinus surgery, which is the main gateway for the treatment of injuries that affect the skull base.[1]

Therefore, the goal of the present study was to explain in detail the anatomical components of the nasal cavity in order to enable an efficient approach in neurosurgical treatments.

Methodology

The methodology concerns a bibliographic review on physiology and nasosinusal endoscopic anatomy. The research was carried out from already prepared material, comprised of books and scientific articles. The research started in November 2019, extending until April 2020. The bibliographic survey contained in the current study was obtained through research in book and scientific articles, found in the Medline virtual databases via PUBMED, SCIELO, and Virtual Library, using the descriptors: *anatomy*, *nasal cavity*, *nasoendoscopy*, and *neurosurgery*.

Initially, the selected material was read using the inclusion criterion, with a 13-year time frame, from 2006 to 2019. After this selection, four books and fice articles were compiled. Articles whose topic was not relevant to the research and were outside of the delimited time frame were excluded.

Then, we started the descriptive analysis of the theme, according to the survey of pertinent information from the respective studies and, finally, the elaboration of the conclusion obtained through the analysis of the compiled texts.

Discussion

Paranasal Sinuses

The paranasal sinuses include the sphenoidal, ethmoidal, maxillary, and frontal sinuses (►**Fig. 1**). The lateral nasal part includes the inferior, middle, superior, and supreme turbinates, as well as the ostiomeatal complex and the nasolacrimal duct and orifices, which are highly vascularized.[2] The paranasal sinuses are extensions, filled with air, from the nasal cavity respiratory part of the following skull bones: frontal, ethmoid, sphenoid, and maxilla.[3]

Ethmoid Bone

The ethmoid bone is located between the orbital cavities and is part of the upper half of the nasal skeleton.[4]

This bone has four main components: the crista galli, the cribriform plaque, the perpendicular plaque, and the bilateral ethmoidal labyrinths, the last of which are formed from the lateral, medial, posterior, superior, and antero-inferior regions.[5]

Located on both sides of the ethmoid bone lateral region, these portions merge and remain joined by the crusty laminae, forming a continuous horizontal plate. In the medial fusion region between the two blades, there is a perpendicular plate called the crista galli.[5]

Medially, the ethmoid bone is limited by three conchae. The middle or first concha, the upper or second concha, and the supreme or third ethmoidal concha.[5] The second concha is located in the upper third of the nasal cavity, with its anterior portion opposite the medial central tendon (►**Fig. 2**).[4]

In the posterior part, the anterior wall of the sphenoid sinus delimits the ethmoidal cells. Anteroinferiorly, the ethmoidal cells undergo an opening to the ethmoidal infundibulum and posterior nasal cavity and choanae. The upper region is then formed by the frontal bone through the ethmoidal fovea.[5]

Finally, it is very important to mention the ethmoidal labyrinth. It is inserted in the crusty plate and has its own bone limits. The lateral part is formed by the lamina papyracea that separates the orbit from the ethmoid labyrinth. This anatomical region is of clinical relevance when thinking about the cases in which the lamina papyracea is dehiscent, as in these cases a pathway for the spread of inflammatory processes to the orbit becomes possible.[5]

Ethmoidal Cells

The ethmoidal cells are located between the orbit and the nasal cavity. These cells are the middle- and upper-nasal mucous membranes, small meatus invaginations for the ethmoid.[3]

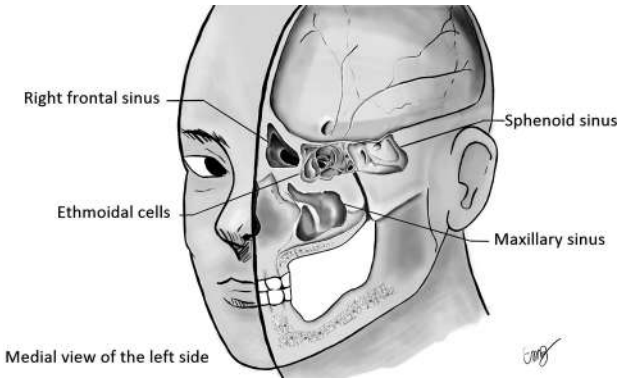

Fig. 1 The paranasal sinuses are composed of the frontal, maxillary, ethmoidal, and sphenoid sinuses. They are filled with air and extensions from the nasal cavity to the skull bones. (Source: Estevan Martin Portela Júnior).

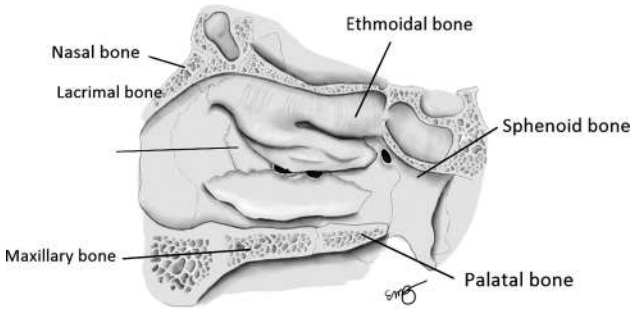

Fig. 2 The ethmoidal bone is located between the orbital cavities, and it is composed by the crista galli, cribriform plaque, perpendicular plaque, and bilateral ethmoidal labyrinths. Medially, it is limited by three conchae, the superior, medium, and inferior conchae. (Source: Estevan Martin Portela Júnior).

Such cells are divided into anterior, middle, and posterior ethmoidal cells. The anterior ones drain into the middle nasal meatus through the ethmoidal infundibulum, both directly and indirectly. The middle ethmoidal cells—also called bullous cells—open directly in the middle meatus. The posterior ethmoidal cells open in the upper meatus. All of these cells are innervated by the nasociliary nerves' anterior and posterior branches.[3]

Lamellae of the Ethmoidal Labyrinth

Bone gills are thin, flattened structures that are usually found very close to each other. The spaces that are formed between the lamellae are called meatus.[3] During the embryonic development, the ethmoid labyrinth lamellae are externalized through the ethmoid on the nose's lateral wall, thus being called basal lamellae. There are five lamellae found in this region: the upper and supreme conchae, which we may or may not have, the middle concha basal lamella, the ethmoidal bulla, and the uncinate process.[5]

1- Uncinate Process

It is a thin bony structure that is located in the anterosuperior to posteroinferior direction. In the super posterior direction, the border is concave and parallel to the ethmoidal bulla's anterior surface. Anteroposteriorly, it is inserted in the middle concha, forming the agger nasi inferior-medial wall. In the lower portion, the uncinate process is inserted in the lower concha and in the palatine bone.[5]

Between the ethmoidal bulla and the uncinate process, at its free edge, is the lower semilunar hiatus, a slit that corresponds to the passage to the ethmoidal infundibulum.[3]

Finally, the uppermost portion is not visible; it can, however, can have three different types of insertion[5]:

- Laterally, it is inserted in the lamina papyracea. Consequently, the infundibulum is closed superiorly in a blind bottom, denominated the terminal recess. In this case, the ethmoidal infundibulum and the frontal recess are separated. Therefore, the frontal recess opens in the middle meatus between the infundibulum and the middle concha;
- Skull base, in the region of the superior ethmoid;
- Middle concha.

In the possibilities of the skull base and middle concha, the frontal recess and frontal sinus drain directly into the ethmoidal infundibulum. Thus, the chance of simultaneous involvement of the maxillary and frontal sinuses is greater since the drains from both sinuses have a common route.[5]

2- Ethmoidal bulla (Second lamella)

The ethmoidal bulla corresponds to the largest anterior ethmoidal cell. It is formed by bullar- lamella pneumatization. Laterally, it comes in contact with the lamina papyracea. Subsequently, it may present variable distances from the middle concha basal lamella and the middle concha diagonal portion. The medial limit is the middle concha's vertical portion. When there is a three-dimensional space between the bulla and the middle concha basal lamella, it is called the retrobulbar recess or lateral sinus, and the entrance to this space is called the upper semilunar hiatus.[5]

3- Middle concha (diagonal portion of the third, or basal, lamella)

To guarantee the stabilization of this lamella, the middle concha has three insertion parts[5]:

- Anterior (vertical portion);
- Average (diagonal portion);
- Posterior (horizontal portion).

Anteriorly, it is inserted in a sagittal direction into the lateral portion of the crusty lamina. Medially, the insertion is in the lamina papyracea and/or in the medial wall of the maxillary sinus, forming the middle meatus' most posterior roof.[5]

It is the middle concha's basal lamella that separates the ethmoidal cells in anterior and posterior. The upper meatus may extend anteriorly and inferiorly, thus causing a bulging anteriorly. The basal lamina's middle third may present irregularities with anterior and posterior bulging. This happens due to the extension of posterior and anterior ethmoidal cells.[5]

The middle concha's posterior portion borders the palatal bone's perpendicular-process ethmoidal crest. Immediately after the insertion of this portion, it meets the local sphenopalatine foramen, which passes the sphenopalatine arteries and veins and the posterior and superior nasal nerves.[5]

Lower Conchae and Meatus

The inferior nasal concha is formed by an independent bone, and it is covered by a mucous membrane that contains large vascular spaces that increase and control the nasal cavity caliber.[3]

The inferior concha is a thin bony blade curved at its free edge, and it inserts on the maxilla nasal surface and the palatal bone's perpendicular blade. Embryologically, it has a different origin from other conchae. The inferior concha results from the endochondral and maxillary region's bony infiltration.[3]

There are three prominences that protrude from the lower concha. The most anterior prominence corresponds to the lacrimal process that connects to the lacrimal bone and the nasolacrimal duct's ostium. The most median prominence, the inferior concha ethmoidal process, connects to the uncinate process and separates the anterior from the posterior fontanelle. The posterior prominence, which is the maxillary process, forms the maxillary sinus medial part.[5]

The inferior nasal meatus is a horizontal passage located in an inferolateral position to the inferior nasal concha. The nasolacrimal duct, which drains tears from the lacrimal sac, opens at the bottom of this meatus[3] (►**Fig. 3**).

Turbinates and Superior Meatus

Super posterior to the ethmoid's medium process is the spheno-ethmoidal recess, which receives the sphenoidal sinus opening.[5]

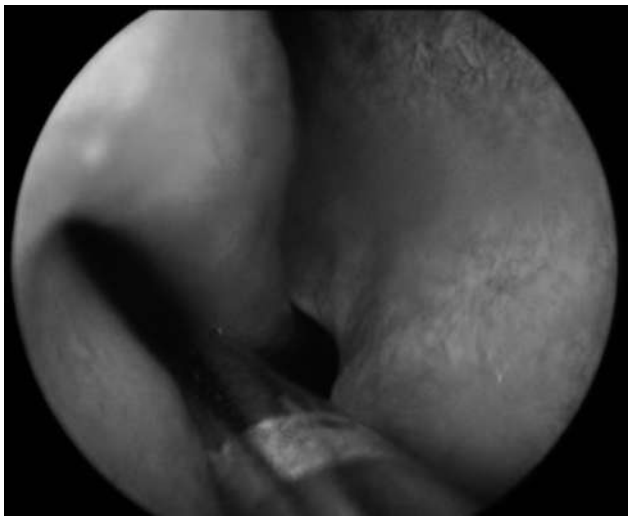

Fig. 3 Inferolateral position to passage the inferior nasal meatus; the nasolacrimal duct opens at the bottom of this meatus. (Personal archive of Dr Marcelo Nery Silva).

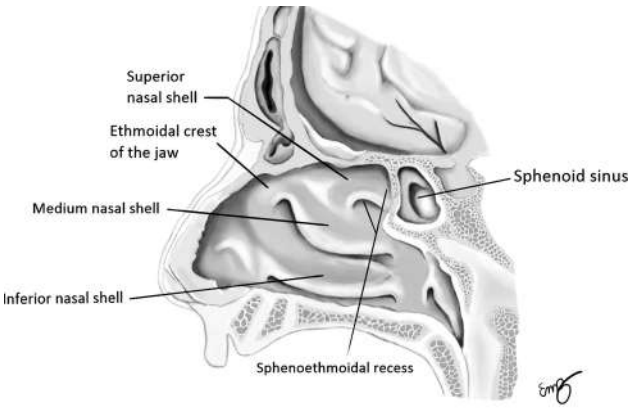

Fig. 4 The superior-posterior part of the ethmoid is the sphenoethmoidal recess, which receives the opening of the sphenoidal sinus. The ethmoidal sinuses open through one or more hole of the upper nasal meatus in which is a narrow passage between the upper and middle nasal turbinates. (Source: Estevan Martin Portela Júnior).

The upper nasal meatus is a narrow passage between the upper and middle nasal turbinates, in which the posterior ethmoidal sinuses open through one or more holes.[3] (►**Fig. 4**). There may even be a fourth or fifth (supreme) turbinate.[5]

Nose Sidewalls Spaces

Semilunar Hiatus

The semilunar hiatus is involved superiorly by the ethmoidal bulla, laterally by the orbit, inferiorly by the uncinate process, and, medially, it communicates with the middle meatus. Laterally and inferiorly, the semilunar hiatus communicates with the infundibulum. The ethmoidal bulla generally consists of a single aerated cell, which projects inferior-medially over the semilunar hiatus.[6]

The lower semilunar hiatus corresponds to a two-dimensional cleft that is located between the posterior margin of the uncinate process and the anterior wall of the ethmoidal bulla. It gives access to a space (therefore, three-dimensional) called the ethmoidal infundibulum.[6]

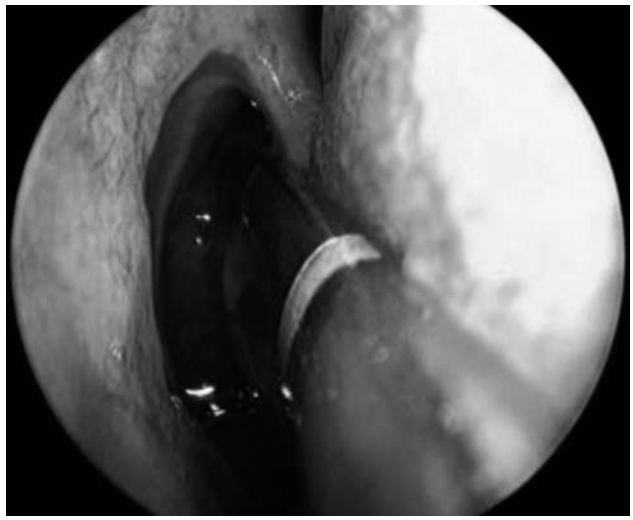

Fig. 5 The lower semilunar hiatus is a two-dimensional space that represents the entrance to the ethmoidal infundibulum. In this endoscopic image, the lower semilunar hiatus is found between the posterior free edge of the uncinate process and the anterior portion of the ethmoidal bulla. (Personal archive of Dr Marcelo Nery Silva).

The upper semilunar hiatus is the two-dimensional structure located between the ethmoidal bulla and the basal lamella, which communicates the retrobullar recess with the middle meatus[5] (►**Fig. 5**).

Ethmoidal Infundibulum

Through the lower semilunar hiatus, there is a three-dimensional space called the ethmoidal infundibulum. Its limits are:

1. Medial wall: uncinate process;
2. Lateral wall: lamina papyracea;
3. Anterior wall: formed by the uncinate process junction with the structures that form the infundibulum lateral wall;
4. Posterior wall: ethmoidal bulla.

The ethmoidal infundibulum connects the ostium maxillary and ethmoidal sinuses to the semilunar hiatus. The greater the uncinated process, the narrower the ethmoidal infundibulum becomes.[5]

Frontal Recess

The frontal recess is a narrowing between the frontal sinus and the anterior middle meatus, usually located in the infundibulum anterosuperior portion. It proceeds through the semilunar hiatus to the middle meatus anterior portion, where it joins the ipsilateral maxillary sinus flow.[6]

Its limits are generally:

1. Anterior: agger nasi and frontal cells;
2. Posterior: variable according to the ethmoidal bulla;
3. Lateral: lamina papyracea;
4. Medial: middle turbinate's most anterior and upper portions. The olfactory fossa, which is the anterior cranial

fossa's most anterior portion, is located superiorly to the middle turbinate insertion;
5. Superior: frontal and ethmoid bone.

Depending on the uncinate process insertion, it can be part of the frontal recess medial or lateral walls, and the frontal recess can open in the middle meatus or in the ethmoidal infundibulum.[5]

Suprabullar and Retrobullar Recess

Located superior and medially to the bullar lamella and the ethmoidal bulla. It is limited superiorly by the roof of the ethmoid, inferiorly by the roof of the ethmoidal bulla, laterally by the lamina papyracea, and posteriorly by the middle turbinate basal lamella. Anteriorly, the suprabular recess is separated from the frontal recess only when the bullar lamella is inserted in the skull base.[5]

The retrobullar recess is the space located in the posterior region of the anterior ethmoidal cells. Its limits are the lamina papyracea, laterally; the ethmoid roof, superiorly; the middle turbinate, posteriorly;-and the basal lamella, antero-inferiorly by the roof and ethmoidal bulla's posterior wall.[5]

Ethmoid Roof and Anterior Ethmoidal Artery

The ethmoid boné is superiorly opened in the two anterior thirds. Because of this, the frontal bone forms the ethmoid roof in this region.[5]

The anterior ethmoidal artery (AEA) is an important anatomical point used to locate the frontal sinus and the anterior skull base. Its injury during an endonasal procedure can cause serious complications, such as profuse bleeding, rhinoliquorrhea, artery retraction to the intraorbital region, and, consequently, orbital hematoma and even brain infections.[7]

In its intranasal path, the anterior ethmoidal artery is found in a bone canal called the anterior-ethmoidal canal. It departs from the orbit through the anterior ethmoidal foramen. This artery is responsible for the anterior ethmoidal cells and frontal sinus irrigation. It emits meningeal vessels in its pathway in the olfactory fossa and goes down to the nasal fossa, where it irrigates the septum anterior third and the adjacent nose lateral wall (►**Fig. 6**). It runs through the ethmoidal roof in a posteroanterior direction, and the spot where it penetrates the skull (cribriform union plate with the olfactory fossa's lateral lamella) is the most fragile and susceptible to lesions.[7]

Sphenoid Sinus

The sphenoid sinus has variable size and shape. It is divided into two asymmetrical parts by an irregular septum. When the sphenoid sinus is well developed, its thin and slender lateral wall forms the cavernous sinus medial wall. The internal carotid artery's intracavernous portion is the cavernous sinus' most medial structure, and, in well-developed sphenoid sinuses, it produces a bony elevation in its lateral

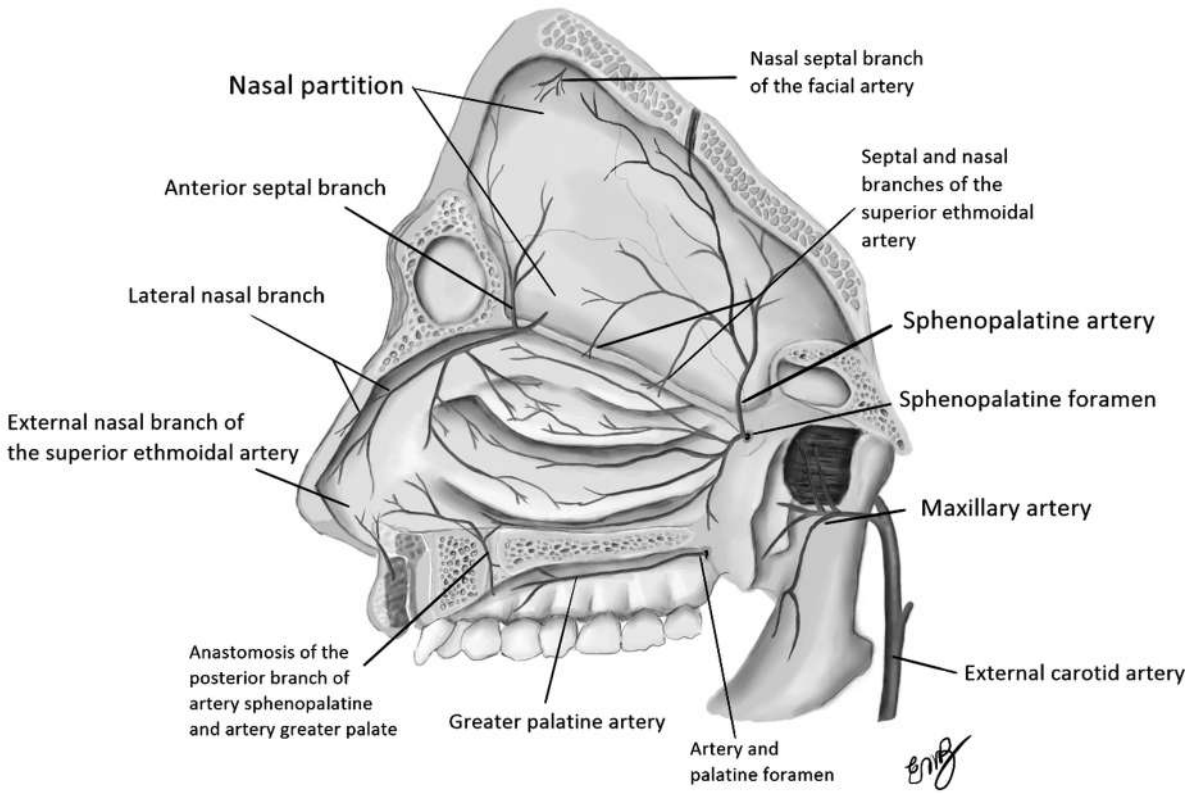

Fig. 6 Mirror image showing the main arterial irrigation of the nose. The anterior-septal branch irrigates the anterior-third of the septum and the lateral wall of the adjacent nose. (Source: Estevan Martin Portela Júnior).

wall, called carotid prominence. This prominence is divided into three segments: presellar, infrasellar, and rectosellar. The presellar segment corresponds to the anterior vertical segment and the internal carotid artery intracavernous portion's anterior curvature. The infrasellar segment corresponds to the carotid artery's short horizontal portion, and the posterior curvature and posterior vertical segment forms the rectosellar segment.[1]

With relative frequency, the optical channel is partially surrounded by the sphenoid sinus, producing a bony protuberance in the anterosuperior portion of its lateral wall. The bone depression is called an opticocarotid recess, and it is located between the optical channel and the carotid prominence presellar segment. The sphenoid sinus's lateral bone wall is usually very thin and may be absent in some areas. It is located over the internal carotid artery and the optic nerve.[1]

The sella turcica and the optical chiasm are located superiorly, inside the roof.[2] Just below the sella's tuberculum, the carotid arteries are closer together, with an average distance of 13.9 mm (range: 10–17 mm). In the anterior wall of the saddle, there is a 20-mm gap between the carotid arteries (range 13–26,5 mm), and, at the level of the clivus, the distance between them is 17.4 mm (range 10.5–26.5 mm).[1]

The pneumatization degree of the sphenoid sinus varies considerably, reaching other structures, such as the clivus and foramen lacerum. Previously, pneumatization may involve the septum and, anterolaterally, the pterygoid-process base.[5] Due to this substantial pneumatization, the sphenoid body is fragile.[3]

Maxillary Sinuses

The maxillary sinuses are the largest paranasal sinuses.[3] They are limited superiorly by the orbital floor, inferiorly by the alveolar and maxilla-palatine processes, and medially by the nose's lateral wall.[5]

Usually bilateral, they occupy the maxillary bone's body. The natural ostium is located deep in the ethmoidal infundibulum, and, in 88% of cases, it is hidden by the uncinate process' lower third internal mucosa. The visualization of the ostium in the middle meatus' endoscopic examination, with a 0° endoscope generally corresponds to an accessory ostium presence[5] (►**Fig. 7**).

The maxillary sinuses' arterial irrigation proceeds mainly from the maxillary artery's upper alveolar branches; however, the descending and greater palatine artery branches irrigate the sinus floor.[3]

They drain into the middle meatus and are later limited by the pterygopalatine and infratemporal fossae.[2] The maxillary sinuses innervation is performed by the anterior, middle, and posterior-superior alveolar nerves, which are maxillary nerve branches.[3]

Frontal Sinus

The frontal sinus goes through the frontal bone pneumatization from the frontal recess.[5] The right and left frontal sinuses are located between the frontal-external and internal blades, after the superciliary arches and the nose root. The

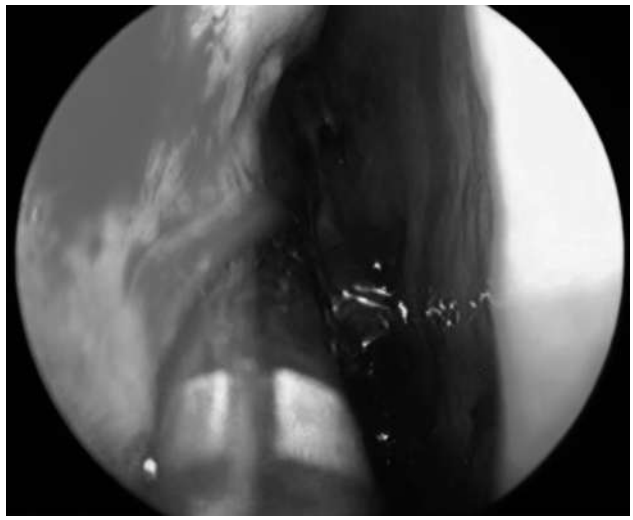

Fig. 7 The accessory maxillary sinus ostium. In 88% of cases, the maxillary sinus' natural ostium is hidden by the internal mucosa of the uncinate process. (Personal archive of Dr Marcelo Nery Silva).

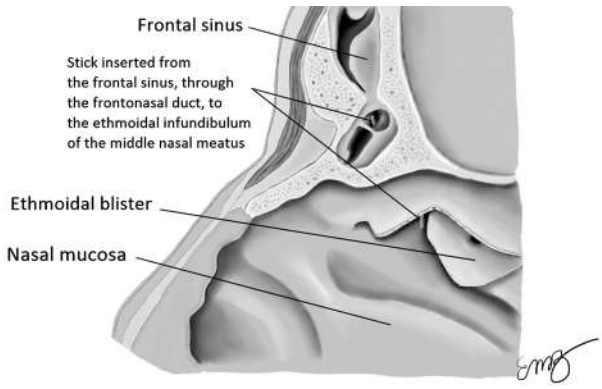

Fig. 8 Sagittal image showing the anatomical relationship between the frontal sinus and the nasal cavity. The frontal sinus drains into the middle meatus. (Source: Estevan Martin Portela Júnior).

asymmetrical air cavities in the frontal bone drain into the nasal cavity through the frontal recess.[2]

The frontal sinus recess can be occupied by several cells, and its anatomical variability is big. In a simplified way, the recess's anterior limit is the agger nasi (when present) and the posterior is the ethmoidal bulla. The uncinate process is the recess's lateral and lower limit when it is inserted in the lamina papyracea, forming the terminal recess.[5] Depending on the uncinate process' anterosuperior insertion, the frontal recess and frontal sinus may drain into the middle meatus or the ethmoidal infundibulum[5] (►**Fig. 8**).

Posterior Ethmoid

The posterior ethmoidal cells open directly into the upper meatus.[3]

They are found posteriorly to the middle turbinate basal lamella, being numbered from one to five. The posterior ethmoid is delimited superiorly by the skull base, laterally by

the lamina papyracea, medially by the middle and upper turbinates' horizontal portion, and later by the sphenoid sinus' anterior wall. All cells and slits belonging to the posterior ethmoid open posteriorly and above the basal lamella, in the upper meatus.[5]

Pterygopalatine Fossa and Sphenopalatine Artery

The pterygopalatine fossa is an elongated pyramidal space below the orbit. Its upper end opens at the lower orbital fissure. Its lower end is closed, except for the sphenopalatine foramen. Laterally, it opens into the infratemporal fossa. It is located between the sphenoid bone's pterygoid process. Posteriorly, it is delimited by the palatal bone's vertical lamina; medially and anteriorly by the maxillary bone posterior wall. The maxilla is located at the front, and its roof is formed by the sphenoid's larger wing. It communicates laterally with the infratemporal fossa through the pterygomaxillary fissure, medially with the nasal cavity through the sphenopalatine foramen, and posterior superiorly with the skull's middle fossa through the round foramen.[5]

The main source of blood in the nasal cavity comes from the sphenopalatine artery, an external carotid system branch. Located in the nasal cavity's posterior region, this artery is responsible for the most severe episodes of epistaxis.[8]

The maxillary artery, a branch of the external carotid artery, originates from the sphenopalatine artery, that passes through the sphenopalatine foramen and provides branches that irrigate the lateral and septal nasal wall mucosa.[5]

Conclusion

Knowledge of the nasal cavity anatomy is essential for the performance of correct and efficient neurosurgeries. There is also a need for more studies and scientific publications on this topic to understand the nasal cavity's anatomy and, therefore, major neurosurgical approaches frequency, like greater security due to the mastery of the studied anatomy.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

Conflict of Interests

The authors have no conflict of interests to declare.

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Chemical Angioplasty with Nitroglycerin for Vasospasm after Subarachnoid Hemorrhage: Case Series and Review

Angioplastia química com nitroglicerina para vasoespasmo após hemorragia subaracnóide: Série de casos e revisão

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Abstract

Introduction Vasospasm is a common and potentially devastating complication in patients with subarachnoid hemorrhage, causing high morbidity and mortality. There is no effective and consistent way to prevent or treat cerebral vasospasm capable of altering the morbidity and mortality of this complication. Animal and human studies have attempted to show improvement in aneurysmal vasospasm. Some sought their prevention; others, the treatment of already installed vasospasm. Some achieved only angiographic improvement without clinical correlation, others achieved both, but with ephemeral duration or at the expense of very harmful associated effects. Endovascular techniques allow immediate and aggressive treatment of cerebral vasospasm and include methods such as mechanical and chemical angioplasty. These methods have risks and benefits.

Objectives To analyze the results of chemical angioplasty using nitroglycerin (GTN). In addition, to perform a comprehensive review and analysis of aneurysmal vasospasm.

Methods We describe our series of 77 patients treated for 8 years with angioplasty for vasospasm, either mechanical (with balloon), chemical (with GTN) or both.

Results Eleven patients received only balloon; 37 received only GTN; 29 received both. Forty-four patients (70.1%) evolved with delayed cerebral ischemia and 19 died

Keywords
- intracranial vasospasm
- balloon angioplasty
- nitroglycerin
- aneurysmal subarachnoid hemorrhage
- cerebral hemorrhage
- vasodilator agents

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(mortality of 24.7%). Two deaths were causally related to the rupture of the vessel by the balloon. The only predictors of poor outcome were the need for external ventricular drainage in the first hours of admission, and isolated mechanical angioplasty.

Conclusions Balloon angioplasty has excellent results, but it is restricted to proximal vessels and is not without complications. Chemical angioplasty using nitroglycerin has reasonable but short-lived results and further research is needed about it. It is restricted to vasospasm angioplasties only in hospitals, like ours, where better and more potent vasodilator agents are not available.

Resumo

Introdução O vasoespasmo é uma complicação comum e potencialmente devastadora em pacientes com hemorragia subaracnóidea, resultando em alta morbimortalidade. Não existe uma forma eficaz e consistente de prevenir ou tratar o vasoespasmo cerebral capaz de alterar significativamente a morbidade e mortalidade desta complicação. Estudos em animais e humanos tentaram mostrar melhora no vasoespasmo aneurismático. Alguns buscaram sua prevenção; outros, o tratamento de vasoespasmo já instalado. Alguns conseguiram apenas melhora angiográfica sem correlação clínica, outros conseguiram ambos, mas com duração efêmera ou às custas de efeitos colaterais muito deletérios. As técnicas endovasculares permitem o tratamento imediato e agressivo do vasoespasmo cerebral e incluem métodos como a angioplastia mecânica e química. Estes métodos apresentam riscos e benefícios.

Objetivos Analisar os resultados da angioplastia química utilizando nitroglicerina (GTN). Além disso, fazer uma revisão e análise global acerca do vasoespasmo aneurismático.

Métodos Descrevemos nossa série de 77 pacientes tratados por 8 anos com angioplastia para vasoespasmo, seja mecânica (com balão), química (com GTN), ou ambas.

Resultados Onze pacientes receberam apenas balão; 37 receberam apenas GTN; 29 receberam ambos. Um total de 44 pacientes (70,1%) evoluíram com isquemia cerebral tardia e 19 faleceram (mortalidade de 24,7%). Dois óbitos foram diretamente relacionados à ruptura do vaso pelo balão. Os únicos fatores preditores de mau resultado foram a necessidade de drenagem ventricular externa nas primeiras horas de admissão e a angioplastia mecânica isolada.

Conclusões A angioplastia com balão tem excelentes resultados, mas é restrita a vasos proximais e não é isenta de complicações. A GTN possui resultados razoáveis, porém efêmeros, e mais pesquisas são necessárias. Fica restrita para as angioplastias por vasoespasmo apenas a hospitais, como o nosso, nos quais não há disponibilidade de agentes vasodilatadores melhores e mais potentes.

Palavras-chave

- vasoespasmo intracraniano
- angioplastia com balão
- nitroglicerina
- hemorragia subaracnóidea aneurismática
- hemorragia cerebral
- agentes vasodilatadores

Introduction

Cerebral vasospasm after aneurysmal subarachnoid hemorrhage (aSAH) is one of the most complex topics in medicine. It usually occurs between 4 and 21 days after subarachnoid hemorrhage (SAH) and represents a major cause of morbidity and mortality.[1–5] Nowadays, there is no consistent way to prevent this complication. Several studies have attempted to improve outcomes in aneurysmal vasospasm, part focused on prevention and part concentrated on treatment of already installed vasospasm. While some achieved only angiographic improvement without clinical correlation, others achieved both, but either with ephemeral duration or at the expense of very deleterious side effects. Endovascular techniques enable immediate and aggressive treatment for cerebral vasospasm and include methods such as percutaneous transluminal angioplasty (PTA) with balloon (mechanical PTA) and intra-arterial vasodilator infusion (chemical PTA). Both methods have risks and benefits, thus we present a series of patients with vasospasm treated by PTA.

Material and Methods

During the period from February 2013 to August 2020, a total of 802 ruptured aneurysms were treated by endovascular

procedures or microsurgical clipping at a single institution. A total of 77 consecutive patients with a diagnosis of cerebral vasospasm underwent PTA using drugs or balloon. There were no exclusion criteria for the procedure or choices for the best candidate.

The treatment was performed under general anesthesia in all cases. Diagnostic angiography was performed through the femoral artery (preferably in the right one) using low-osmolar nonionic contrast agent (Omnipaque , Nycomed, Oslo, Norway). Anticoagulation during the procedure was not employed. Initial intravenous boluses of heparin of 5,000 IU were infused when starting angiography, followed by 1,000 IU at each hour of the procedure. A 6F guide catheter (Chaperon, Microvention, Inc., Tustin, CA, USA; or Neuron, Penumbra, Inc., Alameda, CA, USA) was placed in the internal carotid or vertebral artery. Continuous flushing through catheters was maintained by infusion of 5,000 IU heparin per 1-L sodium chloride solution. Patients with symptomatic proximal stenosis (intracranial internal carotid artery [ICA], M1 segment of the middle cerebral artery [MCA] and A1 segment of the anterior cerebral artery [ACA]) were treated with balloon, while those presenting with distal stenosis were treated with drugs. Chemical PTA was performed by infusing a saline solution with 10% glyceryl trinitrate (GTN) in an average volume of 10mL (ranging from 5 to 20mL). Mechanical PTAs were performed employing a remodeling balloon (HyperForm 4×20 or 4×30; Medtronic, Irvine, CA, USA) over a guidewire (SilverSpeed, Avigo or X-Pedion, Medtronic, Irvine, CA, USA). The balloons were inflated under direct visualization by radioscopy and road-mapping and were kept opened for 3 seconds. All patients underwent control angiogram immediately and computed tomography (CT) scan or magnetic resonance imaging (MRI) within 24 hours after the procedure. At the end of the catheterization, intravenous heparin administration was interrupted but not antagonized. All patients were transferred to the intensive care unit (ICU), and low molecular weight heparin was maintained in prophylactic doses, without reaching anticoagulation. The outcome was evaluated immediately and at a 3-month clinical follow-up. The last consultation was held between 1 and 71 months (an average follow-up of 19.7 months).

Although it is not possible to compare the two groups, one in which the endovascular intervention was performed preferentially in large skull base arteries (carotid siphon, A1 and M1) and the other was performed by vasospasm in smaller distal arteries, we performed a multivariate search analysis searching a predictor of poor prognosis. The objective is not to seek superiority of one group over the other, as the angiographic vasospasm profile is different.

Statistical Analysis

Results of quantitative variables were described as mean, standard deviation (SD), median, minimum and maximum. Categorical variables were described by frequencies and percentages. The Fisher exact test or the chi-squared test was used to assess the association between two categorical variables. For the analysis of factors associated with poor neurological outcome (mRS ≥ 3), logistic regression models were adjusted. The estimated association measure was the odds ratio (OR). Factors associated with survival time were analyzed by adjusting Cox Regression models. The estimated measure of association was the hazard ratio. In all adjusted models, the Wald test was used to assess the significance of the variables. For measures of association between factors and outcomes, 95% confidence intervals (Cis) were presented. P-values < 0.05 indicated statistical significance. The data were analyzed using the computer program Stata/SE v.14.1 (StataCorp, College Station, TX, USA).

Results

Angioplasty for vasospasm was performed in 77 patients, of which 63 were female (81.8%) and 14 were males (18.2%), with a mean age of 52.7 ± 11.2 years old (20 to 75 years old). Hunt & Hess and Fisher mean scores were 2.8 and 3.5, respectively.

In this sample, the 77 patients had a total of 140 aneurysms; 33 patients had multiple brain aneurysms (42.9%), of which the MCA was the most common site, in 51 patients (36.42%). The most common topography of ruptured aneurysm was also the MCA in 23 cases (29.9%), followed by the anterior communicating artery (22 cases; 28.57%) and posterior communicating artery (17 patients or 22%). Ruptured aneurysms from other locations occurred in 15 patients (19.48%). Patient characteristics are summarized in ►**Table 1**.

Forty-five patients had a history of smoking (58.4%) and 32 never smoked (41.6%). The average smoking burden known among 28 smokers was 30.1 ± 16.4 pack-years. Twenty patients (26%) needed to undergo external ventricular drainage (EVD) in the first hours of hospital admission; 38 underwent microsurgical clipping of ruptured aneurysm and 39 underwent endovascular treatment (49.4 versus 50.6%, respectively), and this definitive treatment was performed in an average time of 4.64 days since the ictus (ranging from 0 to 60th ictus day).

Early treatment of the aneurysm, considered until the 3rd day of the ictus, was performed in 45 patients (58.4%). The remaining 32 patients (41.6%) had their ruptured aneurysm closed from the fourth day onwards.

The 77 patients underwent a total of 94 sessions of endovascular treatment with 117 angioplasties. One session corresponds to each time the patient was transported from the ICU to hemodynamics, with a femoral puncture and under the same general anesthesia. PTA is understood in each intervention, either with balloon or with GTN, both of which can be performed in the same session. These sessions were carried out on an average of 9.32 days, varying from the 1st to the 60th day of the ictus.

Sixty-six patients received GTN, in a total of 74 PTAs with GTN (either alone or with a balloon). Thirty-nine patients received balloon, in a total of 43 balloon PTAs (either alone or with GTN). Eleven patients received only balloon; 37 patients received only GTN; 29 patients received both GTN and balloon. There were 74 GTN chemical PTAs and 43 balloon PTAs (63.3 versus 36.7%).

Table 1 Epidemiological characteristics of patients

Age (years old) (mean)	52.7 ± 11.2 (20–75)	
Gender	Female	63 (81.8%)
	Male	14 (18.2%)
Year of ictus	2013	1
	2014	2
	2015	5
	2016	10
	2017	17
	2018	12
	2019	15
	2020	15
Hunt Hess (n)	1	12 (15.6%)
	2	19 (24.7%)
	3	29 (37.7%)
	4	7 (9.1%)
	5	10 (13%)
Fisher (n)	I	1 (1.3%)
	II	7 (9.1%)
	III	21 (27.3%)
	IV	48 (62.3%)
Ruptured aneurysm	MCA	23 (29.9%)
	ACom	22 (28.6%)
	PCom	17 (22.1%)
	Others	15 (19.5%)
Multiple aneurysms	Yes	33 (42.9%)
	No	44 (57.1%)
EVD	Yes	20 (26%)
	No	57 (74%)
Definitive treatment modality	Endovascular	39 (50.6%)
	Clipping	38 (49.4%)

Abbreviations: ACom, anterior communicating artery; EVD, external ventricular drainage; MCA, middle cerebral artery; PCom, posterior communicating artery.

Each patient underwent an average of 1.22 sessions: 62 patients underwent only 1 session, 13 patients underwent 2 sessions, and 2 patients underwent 3 sessions. Each patient underwent an average of 1.52 PTAs: 43 with only one PTA, 29 with 2 PTAs, 4 with 3 PTAs, and 1 patient underwent 4 PTAs. Sessions and angioplasties are summarized in ►**Figures 1** and **2**.

Regarding the clinical/neurological response after each session, 39 patients showed no improvement after the 1st session, 7 improved only temporarily, 17 improved partially, and 14 improved completely. After the 2nd session, 10 patients showed no improvement, 4 partially improved, and only 2 progressed with total improvement. The only 2 patients who underwent a 3rd session both improved partially. ►**Figure 3** shows the clinical response.

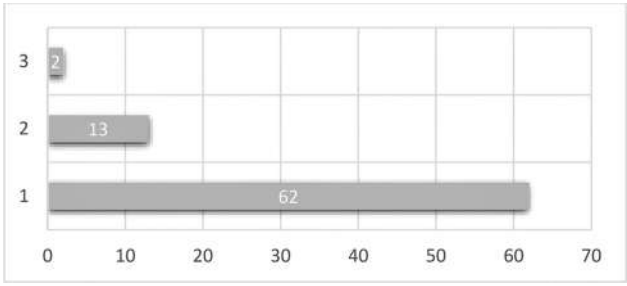

Fig. 1 Number of patients submitted to 1 / 2 / 3 sessions of endovascular treatment for vasospasm – Total of 92 sessions.

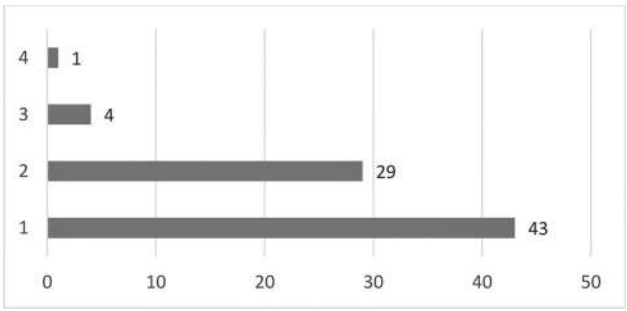

Fig. 2 Number of angioplasties (PTAs) for vasospasm – Total of 114 PTAs.

Fifty-four patients evolved with delayed cerebral ischemia (70.1%). The overall mortality was 24.7% (19 patients), with 2 cases directly related to PTA complication: on insufflation-ruptured left MCA (►**Fig. 2**). All 19 patients died on average 18.5 ± 17,6 days after the ictus, ranging from 5 to 82 days. The Glasgow Coma Scale (GCS) mean score on hospital discharge among the 58 survivors was 12,8 ± 2,4, ranging from 5 to 15. An average follow-up of 19.7 months (ranging from 1 to 71 months) found an average GCS of 13.4 ± 2,4 and an mRS average score of 2.08. ►**Figure 4** shows late mRS.

The multivariate analysis showed no statistical difference as a predictor of poor prognosis, whether death or mRS ≥ 3, among most data. Only needing EVD in the first hours of hospitalization and not showing any clinical improvement after the first endovascular session were predictive of poor long-term neurological status. Need for EVD was also a predictor of death, as well as having received only balloon PTA (►**Tables 2** and **3**).

Discussion

1. EPIDEMIOLOGY

Aneurysmal SAH occurs in ~ 15/100,000 individuals each year.[3] At angiography, about 70% of patients have arterial narrowing and ~ 30 to 40% of them will manifest neurological deficit that is symptomatic vasospasm.[2]

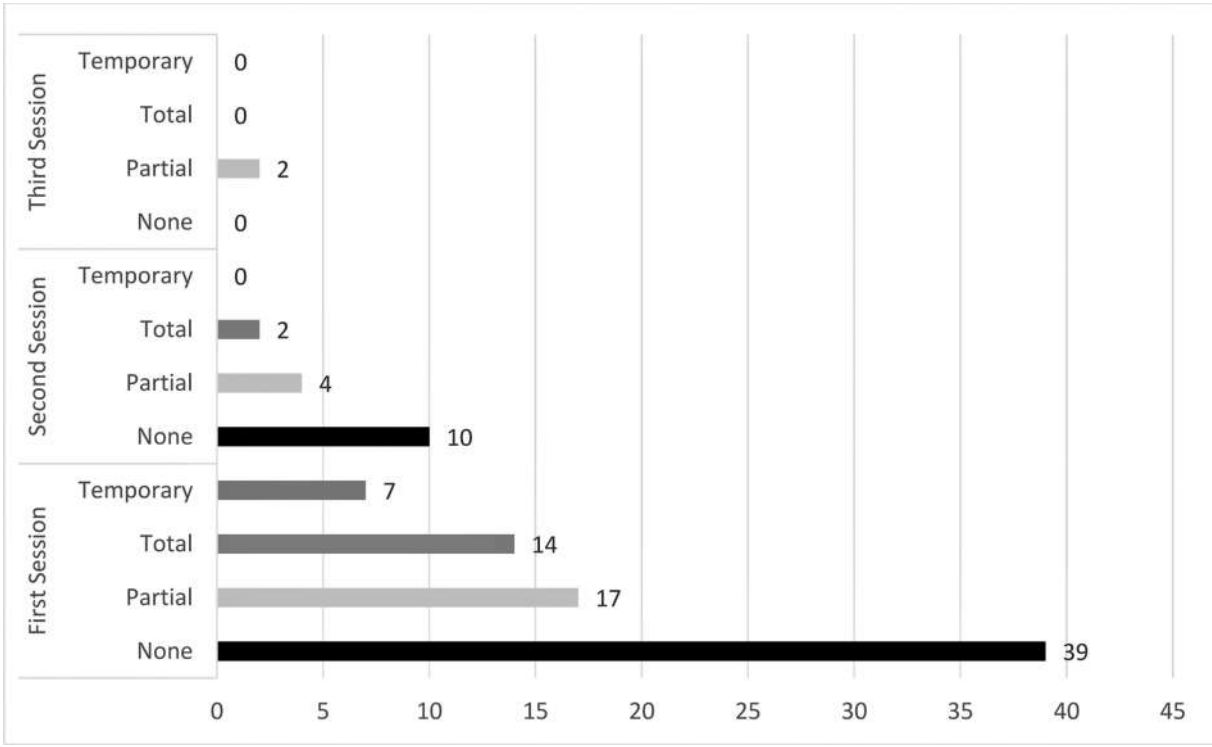

Fig. 3 Clinical / neurological response to each session of endovascular treatment for vasospasm.

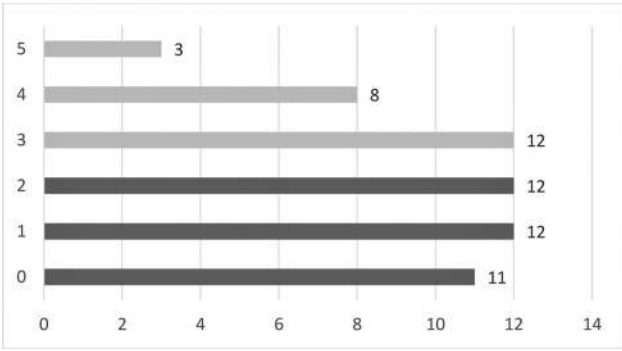

Fig. 4 Late Modified Rankin Scale (mRS) (19.7 months, ranging from 1 to 71).

2. PATHOPHYSIOLOGY

Understanding the pathophysiology of vasospasm is extremely complex. A cascade of events leads to the development of vasospasm due to the thickening of all its layers.

The pathogenesis of aSAH vasospasm involves the release of endogenous spasmogens secondary to the presence of blood in the subarachnoid space of the skull base, and the action of the products of its degradation.[1,6] Adherence of clots also occurs in adventitia, leading to infiltration of inflammatory cells and perivascular nerve degeneration and thickening of the intima can occur due to edema, desquamation, and loss of intercellular junctions. The breakdown products of hemoglobin in the subarachnoid space trigger the contraction of the smooth muscle of the tunica media. Intimal proliferation may occur later due to the formation of necrosis and collagen fibers, which may explain the definitive effect of balloon inflation on mechanical PTA, breaking down these collagen fibers.[1,2] With the increase in the intensity of vasospasm, the compensation mechanism is depleted and, in the absence of adequate collateral circulation (more often occurring in diffuse spasm), delayed cerebral ischemia will develop.[6]

Several theories try to describe the pathophysiology, none mutually exclusive.

A) Immunological response (first cellular and then humoral through the passage of leukocytes through the breakdown of the blood-brain barrier). It has been observed in animal models and in humans with aSAH an increased presence in the cerebrospinal fluid of cytokines, eicosanoids, complement, immunoglobulins, CD4, CD8, T cells, and macrophages.
B) Inflammatory response: it was also seen presence of adhesion molecules (selectins, ICAM-1, VCAM-1, integrins), endothelin-1, and acute phase reagents (interleukin 1 [IL-1], interleukin 6 [IL-6], TNF).
C) Structural effects on the affected vessel wall: cell proliferation mediated by substances released by platelets in the subarachnoid space; p53-mediated endothelial apoptosis, leading to impairment of endothelium-dependent vasorelaxation.
D) Blood degradation products: "spasmogenic" substances such as serotonin, prostaglandins, catecholamines, histamine, angiotensin, oxyhemoglobin, and free radicals are released through this degradation process. Free radical production has been associated with nitric oxide (NO) inactivation, which is a potent vasodilator,

Table 2 Predictive factors for poor outcome (mRS $\geq$ 3)

Quantitative Variables	**mRS < 3**	**mRS ≥ 3**	***p-value****	**OR (IC95%)**	
Age (years old)	50.3 ± 10.6 (20–75)	53.4 ± 11.3 (26–66)	0.301	1.03 (0.98–1.08)	
Definitive Treatment (Days)	5.4 ± 10.4 (0–60)	4.3 ± 2.8 (0–12)	0.634	0.98 (0.91–1.06)	
First Session of Endovascular Treatment (Days)	9.9 ± 9.0 (4–60)	8.5 ± 3.5 (2–15)	0.524	0.97 (0.87–1.07)	
Categorical Variables	**Classification**	***n***	**mRS ≥ 3** n (%)	***p-value***	**OR (95%CI)**
Gender	Female	50	18 (36)	0.453	1.78 (0.40–7.98)
	Male	8	4 (50)		
Hunt Hess	1	11	3 (27.3)		
	2	13	5 (38.5)		
	3	24	8 (33.3)		
	4	4	2 (50)		
	5	6	4 (66.7)		
Hunt Hess (grouped)	1 or 2	24	8 (33.3)	0.545	1.4 (0.47–4.16)
	3, 4 or 5	34	14 (41.2)		
Fisher	1	1	1 (100)		
	2	7	0 (0)		
	3	18	2 (11.1)		
	4	32	19 (59.4)		
Fisher (grouped)	1 or 2	8	1 (12.5)	0.143	5.07 (0.58–44.4)
	3 or 4	50	21 (42)		
Multiple Aneurysms	No	32	14 (43.8)	0.313	0.57 (0.19–1.69)
	Yes	26	8 (30.8)		
MCA	No	42	16 (38.1)	0.967	0.98 (0.30–3.20)
	Yes	16	6 (37.5)		
ACom	No	40	15 (37.5)	0.920	1.06 (0.34–3.33)
	Yes	18	7 (38.9)		
PCom	No	47	19 (40.4)	0.422	0.55 (0.13–2.35)
	Yes	11	3 (27.3)		
Other Aneurysms	No	45	16 (35.6)	0.490	1.55 (0.45–5.42)
	Yes	13	6 (46.2)		
Smoke	No	27	13 (48.2)	0.138	0.44 (0.15–1.30)
	Yes	31	9 (29)		
>20 pack-years	No	11	2 (18.2)	0.822	1.29 (0.14–11.5)
	Yes	9	2 (22.2)		
EVD	No	48	13 (27.1)	**0.004**	**24.2 (2.79–210)**
	Yes	10	9 (90)		
Treatment Modality	Endovascular	28	10 (35.7)	0.737	1.20 (0.41–3.48)
	Clipping	30	12 (40)		
Early definitive treatment ($\leq$ 3 days)	Yes	33	10 (30.3)	0.172	2.12 (0.72–6.25)
	No	25	12 (48)		
Number of Sessions	1	47	19 (40.4)		
	2	9	3 (33.3)		
	3	2	0 (0%)		

(*Continued*)

Table 2 (*Continued*)

Quantitative Variables	mRS < 3	mRS ≥ 3	*p-value*[*]	OR (IC95%)	
Number of Sessions (grouped)	2 or 3	11	3 (27.3)	0.422	1.81 (0.42–7.71)
	1	47	19 (40.4)		
Timing of 1st Session (days)	≤ 7	24	8 (33.3)		
	8 to 11	22	9 (40.9)	0.595	1.38 (0.42–4.60)
	≥ 12	12	5 (41.7)	0.624	1.43 (0.34–5.95)
Number of PTAs	1	30	13 (43.3)		
	2	25	9 (36)		
	3	2	0 (0)		
	4	1	0 (0)		
Number of PTAs (grouped)	2, 3 or 4	28	9 (32.1)	0.381	1.61 (0.55–4.72)
	1	30	13 (43.3)		
PTAs with GTN	0	6	4 (66.7)		
	1	46	16 (34.8)		
	2	5	2 (40)		
	3	1	0 (0)		
PTAs with GTN (grouped)	1, 2 or 3	52	18 (34.6)		3.78 (0.63–22.6)
	0	6	4 (66.7)	0.146	
PTA with Balloon	0	29	11 (37.9)		
	1	27	11 (40.7)		
	2	2	0 (0)		
PTA with Balloon (grouped)	0	29	11 (37.9)	1	1 (0.35–2.89)
	1 or 2	29	11 (37.9)		
PTA and Balloon	No	35	15 (42.9)		
	Yes	23	7 (30.4)	0.342	0.58 (0.19–1.77)
Endovascular Treatment of Vasospasm	GTN and Balloon	23	7 (30.4)		
	GTN only	29	11 (37.9)	0.573	1.40 (0.44–4.47)
	Balloon only	6	4 (66.7)	0.120	4.57 (0.67–31.0)
Ischemia	No	22	6 (27.3)	0.195	2.13 (0.68–6.71)
	Yes	36	16 (44.4)		
Improvement after 1st Session	No	22	13 (59.1)		
	Partial	16	4 (25)		
	Temporary	6	3 (50)		
	Total	14	2 (14.3)		
Improvement after 1st Session (grouped)	Total	14	2 (14.3)		
	Partial	16	4 (25.0)	0.469	2 (0.31–13.1)
	No or tempory	28	16 (57.1)	**0.015**	**8 (1.5–42.6)**

Abbreviations: ACom, anterior communicating artery; CI, confidence interval; EVD, external ventricular drainage; GTN, glyceryl trinitrate; MCA, middle cerebral artery; OR, odds ratio; PCom, posterior communicating artery; PTA, percutaneous transluminal angioplasty.
[*]Cox Regression Model and Wald test, $p < 0.05$.

and increased activity of lipid peroxidases. In turn, NO inactivation may result in increased activity of lipid protein kinase C, with subsequent release of intracellular calcium. Calcium has been shown to activate calmodulin, which in turn activates the myosin kinase light chain, leading to phosphorylation of the myosin light chain that interacts and degrades the thin protein-associated filament to cause vascular smooth muscle contraction and luminal narrowing. Myosin light chain phosphorylation by calcium-dependent activation of the myosin kinase light chain is accepted as the key to vascular contraction.[2–4]

Table 3 Predictive factors for death

Variable	Classification	*n*	Death *n* (%)	*p-value*[*]	OR (95%CI)
Gender	Female	63	13 (20.6)	0.073	2.42 (0.92–6.38)
	Male	14	6 (42.9)		
Hunt Hess	1	12	1 (8.3)		
	2	19	6 (31.6)		
	3	29	5 (17.2)		
	4	7	3 (42.9)		
	5	10	4 (40)		
Hunt Hess (grouped 1)	1 or 2	31	7 (22.6)	0.783	1.14 (0.45–2.90)
	3, 4 or 5	46	12 (26.1)		
Hunt Hess (grouped 2)	1, 2 or 3	60	12 (20.0)	0.096	2.21 (0.87–5.62)
	4 or 5	17	7 (41.2)		
Fisher	1	1	0 (0)		
	2	7	0 (0)		
	3	21	3 (14.3)		
	4	48	16 (33.3)		
Fisher (grouped)	1 ou 2	8	0 (0)		
	3 ou 4	69	19 (27.5)		
Multiple Aneurysms	No	44	12 (27.3)	0.526	0.74 (0.29–1.88)
	Yes	33	7 (21.2)		
MCA	No	54	12 (22.2)	0.512	1.37 (0.54–3.47)
	Yes	23	7 (30.4)		
ACom	No	55	15 (27.3)	0.415	0.63 (0.21–1.91)
	Yes	22	4 (18.2)		
PCom	No	60	13 (21.7)	0.239	1.79 (0.68–4.71)
	Yes	17	6 (35.3)		
Others Aneurysms	No	62	17 (27.4)	0.317	0.47 (0.11–2.05)
	Yes	15	2 (13.3)		
Smoke	No	32	5 (15.6)	0.129	2.21 (0.79–6.13)
	Yes	45	14 (31.1)		
>20 pack-years	No	12	1 (8.3)		
	Yes	16	7 (43.8)		
EVD	No	57	9 (15.8)	**0.002**	**4.09 (1.65–10.1)**
	Yes	20	10 (50)		
Treatment Modality	Endovascular	39	9 (23.1)	0.779	1.14 (0.46–2.8)
	Clipping	38	10 (26.3)		
Early definitive treatment (≤ 3 days)	No	32	7 (21.9)	0.557	1.32 (0.52–3.36)
	Yes	45	12 (26.7)		
Number of Sessions	1	62	15 (24.2)		
	2	13	4 (30.8)		
	3	2	0 (0)		
Number of Sessions (grouped)	1 (ref)	62	15 (24.2)	0.881	1.09 (0.36–3.28)
	2 ou 3	15	4 (26.7)		

(*Continued*)

Table 3 (*Continued*)

Variable	Classification	*n*	Death *n* (%)	*p-value**	OR (95%CI)
Timing of 1st Session (days)	≥ 12 (ref)	15	3 (20.0)		
	8 a 11	28	6 (21.4)	0.411	1.72 (0.47–6.25)
	≤ 7	34	10 (29.4)	0.880	1.11 (0.28–4.45)
Number of PTAs	1	43	13 (30.2)		
	2	29	4 (13.8)		
	3	4	2 (50)		
	4	1	0 (0)		
Number of PTAs (grouped)	1 (ref)	43	13 (30.2)	0.220	0.55 (0.21–1.44)
	2, 3 ou 4	34	6 (17.7)		
PTAs with GTN	0	11	5 (45.5)		
	1	59	13 (22)		
	2	6	1 (16.7)		
	3	1	0 (0)		
PTAs with GTN (grouped)	1, 2 or 3	66	14 (21.2)	**0.045**	**2.85 (1.02–7.95)**
	0	11	5 (45.5)		
PTAs with Balloon	0	37	8 (21.6)		
	1	37	10 (27)		
	2	3	1 (33.3)		
PTAs with Balloon (grouped)	0	37	8 (21.6)	0.466	1.40 (0.56–3.49)
	1 or 2	40	11 (27.5)		
Endovascular Treatment of Vasospasm	(3) GTN and Balloon	29	6 (20.7)		
	(1) GTN only	37	8 (21.6)	0.984	1.01 (0.35–2.91)
	(2) Balloon only	11	5 (45.5)	0.082	2.87 (0.87–9.43)
Ischemia	No	23	1 (4.4)		
	Yes	54	18 (33.3)		
Improvement after 1st Session	No	39	17 (43.6)		
	Partial	17	1 (5.9)		
	Temporary	7	1 (14.3)		
	Total	14	0 (0)		
Improvement after 1st Session (grouped)	No or tempory	46	18 (39.1)		
	Partial	17	1 (5.9)		
	Total	14	0 (0)		

Abbreviations: ACom, anterior communicating artery; CI, confidence interval; EVD, external ventricular drainage; GTN, glyceryl trinitrate; MCA, middle cerebral artery; OR, odds ratio; PCom, posterior communicating artery; PTA, percutaneous transluminal angioplasty.
*Cox Regression Model and Wald test, $p < 0.05$.

E) Neurogenic factors: Contact of the blood from the subarachnoid space with the adventitial layer and the outer tunic of the cerebral vessels would cause a denervation of the parasympathetic and mainly sympathetic network there. This disruption of neuronal regulation mechanisms would cause vessel contraction induced by hypersensitivity of vasoconstrictor neurotransmitters, including calcitonin, substance P, and calcitonin gene related peptide (CGRP).[2]

In a study, Wistar albino rats received a single bolus intracisternal injection of GTN and papaverine and their vasospasm in the basilar artery was assessed by angioresonance.[1] The authors demonstrate an improvement in vasospasm with papaverine, but not with GTN.[1] They concluded that the pathogenesis of the vasospasm is more due to the action of the cGMPase enzyme rather than to the inhibition of NO synthetase by the spasmogens, and deduce that short-acting NO donors are not as effective in ameliorating vasospasm.[1]

Cyclic nucleotides have been thought of as second messengers in various tissues, including platelets and vascular smooth muscle cells.[7] Particular attention has been paid to the intracellular levels of cAMP and cGMP because both are among the important intracellular messengers that can cause relaxation in vascular smooth muscle cells by different pathways.[7] β-adrenergic stimulators and prostacyclin, for example, relax vascular smooth muscle cells by elevating cAMP.[7] Nitrovasodilators, the EDRF, and atriopeptins also relax the vasculature through cGMP-dependent mechanisms.[7] Several investigators reported that in cerebral vasospasm after SAH, cGMP levels were decreased and cAMP levels actually increased.[7]

Another primate study looked at the relation between vasospasm, cGMP and GTN. After laboratory-induced SAH, angiographic vasospasm was found in the basilar and middle cerebral arteries, and a drastic reduction in cGMP level as well as local cerebral blood flow (CBF). With the administration of GTN for 3 hours, the level of cGMP increased, but did not match basal, and vessel diameter increased. There were no significant changes in cAMP levels in SAH and after GTN treatment. The authors concluded that the vasodilatory effect of GTN might not be mediated by an increase in cGMP levels, suggesting an involvement of hyperpolarization of smooth muscle cells. Given the increase in regional CBF, GTN may be therapeutic for the treatment of vasospasm.[7]

A clinical study compared transdermal GTN (9 patients) with placebo in aSAH patients.[7] The medicated group had better results in transcranial Doppler velocities (Lindegaard ratio) and CT perfusion (regional CBF, but not parietal cortical CBF), even though their mean blood pressure was significantly lower. Thus, GTN influences the cerebral vascular tone and once again proved effective against vasospasm.[5]

3. DIAGNOSIS

Clinical vasospasm can manifest different presentations: consciousness impairment, new focal neurological deficit (aphasia and hemiparesis), headache, and seizures.[8] Angiographic vasospasm can be classified as mild, moderate, or severe, according to vessel stenosis (0–33%, 34–66%, and $>67\%$ decrease in arterial diameter, respectively).[8] The clinical presentation of delayed cerebral ischemia (DCI) secondary to aneurysmatic subarachnoid hemorrhage is heterogeneous in terms of timing of presentation, clinical manifestations, location of spasms in the vasculature, severity of vessel stenosis, and response to treatment. Severe vasospasm is associated with severe ischemia and infarction, but hypoperfusion is also reported in areas without macrovascular vasospasm on perfusion studies.[8] Focal neurological deficit is a more reliable sign of segmental vasospasm, especially if there is a correlation with a greater amount of blood on CT in the corresponding vascular territory.[6] In general, there is an increase in headache and signs of meningeal irritation, fever, arterial hypertension, and tachycardia preceding clinical vasospasm, while drowsiness, numbness, and confusion are unspecific signs.[6]

Daily monitoring with transcranial Doppler (TCD) during the peak period of vasospasm is very useful in assessing the evolution of blood velocity in the MCA, the most important and assessable vessel in vasospasm. That accuses vasospasm as the cause of clinical manifestations, when their installation coincides with a progressive speed increasing.[6] The normal speed of blood in the MCA is <60 cm/second, and a speed >120 cm/sec indicates vasospasm, while >200 cm/sec is commonly associated with symptomatic vasospasm and cerebral ischemia.[6] In addition, increase in the Lindegaard index (MCA/ICA) is useful to diagnose vasospasm. As other factors can increase the flow in the MCA, an initial TCD is important to have a parameter for each patient, as well as to enable evaluating the speed. An increase in flow may precede symptomatic vasospasm, and rapid increase in flow of >50 cm/sec/day is highly suggestive of an imminent installation of clinical vasospasm, permitting early treatment.[6]

Unfortunately, we do not have a transcranial DTC in our hospital, which is one of our greatest difficulties in the management of these patients.[6]

4. Treatment

Although various treatment modalities are available, none are really curative.[1,2,9] The cornerstone of the medical treatment of cerebral vasospasm was, for many years, the hemodynamic increase through the "triple H therapy", a combination of hypervolemia, hemodilution, and induced hypertension to decrease blood viscosity and increase CBF and cerebral perfusion pressure.[2] However, patients randomized to hypervolemia showed greater bleeding, congestive heart failure, and infections.[10] Hypervolemia was also associated with a higher cost.[10] Therefore, the current literature suggests that hypervolemia does not improve the outcome and is associated with increased cardiopulmonary complications.[2] Hemodilution has also fallen out of favor as a treatment strategy for vasospasm;, however, there is controversy regarding the "ideal" hemoglobin in patients with aSAH.[2] Although hemodilution increases CBF through better rheology, it also reduces the oxygen transport content and does not result in a net increase in cerebral oxygen supply.[2] A recent study showed that hypertension is still desired in these cases, since hypotension was associated independently with poor functional outcomes at the last clinical follow-up. Besides that, blood pressure variability, which incorporates the dynamic changes in blood pressure over time, has recently gained recognition as a prognostic marker of mortality in these patients.[11]

Most of the experimental settings have demonstrated varying levels of ability to predict accurately what occurs in human aSAH. Therefore, although animal models have been developed to test new therapies, most of the treatment effects have been shown to be less compelling when trials have been conducted in clinical settings.[9]

A meta-analysis with 453 studies showed that outcome from aSAH has improved in recently, partly due to improved treatments and partly due to a better understanding of the mechanisms of vasospasm.[9,12] Mortality declined 0.4% per year, after adjustment for age, between 1973 and 2002.[12,13]

The most widely used and best evidenced chemical PTA drug is nimodipine. However, its injectable form is not

licensed by the National Health Surveillance Agency in Brazil. Other alternative options include milrinone, verapamil, and nicardipine, but they are not available in the Brazilian public health system, being reserved for private patients only. Currently, the use of papaverine is discouraged due to possible neurotoxicity and risk of intracranial hypertension.[14] That is why GTN was left, which would not be the best option for the treatment of vasospasm, but unfortunately it is the only one available in our reality.

Systemic administration of GTN has failed to be established in some clinical settings as preventing vasospasm because of its adverse effects, particularly hypotension.[3] The pathophysiological mechanisms are mainly the dysfunction of the NO-producing enzyme nitric oxide synthase (NOS) and scavenging of NO due to the presence of deoxyhemoglobin and its high affinity for NO.[3,15] One drawback with NONOates is that they have been shown to open the blood-brain barrier at higher doses und thus provoke brain infarction and toxicity.[3,16] Intrathecal sodium nitroprusside, a different class of NO donor, is the only NO donor that has been tested intrathecally in clinical studies after SAH, and has also been proven to dilate constricted vessels.[3]

To try to avoid lowering mean blood pressure, another clinical study performed continuous intravenous dopamine infusion concomitantly with GTN. There was an increase in intracranial pressure early on, but minimal and transient. There was no change in cerebral arteriovenous oxygen difference during GTN infusion, although cerebral perfusion pressure decreased between 75 and 94% of the control value after GTN administration. Therefore, this double infusion showed beneficial effects on the CBF of patients with aSAH.[16]

A similar study of intrathecal GTN infusion, but this time continuously and in rabbits, also showed that vasospasm was prevented with no toxic effects (it did not even affect arterial blood pressure).[3] Similar results were obtained in the group receiving nimodipine (calcium channel antagonist), and both were significantly more effective at preventing basilar artery angiographic constriction compared with the control with NACl.[17] The clinical status and the arterial blood pressure at day 5 did not indicate a drop in blood pressure compared with day 0. Since the vasodilatory effect is present after 5 days of continuous infusion, the authors conclude that there is no drug tolerance in this short period of treatment.[3]

Nitroglycerin for Vasospasm Trend Topics:

- GTN increases CBF, lowers average blood pressure, dilates spastic cerebral arteries, and reduces the clinical occurrence of delayed ischemic neurological deficits.[5]
- The usual clinical dose may cause the theft phenomenon, dilating the intact arteries.[18]
- At a low dose, it significantly improved vasospasm without significant changes in systemic circulation.[18]
- High doses increase vessel size above low dose. However, infusing GTN for a longer time may increase this effect and counteracting systemic hypotension produced using an agent such as dopamine.[19]
- Systemic administration may induce the development of drug tolerance as well as the phenomenon of hypertensive rebound after discontinuation.[4]
- The main disadvantages of intrathecal use: its action time (residual effect up to 5 days), which, if used at higher doses, opens the blood-brain barrier causing toxicity and cerebral infarction.[20]

Conclusions

Balloon angioplasty has good results when performed early; however, this technique is restricted to proximal vessels. Considering the ephemeral effect of nitroglycerin, more efficient drugs need to be developed to treat distal vasospasm, and mainly to prevent its development.

Despite excellent and promising results from the use of this drug in animal models of aSAH, whether intravenous or intrathecal, single bolus or continuous infusion, either to prevent or treat, such results were never faithfully reproduced in human studies. The exact timing of onset, duration, and reduction of GTN administration regarding the appearance of vasospasm may have a strong impact on the success of such a therapy. Some clinical trials with this nitric oxide donor have yielded good or reasonable results. While we recognize the limitation of our article, our extensive experience may contribute to future research, as well as to the study of other doctors who, like us, do not have other better chemical agents to perform drug angioplasty.

Conflict of Interests

The authors have no conflict of interests to declare.

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Paroxysmal Sympathetic Hyperactivity in Patients Victims of Traumatic Brain Injury: Literature Review

Hiperatividade simpática paroxística em pacientes vítimas de trauma cranioencefálico: Revisão da literatura

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Abstract

The present literature review aims to present the physiology of paroxysmal sympathetic hyperactivity (PSH) as well as its clinical course, conceptualizing them, and establishing its diagnosis and treatment. Paroxysmal sympathetic hyperactivity is a rare syndrome, which often presents after an acute traumatic brain injury. Characterized by a hyperactivity of the sympathetic nervous system, when diagnosed in its pure form, its symptomatologic presentation is through tachycardia, tachypnea, hyperthermia, hypertension, dystonia, and sialorrhea. The treatment of PSH is basically pharmacological, using central nervous system suppressors; however, the nonmedication approach is closely associated with a reduction in external stimuli, such as visual and auditory stimuli. Mismanagement can lead to the development of serious cardiovascular and diencephalic complications, and the need for neurosurgeons and neurointensivists to know about PSH is evident in order to provide a fast and accurate treatment of this syndrome.

Keywords
- autonomic nervous system
- craniocerebral trauma
- primary dysautonomias

Resumo

O presente artigo de revisão de literatura tem como objetivo apresentar a fisiologia da hiperatividade simpática paroxística (HPS), bem como sua evolução clínica, conceituando-as, estabelecendo seu diagnóstico e o tratamento. A HPS é uma síndrome rara, que geralmente se apresenta após uma lesão cerebral traumática aguda. A HPS é caracterizada por uma hiperatividade do sistema nervoso simpático, e quando diagnosticada na sua forma pura, apresenta sintomatologia através de taquicardia, taquipneia, hipertermia, hipertensão, distonia e sialorreia. O tratamento da HPS é basicamente farmacológico, por meio do uso de supressores do sistema nervoso

Palavras-chave
- disautonomias primárias
- sistema nervoso autonômico
- trauma craniocerebral

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central, porém a abordagem não medicamentosa está intimamente associada à redução de estímulos externos, como visuais e auditivos. A má gestão pode levar ao desenvolvimento de complicações cardiovasculares e diencefálicas graves, e a necessidade de neurocirurgiões e neurointensivistas saberem sobre o HSP para fornecer um tratamento rápido e preciso dessa síndrome é evidente.

Introduction

The traumatic brain injury (TBI) is one of the main causes of death and severe sequelae.[1] Severe TBI is characterized by a Glasgow Coma Scale (GCS) score between 3 and 8, which may require a long hospital stay, being a cause of prolonged disability.[2,3] Often, after suffering a severe TBI,[4] the patient can develop paroxysmal sympathetic hyperactivity (PSH), which is an uncommon complication[5] that can occur in the first 24 hours[6] or months after the trauma,[2] with incidence of between 8 and 33%[7] in patients admitted with TBI in the intensive care unit (ICU),[1] being frequent in young adult patients.[8] In 10% of the cases of HSP in children, it occurs due to TBI, in association with a prolonged rehabilitation.[7]

Paroxysmal sympathetic hyperactivity was first described by Penfield in 1929 with the nomenclature of "autonomic diencephalic crisis"[9], being characterized by a hyperadrenergic syndrome, which occurs following an acute brain injury[10] in response to a non-nociceptive stimulus.[11] Paroxysmal sympathetic hyperactivity is a severe and debilitating sequel,[7] which develops less frequently after ischemic stroke[12] (5%),[13] intra-aqueductal abscess,[14] ischemic encephalopathy,[15] cerebral hypoxia[6] (10%),[16] hydrocephalus,[11] autoimmune encephalitis,[4] fatty cerebral embolism,[17] agenesis of the corpus callosum,[18] central nervous system (CNS) infection, hypoglycemia, and complications related to neoplastic lesions.[19] Often, it occurs after the interruption of the administration of sedatives and narcotics in the ICU,[6] contributing significantly to the mortality of these individuals,[20] being associated with a worse neuropsychological outcome,[2] and is expected prospectively when the patient presents poor outcomes after TBI, such as a long stay in the ICU, low GCS score, increased frequency of infections during hospitalization, need for tracheostomy, and long period of post-traumatic amnesia.[7]

Paroxysmal sympathetic hyperactivity is characterized by an excess of catecholamines,[2] arterial hypertension,[5] transient paroxysmal fever,[15] sweating,[19] tachycardia,[1] manifesting itself motorly through abnormal body posture associated with muscle spasticity[15] related to decerebrate and decorticate movements;[9] in an uncommon way, patients present pupillary dilation,[6] high eye pressure,[21] agitation[4] and sialorrhea.[18] These symptoms may have a duration of minutes or hours, and may occur multiple times in the same day.[22] The syndrome is classified as pure PSH when there is only discharge of sympathetic activity, and mixed in situations that evolve in association with sympathetic and parasympathetic hyperactivities.[13,19] The latter appears through bradypnea, bradycardia, arterial hypotension, hypothermia, and miotic pupils.[18]

Since PSH is a rare syndrome associated with poor post-TBI outcomes and it is difficult to diagnose, the present study aims to present its pathophysiology and symptoms, conceptualizing them, thus advocating its diagnosis and treatment.

Materials and Methods

The present paper is a literature review using the following databases: PubMed, Scielo, Scientific Direct, Ebsco, LILACS, Trip DataBase and Cochrane, using the terms: *Paroxysmal Sympathetic Hyperactivity*. Articles from 2004 to 2019 were selected, resulting in a total of 33 articles that met the inclusion criteria considering their citations and respective impacts.

Results

Physiopathology

The primary formation sites of the autonomic response in the CNS are the spinal cord, the brainstem, and the hypothalamus.[12] The autonomic nervous system (ANS) performs cardiac and vascular control through the regulation of exocrine and endocrine glands and of cardiac and smooth muscles, influencing the modulation of tissues and organs of different systems.[21] There is no postulated pathophysiology for HSP, but the following theories are the most accepted: due to the overlap of the sympathetic nervous system over the parasympathetic,[6] which may be associated with brainstem damage due to TBI or neoplasia[19]; axonal shear injury and consequent disinhibition of subcortical sympathetic excitatory structures[8]; injury that occurs from the limbic cortex to the sympathetic centers, which can remove the tonic inhibition from the insular cortex, developing an uncontrollable sympathetic storm[10]; and lesions involving the splenium or the corpus callosum and the right posterior branch of the internal capsule.[12]

The dysregulation of the heart rhythm occurs due to the general cardiovascular decrease at rest due to the sympathetic system19 and vagal activity by the ANS in the sinus node of the heart.[21] During PSH, there may be a decrease in the sensitivity of the baroreflex complex, which is closely linked to cardiovascular complications and to an increase in the occurrence of arterial hypertension.[21] The increase in catecholamines causes high rates of epinephrine and norepinephrine identified in the blood plasma; these neurotransmitters can lead to the development of a persistent comatose state.[2]

Decerebrate and decorticate postures can be explained by lesions located in the anterior hypothalamus, the midbrain, the centers of the cerebral cortex (orbitofrontal, anterior temporal and insula) and in subcortical areas (amygdala, periaqueductal gray substance, solitary tract nucleus and cerebellar worms).[18] The thermal deregulation present in PSH occurs due to the involvement of the hypothalamus or through the hypermetabolic state associated with muscle contractions.[22]

Clinical Course

After the brain injury, the symptomatic presentation of PSH occurs in between 1 and 60 days, and should be monitored during the first weeks.[7] It manifests itself by increasing the activity of the sympathetic and motor nervous system in response to a typically benign stimulus, which normally does not trigger an intense physiological response.[11] It has three phases: the first begins on admission at the ICU, ending with the cessation of paralysis or sedation[14]; the second occurs with the end of regular sedation, and ends with the extinction of regular PSH episodes.[17] At the beginning of this phase, episodes are frequent, prolonged and intense.[14] Some episodes may occur due to a detectable agent such as pain, exposure to light, and passive movement such as bathing,[17] changing the decubitus position , muscle stretching, endotracheal suction, constipation, twisted urinary catheter, and emotional and environmental stimuli, such as loud sound. Finally, the third phase begins, with the end of regular episodes, although patients with severe PSH may present with sequelae, such as joint deformities and reduced range of motion.[14]

The most common symptoms of PSH are hyperthermia[23]; excessive diaphoresis[12]; posture in extension,[3] decerebrate, decortication, rigidity and spasticity[14]; dystonia; tachycardia[7]; excessive salivation; tachypnea; and arterial hypertension.[24] These signs and symptoms vary from episode to episode, as well as from individual to individual.[6] The interruption of diaphoresis is used as a mark between the second and third phases, frequently occurring on the 74th day after the brain injury.[9] When an episode of mixed PSH occurs, the symptoms manifested are miosis, tearing, bradycardia, bradypnea, hypotension, hypothermia, tidal breathing, and yawning.[25]

Diagnosis

The diagnosis is established on an exclusion basis, deciding on other possible diagnoses, and requires a wide degree of suspicion.[17] It is performed through anamnesis and detailed physical examination, associated with continuous monitoring of heart rate, electrocardiogram, blood pressure, and temperature.[23] Imaging tests such as computed tomography (CT) and magnetic resonance imaging (MRI) are not necessary for the diagnosis of PSH; however, they contribute to the confirmation of the diagnosis, showing the type of lesion (axonal or diffuse) and its morphology, such as ischemia and cerebral hemorrhage.[17] As a diagnostic criterion for PSH, Baguley et al.[26] developed a combined scale, through the association of a score of presence and clinical severity, the Severity of Clinical Characteristics Scale, and the score of characteristics of PSH episodes (►**Table 1**). The final score is used for the diagnostic calculation of PSH.

For the diagnosis of exclusion for infections, routine hematological and biochemical tests, such as blood, urine, tracheal aspirate, and sputum culture should be performed.[23] And the diagnostic test based on the administration of intravenous morphine sulfate should be performed to check the control of dysautonomias;[18] if the result is positive, the patient is diagnosed with PSH.

Treatment

The treatment of PSH is pharmacological, nonpharmacological, and the prevention of specific sympathetic symptoms.[11] Drugs that depress the CNS, with consequent suppression of the ANS, are often used,[6] such as opioid agonists, nonselective β-blockers,[8] dopaminergic agonists, α-blockers, sedatives,[6] and α agonists.[23] Therefore, drugs such as bromocriptine, clonidine, dantrolene,[27] intrathecal baclofen,[23] gabapentin, and benzodiazepines[7] are widely used. This last group presents good results in the symptomatic treatment of PSH,[4] and β blockers decrease the synthesis of catecholamines,[18] and are administered due to their lipophilic characteristic, and because they easily cross the blood-brain barrier.[16] In the ICU, intravenous drugs such as morphine, fentanyl and midazolam are the first line of treatment.[6] Morphine, an opioid agonist, performs analgesia and alters the extreme changes of the ANS, as well as dystonia by suppressing the sympathetic flow.[9] Sedatives such as dexmedetomidine and propofol are used to manage episodes of PSH in the ICU. The first is an active α-2 adrenergic agonist intravenous substance that can be administered through continuous infusion.[16]

The nonpharmacological treatment is based on thermal control of the environment,[28] associated with body cooling through devices, such as blankets[29]; decrease in probable visual and auditory stimuli from the environment[30]; in association with body exercises and massages.[29] The management of PSH rehabilitation aims to minimize the disabilities and complications that can be avoided, as well as to increase the chances of the patient recovering a good quality of life.[14]

Complications

When treated incorrectly, PSH leads to an increased risk of secondary brain injury.[6] The high adrenergic activity of PSH[4] in association with several episodes of the phenomenon can result in secondary morbidities such as elevated intracranial pressure, cardiac injury, metabolic disorders,[19] systemic abnormalities throughout the body, and increased mortality.[21] A hypermetabolic state during sympathetic hyperactivity can reduce body weight by 25% during just one episode. Lee et al.[19] identified an increased concentrations of muscle enzymes after the occurrence of PSH. Hypernatremia may occur due to intense diaphoresis.[6] Paroxysmal sympathetic hyperactivity leads to the evolution of cerebral vasoconstriction, which contributes to local edema and increased intracranial pressure.[31] A cardiac sequela can

Table 1 Paroxysmal Sympathetic Hyperactivity - Assessment Measure

Clinical Feature Scale (CFS)					
	0	**1**	**2**	**3**	**Score**
Heart rate	< 100	100–119	120–139	≥ 140	
Respiratory rate	< 18	18–23	24–29	≥ 30	
Systolic blood pressure	< 140	140–159	160–179	≥ 180	
Temperature	< 37	37–37.9	38–38.9	≥ 39	
Sweating	Absence	Mild	Moderate	Severe	
Posturing during episodes	Absence	Mild	Moderate	Severe	
				CFS Subtotal	
Severity of clinical features			**Absence**	0	
			Mild	1–6	
			Moderate	7–12	
			Severe	≥ 13	
Diagnosis Likelihood (DLT) - Score 1 point for each feature present					
Clinical features occur simultaneously					
Episodes are paroxysmal in nature					
Sympathetic over-reactivity to normally non-painful stimuli					
Features persist ≥ 3 consecutive days					
Features persist ≥ 2 weeks post brain injury					
Features persist despite treatment of alternative differential diagnoses					
Medication administered to decrease sympathetic features					
≥ 2 episodes daily					
Absence of parasympathetic features during episodes					
Absence of other presumed cause of features					
Previous acquired brain injury					
				Subtotal DLT	
Combined Total (CFS + DLT)					
PSH diagnostic likelihood			**Unlikely**	< 8	
			Possible	8–16	
			Probable	> 17	

Baguley et al[26]

lead to the development of arrhythmias, of ischemia and of cardiac dysfunction, consequently reducing cerebral perfusion.[21] The use of splints during episodes of PSH can lead to areas of pressure and tendon rupture, as well as to the lack of voluntary movement, and may cause the development of locked-in syndrome.[14]

Discussion

Paroxysmal sympathetic hyperactivity has numerous names, ~ 31,[23] such as sympathetic discharge,[6] diencephalic seizures, autonomic discharge, paroxysmal autonomic instability associated with dystonia, dysautonomia,[4] paroxysmal sympathetic hyperactivity,[3] and dysfunction of the autonomic nervous system.[21] The name of diencephalic seizure for PSH is somewhat incorrect, because the result of the electroencephalogram is normal.[8,27] Paroxysmal sympathetic hyperactivity is used as a diagnosis of exclusion, but it can coexist with other complications, such as infections.[4] In 2014, an international consensus group defined PSH as "a syndrome in which an individual who has suffered an acute acquired brain injury develops increases in transient paroxysmal sympathetic activities, such as tachycardia, tachypnea, hypertension, hyperthermia, and diaphoresis, as well as motor manifestations, such as dystonia"[26].

A differential diagnosis for PSH is serotonin syndrome, the latter developing strictly due to complications after pharmacological administration (fentanyl or tramadol), in which the excessive presence of postsympathetic serotonergic receptors occurs. Primarily, this drug complication affects the CNS, being characterized by changes in mental status, signs of neuromuscular irritation and autonomic instability, but it can manifest itself through increased muscle tone,

diaphoresis, and fever,[32] commonly present in PSH. Some syndromes can simulate PSH, such as neuroleptic malignant syndrome, malignant hyperthermia, pheochromocytoma, hyperthyroidism, sepsis,[23] drug and alcohol withdrawal syndrome, acute myocardial infarction, and thromboembolic disease.[17] Therefore, the diagnosis of PSH is made by confirming the intracranial lesion through imaging tests,[17] as well as by routine laboratory tests for infectious, blood count, and biochemical conditions.[23]

The management of PSH is symptomatic, through its prevention in association with pharmacological administration, as well as nonpharmacological methods.[11,28–30] In a study, Tang et al.[33] demonstrated that the α agonist drug dexmedetomidine, a sedative used for patients recovering from TBI in the ICU, can be used to prevent PSH. The family of the patient can perceive the onset of an episode of PSH from the worsening of the mental state of the patient; with this, they can warn the clinical staff[6] so that the management occurs as soon as possible to avoid the development of serious sequelae.

The importance of knowledge by neurosurgeons and neurointensivists about the diagnosis, treatment and prevention in an early and accurate way of the symptoms of PSH is evident to avoid the evolution of serious results.

Conflict of Interests

The authors have no conflict of interests to declare.

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Neurosurgery in the Treatment of Alcohol Use Disorder: A Systematic Literature Review

Neurocirurgia no tratamento do transtorno por uso de álcool: Uma revisão sistemática da literatura

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Abstract

Alcohol abuse has impacts on public health worldwide. Conservative treatment to achieve abstinence consists of detoxification combined with psychotherapy and the use of drugs, but it is estimated that only half of the individuals achieve long-term abstinence with the available treatments. In this sense, neurosurgery appears as a therapeutic proposal. The present study aimed to gather information about the circuitry related to alcohol use disorder (AUD), to describe possible surgical targets, and to establish whether a surgical approach could be a safe and effective treatment option. A systematic review of the literature was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. The 14 selected articles analyze ablative operations, deep brain stimulation (DBS), and a new procedure in which the patient is first submitted to repetitive transcranial magnetic stimulation to evaluate their response, and later an implant is surgically positioned on the evaluated target to obtain more lasting results. The most relevant outcomes were found when the anterior cingulate cortex (ACC) and the nucleus accumbens (NAcc) were used as targets, demonstrating a large reduction in alcohol intake and even its cessation. However, important side effects were observed, such as psychotic symptoms, right frontal venous infarction, seizures after implantation in the ACC and a hypomanic period after DBS in the NAcc, which could be reversed. Due to the lack of studies involving the surgical treatment of AUD, more clinical trials are needed to compare targets, to assess surgical techniques, and to estimate the safety of these techniques.

Keywords
- alcoholism
- ablation techniques
- deep brain stimulation
- neurosurgery

Resumo

O abuso de álcool tem impacto na saúde pública em todo o mundo. O tratamento conservador para alcançar a abstinência consiste na desintoxicação combinada com psicoterapia e uso de drogas, mas estima-se que apenas metade dos indivíduos alcance

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a abstinência de longo prazo com os tratamentos disponíveis. Nesse sentido, a neurocirurgia surge como proposta terapêutica. O presente estudo teve como objetivo reunir informações sobre a neurocircuitaria relacionada ao transtorno por uso de álcool, descrever possíveis alvos cirúrgicos e estabelecer se a abordagem cirúrgica pode ser uma opção de tratamento segura e eficaz. Foi realizada uma revisão sistemática da literatura de acordo com a declaração Principais Itens para Relatar Revisões sistemáticas e Metanálises (PRISMA, na sigla em inglês). Os 14 artigos selecionados analisam técnicas ablativas, estimulação cerebral profunda (ECP) e um novo procedimento no qual o paciente é primeiramente submetido à estimulação magnética transcraniana repetitiva para avaliar sua resposta e, posteriormente, um implante é posicionado cirurgicamente no alvo avaliado para obter resultados mais duradouros. Os desfechos mais relevantes foram encontrados quando o córtex cingulado anterior (CCA) e o núcleo accumbens (NAcc) foram usados como alvos, demonstrando uma grande redução na ingestão de álcool e até mesmo sua cessação. No entanto, foram observados efeitos colaterais importantes, como sintomas psicóticos, infarto venoso frontal direito e convulsões após implantação no CCA e período hipomaníaco após ECP no NAcc, que podem ser revertidos. Devido à falta de estudos envolvendo o tratamento cirúrgico do transtorno por uso de álcool, mais ensaios clínicos são necessários para comparar alvos, avaliar técnicas cirúrgicas e estimar a segurança dessas técnicas.

Palavras-chave
- alcoolismo
- técnicas de ablação
- estimulação cerebral profunda
- neurocirurgia

Introduction

Alcohol is an ancient substance rooted in social practices and related to cultural, religious, and economic issues. Its abusive consumption has an important impact on public health worldwide. It is estimated that, in 2016, it led to 3 million deaths, corresponding to 5.3% of the total deaths in the world and exceeding those caused by tuberculosis, HIV, diabetes, hypertension, and violence.[1] In addition, it is an important morbidity factor that is associated with mental and behavioral disorders, cardiovascular and liver diseases, and with an increased incidence of suicide and injuries to third parties.[2]

Alcohol use disorder (AUD) is characterized by a pattern of problematic use, leading to clinically significant impairment or suffering. It includes withdrawal symptoms, tolerance, and craving, in addition to an abandonment or a decrease in professional, social, or recreational activities.[3]

Conservative treatment to achieve abstinence consists of detoxification combined with psychotherapy and the use of drugs. The drugs used are benzodiazepines as coadjuvants in detoxification and alcohol withdrawal, constituting the acute phase of treatment. Disulfiram, naltrexone, and acamprosate are used to prevent relapse, making up the chronic phase.[4]

It is estimated that only half of the individuals achieve long-term abstinence with the available treatments.[4,5] Neurosurgery using ablative techniques or deep brain stimulation (DBS) appears in this sense as a therapeutic proposal. Deep brain stimulation uses electrodes implanted in certain targets established millimetrically by stereotaxy, seeking to modulate neuronal electrical activity.[6]

Given the global epidemiological magnitude of alcoholism, the high rate of recurrence after conservative treatment, and its economic impact on society, there is a demand for more studies on surgical treatments for these patients that describe the surgical targets and address criteria for surgical indications. Thus, the aim of the present study was to establish whether surgical treatment is a valid and effective therapeutic option in the treatment of alcoholism.

Methods

Literature Search

The present study was conducted and reported according to the Preferred Reporting Item for Systematic Reviews and Meta-Analysis (PRISMA) statement.

An electronic search was conducted in the Biblioteca Virtual en Salud (BVSalud), PubMed, and Cochrane Library databases in June 2020. The search was performed using medical subject headings (MeSH) combined with Boolean operators. The following search terms were used: *alcoholism* AND *neurosurgery*, *alcoholism* AND *deep brain stimulation*, and *alcoholism* AND *Stereotaxic Techniques*.

The following filters were used: available in full text, studies written in English, Spanish, or Portuguese; studies in humans; of all ages; and both genders. All articles published before May 2020 were retrieved.

Study Selection

The inclusion criteria were the following: available in full text, randomized clinical trials, and case reports about neurosurgery in patients with AUD. Studies were excluded if they involved noninvasive procedures or were animal-related; if they did not apply to the key question; if they did not address a relevant outcome; if they did not have a clear description of the methods; or if they were review articles,

abstracts, editorials, comments, or studies unrelated to surgical procedures performed in humans.

Duplicated studies were excluded using Zotero (version 5.0.66, Andrew W. Mellon Foundation, Institute of Museum and Library Services, Alfred P. Sloan Foundation, VA, USA). Titles and abstracts were reviewed independently by two authors (Almeida B. V. and Silva L. J.) during an initial screening procedure according to the aforementioned criteria. All eligible articles were retrieved, and whether the articles were available in full text determined the final selection. The selection process and the selected articles are shown in ►**Fig. 1** and in ►**Table 1**, respectively.

Data Extraction

The data extracted from the selected studies were study design (randomized controlled trial, cohort, or case report), study sample (number of patients with schizophrenia), maximum follow-up, complications, and relevant outcome.

Neurocircuitry

Alcohol addiction is closely related to the reward system of the brain, which is part of the mesocortical and mesolimbic dopaminergic system, whose neurons are located in the ventral tegmental area (VTA) and project to the nucleus accumbens (NAcc), the septum, and the amygdala.[4,5] Beyond dopamine, glutamatergic activity mediates natural reward as well as alcohol- and drug-associated reward. Elevated dopamine release,[4] elevated glutamatergic transmission, and extracellular levels of glutamate in the NAcc, the basolateral amygdala, the cortex, the hippocampus, the VTA, and the posterior VTA (pVTA) are associated with ethanol consumption.[7,8]

The addiction neurocircuitry model is a theory used to explain how the neurobiological processes of alcohol addiction affect brain connections. It consists of the following three major components: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation.[9]

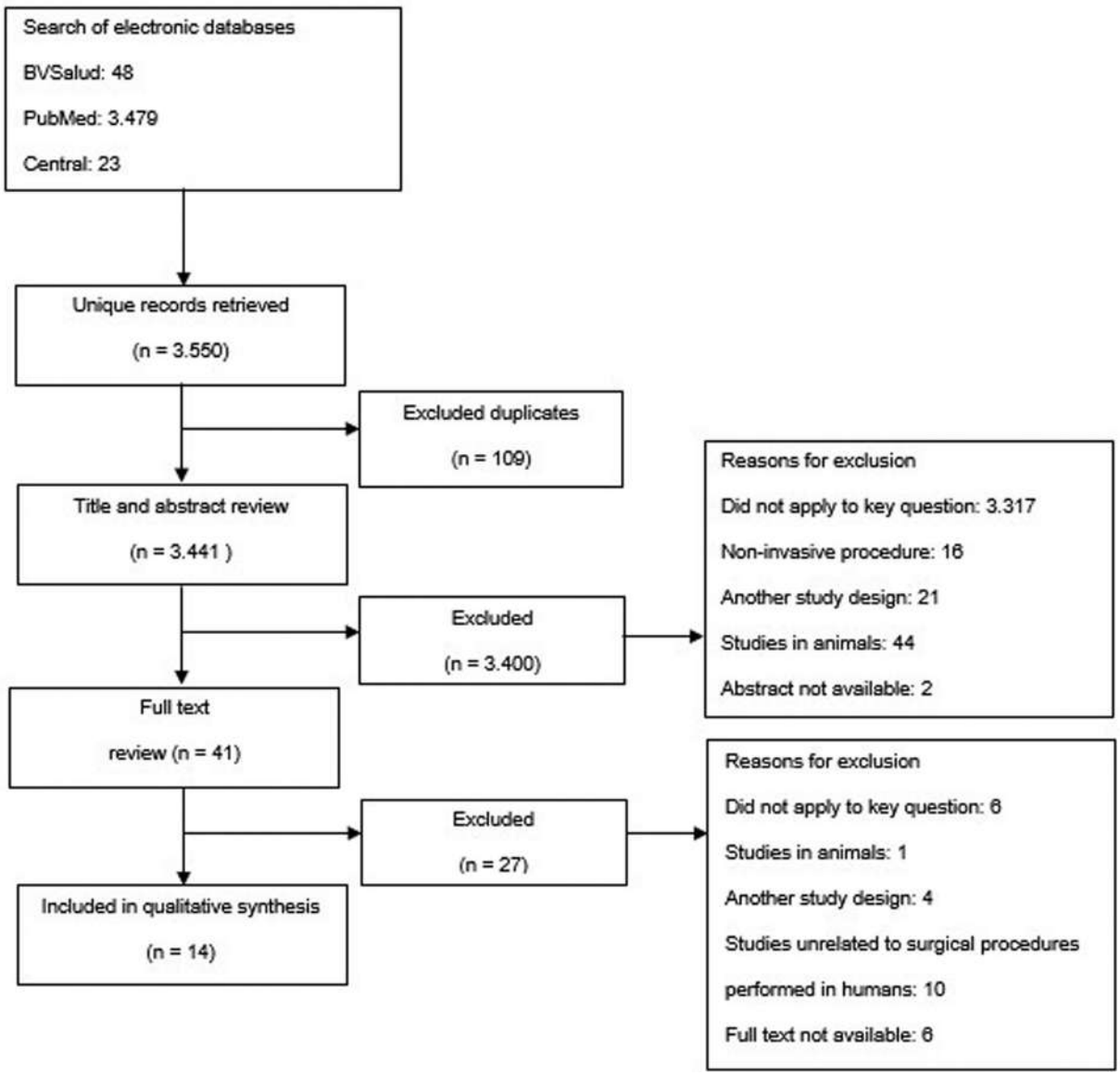

Fig. 1 Flowchart of literature review.

Table 1 Characteristics of the studies included in the review according to the author, year, location, study design, and sample

Citation (no.)	Author (year)	Location	Study design	Sample (no.)
13	Kanaka et al., 1978	Madras, India	Prospective cohort	73 Patients (25 with alcohol addiction)
15	Müller et al., 1973	Göttingen, Germany	Prospective cohort	22 Patients (1 with alcohol addiction)
16	Dieckmann et al., 1978	Homburg, Germany	Prospective cohort	13 Patients with alcohol addiction
14	Lenhard et al., 2005	Mannheim, Germany	Case report	1 Patient with alcohol addiction
18	Kuhn et al., 2007	Cologne, Germany	Case report	1 Patient with alcohol addiction
4,5,20	Müller et al., 2009; Voges et al., 2013; and Müller et al, 2016	Magdeburg, Germany	Case series	5 Patients with alcohol addiction
17	Wu et al., 2010	Xi'an, China	Prospective cohort	12 Patients with alcohol addiction
19	Kuhn et al., 2011	Cologne, Germany	Case report	1 Patient with alcohol addiction
21	Heldmann et al., 2012	Magdeburg, Germany	Case report	1 Patient with alcohol addiction
12	Göktepe et al., 1975	London, England	Retrospective cohort	208 Patients (2 patients with alcohol addiction)
22	De Ridder et al., 2016	Dunedin, New Zealand	Case report	1 Patient with alcohol addiction
11	Leong et al., 2020	Dunedin, New Zealand	Case series	8 Patients with alcohol addiction

The binge/intoxication portion of the cycle is characterized by the rewarding effects and drug-seeking behavior of any drug addiction.[9] Positron emission tomography (PET) studies have shown that intoxicating doses of alcohol and drugs release dopamine and opioid peptides in the ventral striatum. Beyond that, γ-aminobutyric acid (GABA), glutamate, serotonin, acetylcholine, and endocannabinoid systems, which act at the level of either the VTA or of the NAcc, are related to this stage.[10]

The neurobiological mechanisms of the withdrawal/negative affect stage involve decreases in dopaminergic, serotonergic, and GABAergic transmission and increases in N-methyl-D-aspartate receptors glutamatergic transmission in the NAcc. Also, the hypothalamic–pituitary–adrenal axis and the brain stress system are dysregulated by chronic alcohol use, leading to elevated adrenocorticotropic hormone, corticosterone, and amygdala corticotropin-releasing factor (CRF) during acute withdrawal. As tolerance and withdrawal evolve, elements of brain stress systems are recruited in the extended amygdala and contribute to the development of negative emotional states that lead to further drinking.[10] The amygdala is connected to the NAcc through the bed nucleus of the stria terminalis. It is also connected to the orbitofrontal cortex, which may be the mechanism by which withdrawal/negative affects influence the preoccupation/anticipation stage.[9]

That said, the preoccupation/anticipation stage, characterized by craving and executive function deficits, involves prefrontal activation mediated by glutamate.[9,10] Beyond that, human imaging studies have reported that deficits in executive function could be associated with decreases in frontal cortex activity, which interfere with decision-making, self-regulation, inhibitory control, and working memory, and might involve disrupted GABAergic activity in the prefrontal cortex.[10]

In addition, the NAcc and especially the habenula, which is also involved in the reward system, project to the dorsal anterior cingulate cortex (dACC), contributing to the association between rewards and actions. The activity in the dACC increases when the received reward does not reach the desired level, also influencing actions related to craving.[11]

Results

From the 3,550 studies retrieved in the present research, 14 were included in the review and are synthetized in ►**Table 2**.

Göktepe et al. evaluated the effects of stereotactic subcaudate tratotomy in 208 patients with some psychiatric disorder. Of these, only 134 had their information fully evaluated, 2 of them with alcoholism. The results were poor since the two patients remained unchanged after surgery.[12]

In a study by Kanaka et al., 73 drug-addicted patients, 25 of whom were alcohol dependent, underwent a stereotactic cingulotomy from 1970 to 1976. For the authors, it was considered a failure if the patient drank alcohol after surgery. Following this criterion, among the 25 patients, 17 had a successful result and 1 died a week after surgery due to unrelated causes.[13]

Lenhard et al. discussed the use of anterior stereotactic cingulotomy in a case report of a 67-year-old woman. She had a history of severe alcohol intake since the age of 30 years old, characterized by high daily consumption of alcohol

Table 2 Study result synthesis according to the procedure

Procedure	Author (year)	Number of patients with alcohol addiction	Maximum follow-up	Outcome	Complications
Stereotactic Subcaudate Tractotomy	Göktepe et al., 1975	2	2.5–4.5 Years	Poor outcome: both remained unchanged	In the whole group of 134 patients with some psychiatric disorder, epilepsy, a tendency to eat excessively, volubility, extravagance, reduction in social standards, and a lack of consideration for others were observed.
Stereotactic cingulotomy	Kanaka et al., 1978	25	1–6 Years	17 (68%) Successful 7 Failed	No complications.
Stereotactic anterior cingulotomy	Lenhard et al., 2005	1	23 Years	Reduced frequency of relapses, prolongated periods of abstinence, and decreased alcohol intake.	Stress-induced relapses accompanied by disturbed oral impulse-control behavior; mood instability and increased interpersonal conflicts; decreased general motivation.
Stereotactic ventromedial hypothalotomy	Müller et al., 1973	1	11 Months	Poor outcome: patient relapsed into alcoholism.	No complications.
	Dieckmann et al., 1978	13	2–3 Years	Improvement in family life and work. Two patients remained abstinent during the follow-up period, and nine were able to control consumption.	Two patients with vegetative crises (1 death), 9 with vision disorder, 10 with lack of impulse, and 12 with amnestic syndrome.
Stereotactic ablation of NAcc	Wu et al., 2010	12	27 Months	Nine patients had no relapse during the follow-up period, and three patients relapsed. The therapeutic effect was excellent in 10 cases (83.3%), good in 1 case (8.3%), and poor in 1 case (8.3%).	One subject had hyposmia, but he recovered 4 months later.
DBS in NAcc	Kuhn et al., 2007	1	12 Months	Drastic reduction in alcohol consumption. Normalization of gamma-glutamyl transferase and carbohydrate deficient transferrin values. AUDIT score changed from 28 points to 1 point.	No complications.
	Kuhn et al., 2011	1	12 Months	Completely ceased alcohol consumption after 12 months. ADS and the OCDS fell below pathological scores. Improvement in cognitive control deficit, as reflected in the ERN amplitude.	No complications.
	Müller et al., 2009; Vogues et al., 2013; and Müller et al., 2016	5	8 Years	Patient one remained abstinent without any relapse. His AUQ dropped from 29 pre-surgery to 8 after 6 and 12 months, respectively. OCDS obsession and compulsion scores were 11 and 18, respectively, before DBS and dropped to zero at 6 and 12 months of follow-up Patient two remained abstinent without any relapse. His AUQ dropped from 53 pre-surgery to 8 after 6 and 12 months, respectively. His OCDS obsession and compulsion score was 18 and 19, respectively, before DBS and dropped to zero at 6 and 12 months of follow-up. Lost follow-up after 6 years. Patient three did not remain entirely abstinent, but his drinking behavior improved considerably. His relapses were due to negative stress that he could not handle otherwise. He died after 8 years of follow-up, unrelated to DBS. After staying abstinent for more than 16 months, patient four had a few very short relapses over the next 12 months because of personal stress. After that, he had a long time of relapse due to electrode dislocation. He died after 4 years of follow-up, unrelated to DBS. Patient five reported an immediate and ongoing absence of craving. The patient had 4 short relapses for 1–3 days due to personal stress but remained abstinent otherwise.	One case of a hypomanic period that remitted after adaptation of the stimulation parameters. Electrodes of patient four were dislocated sometime after surgery, leading to relapse, which could be resolved after replacement.

Table 2 (*Continued*)

Procedure	Author (year)	Number of patients with alcohol addiction	Maximum follow-up	Outcome	Complications
	Heldmann et al., 2012	1	18 Months	Patient achieved abstinence and reported a virtually complete reduction of his sensitivity to alcohol-related cues.	Short period of hypomania, which stopped upon changing stimulation parameters.
rTMS + implant in dACC	De Ridder et al., 2016	1	18 Months	Patient remained alcohol, anxiety, and agoraphobia free during follow-up and quit smoking one year after the surgery.	No complications
	Leong et al., 2020	8	12 Months	Patients did not completely discontinue drinking, but there was an 80% decrease in alcohol consumption. Two patients did not respond and relapsed at 12 months of follow-up. Improvements were observed in depression and obsessive-compulsive drinking.	Psychotic symptoms, right frontal venous infarct, seizure, and reckless impulsive behavior

Abbreviations: ADS, alcoholism dependence scale; AUD, alcohol use disorder; AUDIT, alcohol use disorders identification; AUQ, alcohol urge questionnaire; dACC, dorsal anterior cingulate cortex; DBS, deep brain stimulation; NAcc, nucleus accumbens; OCDS, obsessive-compulsive drinking scale; rTMS, repetitive transcranial magnetic stimulation.

(500 g of ethanol). Lesions were made in the left part of the anterior cingulate cortex, in the left caudate body, and in the dorsal medial thalamic nucleus. In the long term, the patient had fewer episodes of relapses related to stress; however, these relapses started to be accompanied by a disturbed oral impulse, such as the ingestion of perfumes, hairsprays, and other alcoholic liquids. She also had mood instability with increased interpersonal conflicts. Despite this, there was a decrease in alcohol intake and prolonged periods of abstinence.[14]

A different result was observed by Müller et al. using a stereotactic technique to approach the ventromedial hypothalamus. In this study, 22 male patients were operated on from 1962 to 1972. One patient suffered with severe alcoholism for 10 years and drug addiction in the year before surgery. Previous treatment in psychiatric hospitals had not been successful. The patient was followed up for 11 months, and the result was considered bad since he continued with alcoholism.[15]

Using the same target, Dieckmann et al. evaluated 13 patients with alcohol and drug addiction. As a result, there was an improvement in family life and work. Two patients remained abstinent during the follow-up period, and nine were able to control consumption. However, the side effects were notable, especially in those submitted to bilateral anterior hypothalotomy. Among them, two patients died due to a vegetative crisis, and other side effects were visual disorders, severe lack of energy, and amnestic syndrome.[16]

Using the stereotaxic technique for NAcc ablation, Wu et al. treated 12 patients with alcohol dependence. During the follow-up, 9 cases had no recurrence and had not consumed alcohol for >6 months, with 7 of these remaining without alcohol for >1 year. Relapse occurred in three cases after surgery. The result was considered excellent in 10 cases (83.3%), good in 1 case (8.3%), and poor in 1 case (8.3%). The Alcohol Dependence Severity Scale (SADS) reflected a large reduction in withdrawal symptoms in the postoperative period compared with the preoperative period ($p < 0.05$). The 2 parameters that assessed the desire for alcohol (frequency and duration) were significantly reduced 6 months after surgery in these patients ($p < 0.05$).[17]

Kuhn et al. used DBS in the NAcc to primarily reduce anxiety symptoms in a 54-year-old patient who had suffered from agoraphobia with panic attacks, depressive disorder, and alcohol abuse. There was no improvement in his primary disorder, but a rapid and drastic reduction in his alcohol consumption was observed. Within 1 month of treatment, the amount of alcohol consumed decreased from 10 to 1 or 2 drinks per day, and the Alcohol Use Disorders Identification Test (AUDIT) score changed from 28 points to 1 point. Twelve months after implantation of the electrodes, the patient only consumed alcohol occasionally.[18]

Later, Kuhn et al. had the same positive result using DBS in the NAcc of a 69-year-old man who had been suffering from alcohol dependence for >30 years. Eight months after the start of DBS, the patient occasionally consumed alcohol, and after 1 year he stopped drinking completely. The authors also found a normalization of the value of the error-related

negativity (ERN), which assesses the integrity of the anterior midcingulate cortex and the network that controls executive function.[19]

Müller et al. and Vogues et al. had similar results using DBS in the NAcc to treat chronic alcoholism in five patients. Patient 1, a 36-year-old man, started drinking at 12 years old, with $\sim$ 2 L of alcoholic drinks per day. Pharmacological treatment was performed with acamprosate without success. After the start of DBS, he remained sober during the 8-year follow-up period. There was no more desire for alcohol, activities of daily living could be performed normally, and there were no side effects.[4,5,20]

Patient 2, a 37-year-old man, started drinking at the age of 11 years old. He was also treated with acamprosate, but without effect. After the start of DBS, he remained abstinent during a 6-year follow-up period, with complete cessation of cravings. Shortly after surgery, he developed a hypomanic period for $\sim$ 1 week, which was resolved after adapting the stimulation parameters. In addition to the effects on alcohol, his nicotine consumption decreased considerably.[4,5,20]

Patient 3, a 40-year-old man, started drinking in his early teens and increased his daily intake over the years. Although he did not remain totally abstinent after surgery, the number of relapses and the amount of alcohol ingested decreased. His relapses were due to negative stress that he could not handle otherwise. He died after 8 years of follow-up, unrelated to DBS.[4,5,20]

Patient 4, who was 51 years old, had been addicted to alcohol for almost 20 years. After starting DBS therapy, this patient reported an immediate disappearance of cravings. After staying abstinent for $>$ 16 months, he had some very short relapses in the next 12 months due to personal stress. After $\sim$ 2.5 years, the patient was lost to follow-up and had a prolonged relapse. Later, during a hospitalization due to a generalized seizure, displacement of the brain electrodes was discovered. After replacement, the patient reported a beneficial effect similar to what he had experienced shortly after surgery. He had a few more relapses after that. He died after 4 years of follow-up, unrelated to DBS.[5,20]

Patient 5, who was 55 years old, was addicted to alcohol for $\sim$ 20 years. After DBS, this patient also reported an immediate disappearance of cravings. Since the start of DBS, the patient had some relapses due to personal stress.[5,20]

Heldmann et al. investigated the effects of DBS on the NAcc using PET in a 38-year-old man with severe alcohol dependence. The PET showed activations related to gains and losses in the paracingulate cortex, the temporal poles, the precuneus, and the hippocampus under active DBS, which are brain areas that have been implicated in behavioral control. Except for the temporal pole, these activations were not seen when DBS was deactivated.[21]

De Ridder et al. used a different neuromodulation technique in a 38-year-old male patient with intractable alcohol dependence associated with anxiety and agoraphobia. First, double-cone coil transcranial magnetic stimulation was performed to verify whether an implant could be beneficial in that case, aiming to reach the dACC. As he had a great but transitory result, in order to achieve permanent benefits, an electrode was implanted onto the dACC/supplementary motor area (SMA) bilaterally. To do this, an open neurosurgical approach was performed consisting of a small right-sided frontal craniotomy for a transfalcine approach to insert two electrodes. In the 18 months of follow-up, the patient remained alcohol, anxiety, and agoraphobia free. Beyond that, he quit smoking 1 year after the surgery.[22]

Later, based on the methodology by De Ridder et al., Leong et al. performed surgical electrode implantation in the rostrodorsal anterior cingulate cortex (rdACC) in eight individuals with severe AUD. There was a 60.7% reduction in the alcohol craving score. The participants did not completely discontinue drinking, but there was an 80% decrease in alcohol consumption. Two patients did not respond and relapsed at 12 months of follow-up. Beyond that, improvements were observed in terms of depression and obsessive-compulsive drinking. The same was not observed for anxiety. The following side effects were observed: 2 cases of infection after internal pulse generator insertion; 1 case of psychotic symptoms 3 days postsurgery; 1 case of right frontal venous infarct 1 day postsurgery, whose hemiparesis completely resolved after 3 weeks, but there were 2 seizure episodes 26 weeks postsurgery; and 1 case of exhibited reckless impulsive behavior for 3 weeks upon returning home postsurgery.[11]

Discussion

When analyzing the results, we observed three approaches that had the best outcomes, which were stereotactic cingulotomy, use of the NAcc as a target, and the association of repetitive transcranial magnetic stimulation (rTMS) and an implant in the dACC.

The first study we found related to surgical treatment for alcoholism was conducted by Müller et al., in which the patients underwent a stereotactic hipothalotomy. The authors described poor results since the patient relapsed into alcoholism. Later, in a study by Dieckmann et al. using the same target, despite some beneficial results presented, the side effects were considerable,[15,16] which makes this target unviable in the ablative technique.

In the meantime, Göktepe et al. evaluated several patients with different psychiatric disorders who underwent stereotactic subcaudate tratotomy. The use of a surgical approach in these cases was a consequence of the rise of psychosurgery, led by Egas Moniz in 1935, with a surgical procedure known as lobotomy. The advances in imaging techniques and the rise of stereotactic surgery made achieving better results with fewer side effects possible.[12,23] Despite the poor results described by Müller et al., it was possible to envision a surgical treatment for AUD.

Cingulotomy was also an important surgical approach exploited by neurosurgeons during this period. Changes in the cingulate gyrus have been found in studies using neuroimaging in patients with alcoholism. One of the main findings was significantly reduced gray matter bilaterally. These changes were also found in the insula, in the orbitofrontal cortex, in the prefrontal cortex, and in the putamen, which are all important elements of the mesocorticolimbic

system.[24,25] In addition, maladaptive interactions in this system were observed, as well as decreased axonal integrity of the anterior corpus callosum, of the minor forceps, of the anterior corona radiata, of the cingulum, of the anterior limb of the internal capsule, and of the external capsule.[24] These changes were related to the greater impulsivity found in patients with alcoholism[24,26] and may explain the reasonable results when using cingulotomy as an approach.

After years of evolution in the knowledge of connections related to psychiatric disorders and substance abuse, including alcohol, the NAcc has become an important surgical target, with good results. As already elucidated, it plays a central role in the mesocorticolimbic system, being intrinsically related to addiction disorders.[4,5,7,10] The NAcc has also been studied as an important target in other disorders, such as obsessive-compulsive disorder (OCD), Tourette syndrome (TS), and anxiety disorder (AD), due to the importance of the mesocorticolimbic system in these contexts.[19,27,28] The influence of this target on alcoholism was first observed in one of these studies in a patient with AD.[18]

An important finding after DBS in the NAcc was the normalization of the ERN, an electrophysiological marker that is reduced in patients with alcohol-related disorders, demonstrating a positive effect on cognition. This may be related to the suppression of cravings and, consequently, less alcohol consumption.[19]

In addition to the effects on alcoholism, another important benefit observed in studies involving DBS in the NAcc was a decrease or even cessation in smoking, showing the importance of this target and the role of the mesocorticolimbic system in the abuse of various substances and in compulsory habits. Other similar findings were made by Mantione et al. when a patient who underwent DBS for OCD presented smoking cessation and weight loss.[4,5,26,29]

Regarding DBS, it is postulated that it acts by interfering in the glutamatergic and dopaminergic systems in the NAcc, indirectly influencing the dopaminergic synaptic efficiency and, consequently, resulting in the normalization of neurotransmission associated with these systems.[18] This type of approach is generally preferable in relation to ablation, mainly due to its reversibility. However, the costs are much higher, which makes it infeasible in many occasions.[17,30]

Although noninvasive procedures are not the focus of the present study, two recent studies have demonstrated the benefits of using rTMS as a prognostic test, associated with subsequent surgical implantation of an electrode in the rdACC. In the first study, only positive results related to AUD, depression, and agoraphobia were observed in the case report, with no adverse effects. In the second study, when applying the same methodology to eight patients, it was observed that the patients, although in a smaller quantity, continued to drink. The patients attributed this result to their drinking habit, which depends on interactions between the prefrontal cortex and the dorsolateral striatum. This would probably require a different target. Although important side effects were observed, these studies show promising results. Therefore, more studies are needed to prove the efficacy and security of this procedure.[11,22,31]

The positive results found when using the rdACC are probably linked to its role in inhibiting the response when the individual needs to make decisions. This is very important, not only in impulsivity but also for patients to achieve abstinence, since it influences the response to stimuli related to alcohol.[32]

Regardless of the positive results that have been observed when using the NAcc as a target in DBS and the association between rTMS and implants in the dACC, further studies about the effect of these and other targets on the neurocircuitry of alcohol addiction are needed to support the use of this procedure as an efficient and secure treatment option. The lack of clinical trials on alcohol abuse was the most important limitation found in the present study.

Another important limitation was the subjectivity of the data analysis in some publications and the different evaluation parameters used. Many studies used only the results observed by the patients and family members themselves and the amount of drinking ingested before and after surgery. Others used some important evaluation parameters, such as the AUDIT and the Alcoholism Dependence Scale. These differences in the evaluation of patients generates biases when comparing target results. That said, it is important to establish a common parameter for the pre- and postoperative evaluation of patients with AUD for scientific studies.

Conclusion

In conclusion, exploiting the surgical approach for patients with AUD is important since only half of the patients achieve long-term abstinence with conservative treatment. The most promising surgical targets we found were the cingulate cortex and the NAcc. Deep brain stimulation is becoming an effective technique. A recent surgical approaching associating rTMS with surgical implantation of an electrode showed interesting results and should be evaluated in more studies using the dACC and different targets.

Conflict of Interests

The authors have no conflict of interests to declare.

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Nasal mucoepidermoid carcinoma after radiotherapy: Case report

Carcinoma mucoepidermoide nasal pós-radioterapia em macroadenoma hipofisário recidivante: Relato de caso

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Abstract

Introduction Mucoepidermoid carcinoma (MEC) is a tumor originated from the epithelium of the glandular excretory ducts and has highly variable biological potential. It is the most prevalent cancer of the salivary glands. The present report aims to describe a case of nasal mucoepidermoid carcinoma that developed after adjuvant radiotherapy (RT) treatment of a recurrent pituitary macroadenoma.

Case Report Male patient, 62 years old, presented with recurrent nasal epistaxis on the right, associated with intense pulsatile headache, visual analogical scale (VAS) 10/10, with improvement only with the use of opioids and morphine. After undergoing oncological screening and study by imaging exams, the presence of an expansive seal lesion with suprasellar extension was seen, involving the medial wall of the cavernous segment of the right carotid artery and the anterior cerebral artery, as well as the presence of a new expansive lesion in the right nasal cavity, with ethmoid bone invasion superiorly and medial orbit wall invasion laterally, compressing the ipsilateral optic nerve canal.

Discussion Sinonasal neoplasms represent a small portion of all malignancies of the upper aerodigestive tract, accounting for $< 5\%$ of these neoplasms. The development

Keywords
- mucoepidermoid carcinoma
- neurosurgery
- radiotherapy
- pituitary adenoma

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of MEC involves risk factors such as occupational issues, history of trauma and surgery involving the nasal area, and radiation exposure, as in previous RT.
Conclusion Mucoepidermoid carcinoma is an uncommon neoplasia and can be associated with RT treatment, as used in cases of recurrent pituitary macroadenoma. In general, surgical resection to obtain free margins of neoplastic tissue is the aimed treatment, seeking better prognosis.

Resumo

Introdução O carcinoma mucoepidermoide (CME) é um tumor que se origina do epitélio dos ductos excretores glandulares e possui potencial biológico altamente variável. Trata-se do câncer de maior prevalência nas glândulas salivares. O objetivo do presente relato é reportar um caso de carcinoma mucoepidermoide nasal que se desenvolveu após tratamento radioterápico adjuvante de um macroadenoma hipofisário recidivante.
Relato de caso Paciente do sexo masculino, 62 anos, apresentou epistaxe nasal recorrente à direita, associada a cefaleia pulsátil intensa, escala visual analógica (EVA) 10/10, com melhora unicamente com o uso de opioides e morfina. Após realização de screening oncológico e estudo por exames de imagem, foi visualizada presença de lesão expansiva selar com extensão suprasselar, envolvendo a parede medial do segmento cavernoso da artéria carótida direita e a artéria cerebral anterior, assim como presença de nova lesão expansiva em cavidade nasal à direita, com invasão do etmoide, superiormente, e da parede medial da órbita, lateralmente, exercendo compressão em canal do nervo óptico ipsilateral.
Discussão O desenvolvimento do CME, com base nos relatos deste tema, envolve fatores de risco como questões ocupacionais, antecedentes de traumas e cirurgias na área nasal e exposição radioativa, como em radioterapias prévias. De forma geral, a conduta de ressecção cirúrgica com a obtenção de margens livres de tecido neoplásico é o tratamento objetivado, visando melhores prognósticos.

Palavras-chave
- carcinoma mucoepidermoide
- neurocirurgia
- radioterapia
- neoplasias hipofisárias

Introduction

Mucoepidermoid carcinoma (MEC) is a tumor that originates from the epithelium of the glandular excretory ducts[1] with highly variable biological potential.[2] It is the most prevalent cancer in the salivary glands, especially in the parotids (between 60 and 70% of cases).[3] Although there are reports of involvement in other epitheliums of the head and neck, there are still few cases linked to the nasal mucosa. A study by Calderón-Garcidueñas et al.,[4] including 256 patients with nasosinusal malignancy, did not observe any case of mucoepidermoid carcinoma in this location.

Regarding the etiology, occupational factors related to contact with harmful substances to the nasal mucosa are predisposing to minor trauma and chronic irritation, which can lead to cancers of this characteristic.[1,4] Furthermore, there are reports that mention previous nasal lesions and a history of surgical procedures[5] in these areas as possible explanations for the development of these malignancies. In addition, radiation exposure is also identified as a risk factor[4] in such cases.

The purpose of the present report is to describe a case of nasal MEC that had developed after an adjuvant radiotherapy (RT) treatment of a recurrent pituitary macroadenoma.[6,7] This is a rare case due to the circumstances surrounding the appearance of this tumor, as well as its anatomical region, which represents a tiny portion of the head and neck tumors. After a literature review, it was found that the topic in question is rarely discussed, and no similar reports to what is described in the present report were found.

Case Report

A 62-year-old male patient, in November 2019, sought a specialist after presenting with recurrent right-sided nasal epistaxis, associated with intense pulsatile headache, visual analogue scale (VAS) 10/10, with improvements only with the use of opioids and morphine. He initially resorted an otorhinolaryngology service, which performed a biopsy of a lesion visualized in the nasal cavity through nasofibroscopy and confirmed a malignant lesion whose etiology remained to be defined.

Because of the previous history of endonasal transsphenoidal surgery for resection of a recurrent pituitary macroadenoma in 2005 and 2006 in another health service, as well as local adjuvant RT in 2007 after the second surgery, tranexamic acid was prescribed in doses of 240 mg, every 8 hours, and the patient was referred to our care.

After oncological screening and study by computed tomography (CT) and magnetic resonance imaging (MRI) of the skull and the face with thin slices and contrast, an expansive sellar tumor with suprasellar extension was seen, involving the medial wall of the right carotid artery cavernous segment, as well as the cerebral anterior artery (without evident growth compared with annual serial imaging exams undergone by the patient).

In that same exam, it was also observed the presence of a new expansive lesion in the right nasal cavity, characterized by its invasive nature, homogeneous contrast highlight, with invasion of the ethmoid bone superiorly and of the medial orbit wall laterally, compressing ipsilaterally the optic nerve canal. The neoplasm was apparently contiguous with the sellar lesion in a study conducted in the region, with an apparent separation plan between the tumors. The preoperative work-up is described in ►**Figs. 1–3** and **4**.

Thus, a multidisciplinary team (neurosurgery, otorhinolaryngology, and head and neck surgery) decided on the initial attempt to resect the lesion in the right cavity by the transnasal route and, depending on the intraoperative freezing of the sellar lesion portion, resection of the sellar and suprasellar portion would be indicated by the endonasal transsphenoidal route.

In the intraoperative period, a neoplasm of malignant behavior was found, infiltrating the medial wall of the orbit (papyraceous lamina) and the ethmoid bone superiorly, bleeding and friable (►**Figs. 5** and **6**), occupying the upper portion of the nasal cavity on the right. After total macroscopic resection of the tumor, freezing biopsy was performed on all margins of the lesion, confirming that they were free from malignant infiltration.

Regarding the freezing biopsy of the posterior portion of the lesion (sellar portion), a benign lesion that, in an anatomopathological study, confirmed a pituitary macroadenoma without signs of malignancy, became evident. Thus, after finding evidence of absence of malignancy at the posterior limit of the lesion, it was decided to conclude the surgery to not add morbidity to the case (sellar and suprasellar lesion without evidence of growth and without associated symptoms).

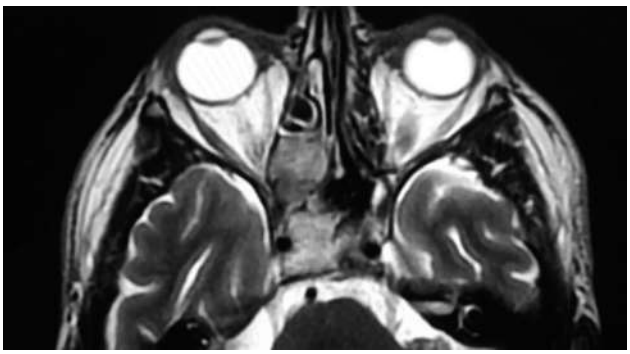

Fig. 1 T2-weighted MRI showing lesion in the right nasal cavity with infiltration of the medial orbital wall and ethmoid bone with evidence of a sellar lesion involving the right carotid artery.

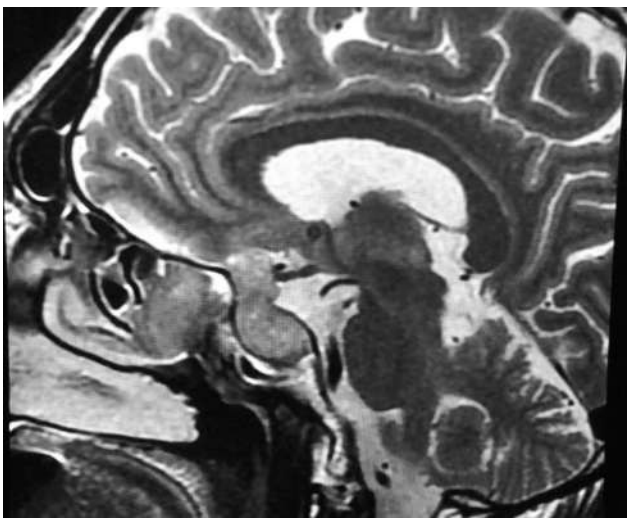

Fig. 2 T2-weighted sagittal MRI showing anterior lesion in the nasal cavity (carcinoma) and posterior lesion in the sellar / suprasellar region (adenoma).

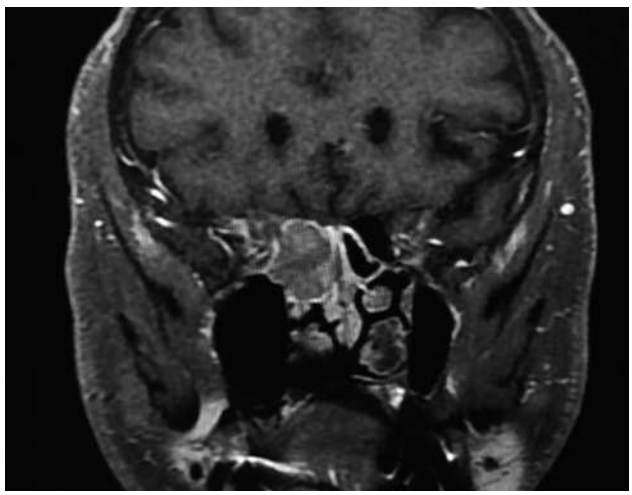

Fig. 3 T1-weighted MRI in the coronal section with gadolinium showing lesion in the nasal cavity.

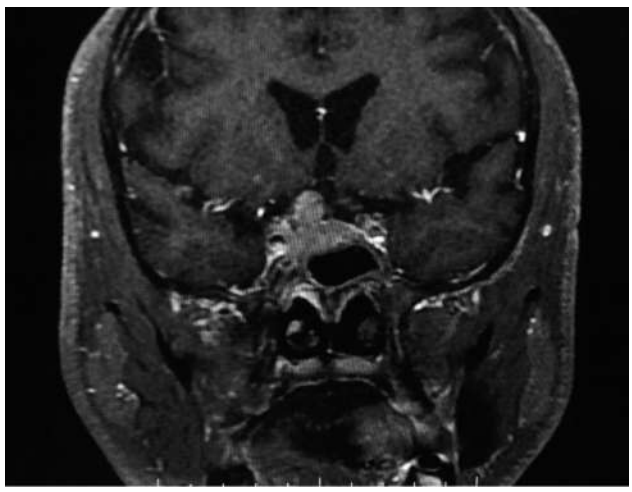

Fig. 4 T1-weighted MRI with contrast of the lesion in the sellar region with parasellar and suprasellar extension.

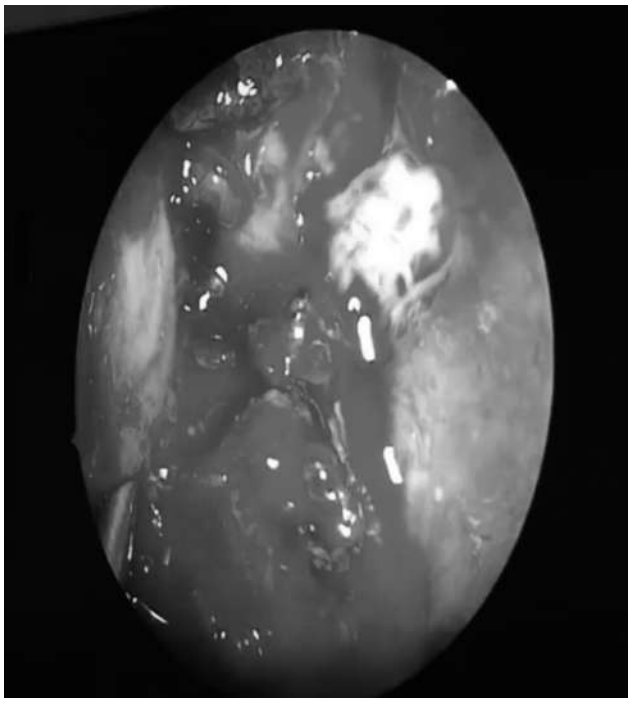

Fig. 5 Endoscopy showing lesion in the nasal cavity at the center with extension up to 6 hours. At 12 o'clock and at 2 o'clock, whitish, dura mater of the frontal lobe. At 9 AM, medial orbital wall. At 3 PM, nasal septum, posteriorly.

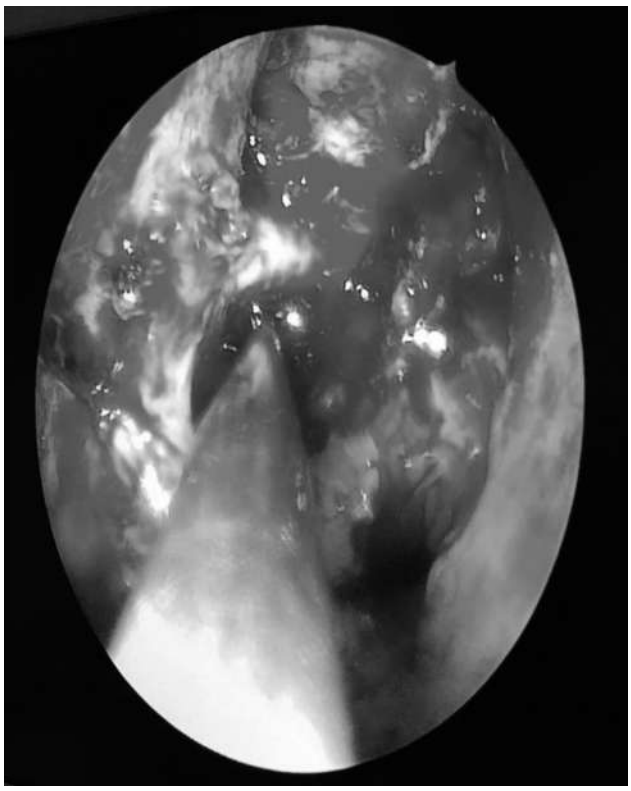

Fig. 6 Image after total resection of a lesion in the nasal cavity. Aspirator located in the optocarotid recess on the right.

The anatomopathological study of the nasal cavity lesion showed nasal MEC (►**Fig. 7**). After a day of hospitalization, the patient was discharged without any associated motor or sensory deficits and without evidence of nasal bleeding. He was referred to an oncology service for follow-up adjuvant therapy (radio and chemotherapy).

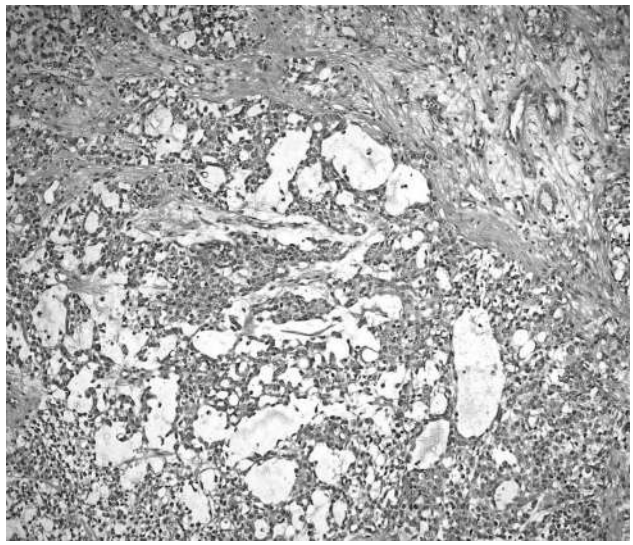

Fig. 7 Epithelial cells with atypia and mucoproducing areas. Hematoxylin and Eosin (H & E) × 100.

Discussion

Sinonasal neoplasms represent a small portion of all malignancies of the upper aerodigestive tract, accounting for < 5% of all these neoplasms.[8,9] Mucoepidermoid carcinoma is the most common malignant tumor of the major and minor salivary glands, and it also has a broad spectrum of occurrence, which can be developed from the mucosa of the nasal cavity and sinuses to the trachea and lung.[3] However, the vast majority of primary sinonasal malignancies are squamous cell carcinomas, while MEC represents < 0.1% of primary sinonasal neoplasms.[10]

Given the rarity of these tumors, when studying the existing literature in search of a correlation between MEC and pituitary adenomas, a scarcity of similar reports was observed and, when interpreting population database studies, there were limitations. The studies that include sinonasal tract MEC are grouped with data on sinonasal carcinomas or head and neck MEC,[8,11] making it difficult to conclude about adjacent tumors and their treatment.

The development of MEC, based on reports on this topic, involves risk factors such as occupational issues,[1,4] history of trauma and surgeries[5] in the nasal area, and radioactive exposure, as in previous radiotherapies.[1,4] Labor hazards include interactions with components that are harmful to the respiratory tract – such as sawdust, industrial toxins, chromium, nickel, formaldehyde, and pollutants, as well as substances related to the handling of leather, textiles, and clothing. In these questions related to work routines, there was no correlation with the history of this clinical case.

Regarding the other predisposing factors, the patient had a history of surgery by the sublabial transsphenoidal

approach on two occasions, as well as of RT treatment after his second operation. In this sense, the issue of the previous RT is highlighted in the literature. There even are links between the use of conservative RT fields in the treatment of neoplasms of the skull base and the development of new tumors, due to contiguity dissemination[6] and, possibly, to the damage to healthy adjacent tissues. Thus, it is believed, based on the history of treatment of the sellar lesion by RT, that this conduct may have a relevant influence on the origin of MEC in the nasal septum of the patient.

Regarding therapeutic intervention in pituitary adenomas, except for prolactinomas, surgical resection is the recommended initial treatment, using the transsphenoidal approach.[12,13] In these circumstances, in face of operations performed by excellent pituitary surgeons, reports indicate that the achieved remission in microadenomas had an index of 80 to 90%, while in macroadenomas the index was from 40 to 70%, with a 10 to 20% recurrence rate due to remaining tumors over the years.[13]

Concerning the possibility of RT, studies point to it as a treatment recommended in very specific situations; for example, when tumors cannot be safely dried out or hormonal levels are not controlled even after neurosurgical interventions and previous drug treatment.[14]

Another situation in which RT is shown in articles to be effective is in the case of adjuvant treatment of clinically nonfunctioning adenomas when tumor residues are identified on MRI.[15]

Conclusion

Mucoepidermoid carcinoma is an uncommon neoplasia and can be associated with RT treatment, as used in cases of patients with a recurrent pituitary macroadenoma.

It presents itself as a rare complication, which is evident from the lack of reports in the literature. The elements discussed allow to emphasize the need for attention to the specific circumstances in which RT is indicated as a therapeutic measure, considering the accuracy of the available technologies for irradiation, the viability of precise incidence at the tumor site, and the intrinsic aspects of the clinical history of the patient. In general, the conduct of surgical resection by a professional of excellence in surgery with the attainment of free margins of neoplastic tissue is the aimed treatment, in favor of better prognosis.

Conflict of Interests

The authors have no conflict of interests to declare.

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Solitary Dorsal Intramedullary Schwanomma – A Rare Lesion

Schwanomma intramedular dorsal solitário – Uma lesão rara

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Abstract

Intramedullary schwanommas are rare, and most cases are reported in cervical region. Less than 20 dorsal intramedullary schwanommas have been reported till date in literature. This is due to their cell of origin, the Schwann cell, which is not normally found within the parenchyma of the brain and spinal cord; therefore it is not surprising that these lesions are rare. We report a rare solitary dorsal intramedullary schwanomma in a young adult patient who presented with paraplegia.

Keywords
- dorsal
- intramedullary
- schwanomma

Resumo

Schwanommas intramedulares são raros, e a maioria dos casos são relatados na região cervical. Menos de 20 schwanommas intramedulares dorsais foram relatados até o momento na literatura. Isso se deve à sua célula de origem, a célula de Schwann, que normalmente não é encontrada dentro do parênquima do cérebro e da medula espinhal; portanto, não é surpreendente que essas lesões são raras. Nós relatamos um raro schwanomma intramedular dorsal solitário em um paciente adulto jovem que apresentou paraplegia.

Palavras-chave
- dorsal
- intramedular
- schwanomma

Introduction

Schwanommas account for 30% of primary intraspinal tumors. Intra-spinal schwanommas are usually located in the intradural extramedullary (IDEM) space, and are rarely intramedullary. Intramedullary schwanommas (ISs) only account for 0.3% of intraspinal tumors, and for 1.1% of intraspinal schwanommas.[1] Most ISs are found in the region of the cervical cord, and less than 20 cases of been reported in dorsal region to date. The cell of origin of the schwanomma is the Schwann cell, which is not normally found within the parenchyma of the brain and spinal cord; therefore, it is not surprising that these lesions are rare. Several theories have been postulated to explain the origin of these tumors, but none has gained universal acceptance. We report a rare case of solitary dorsal IS in a young patient who presented with paraplegia.[2,3]

Case

A 20-year-old female patient presented with back pain that had been felt for 1 year, with gradually progressive weakness in both lower limbs in the previous 2 months. Upon neurological examination, she had paraparesis in both lower limbs with a power of 3/5 on the myelomeningocele (MMC) scale. She also had bowel and bladder incontinence. Her sensory examination revelaed loss of sensation below the level of D5.

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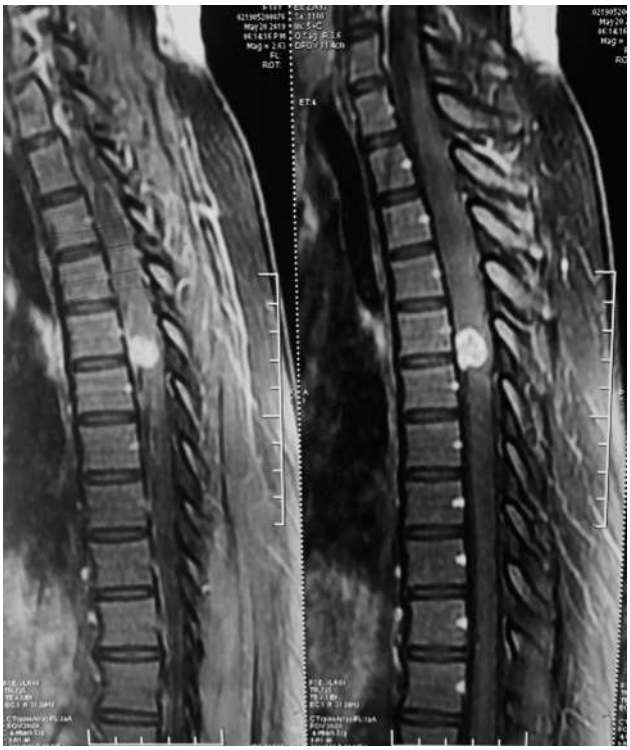

Fig. 1 Preoperative magnetic resonance imaging (MRI) scan of the dorsal spine with contrast showing the intramedullary contrast-enhancing lesion.

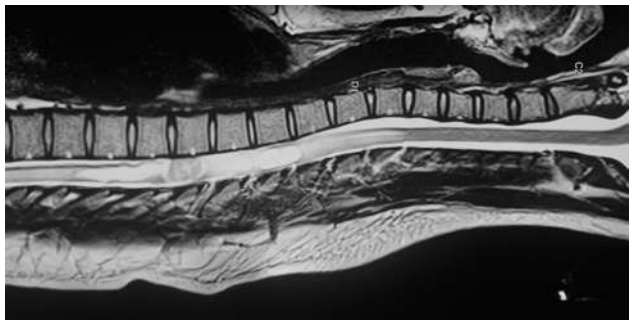

Fig. 3 Preoperative MRI of the dorsal spine: T2-weighted images showing the intramedullary lesion and cord expansion with syrinx formation.

She was submitted to a magnetic resonance imaging (MRI) scan of the dorsal spine with contrast, which revealed a well-defined heterogeneously enhancing intramedullary lesion with expansion of cord and perilesional edema at the level of D5 to D6 (►**Figs. 1–23**). The patient operated with the differential diagnoses of intramedullary tuberculoma or glioma in mind. She underwent dorsal (D4 to D6) laminotomy with complete excision of the lesion. Intraoperatively, a greyish-white, well-defined, firm, non-suckable intramedullary lesion was found (►**Figs. 4–567**). Postoperatively, there was minimal improvement in power in both lower limbs. The patient was discharged with an indication for physiotherapy and regular follow-up.

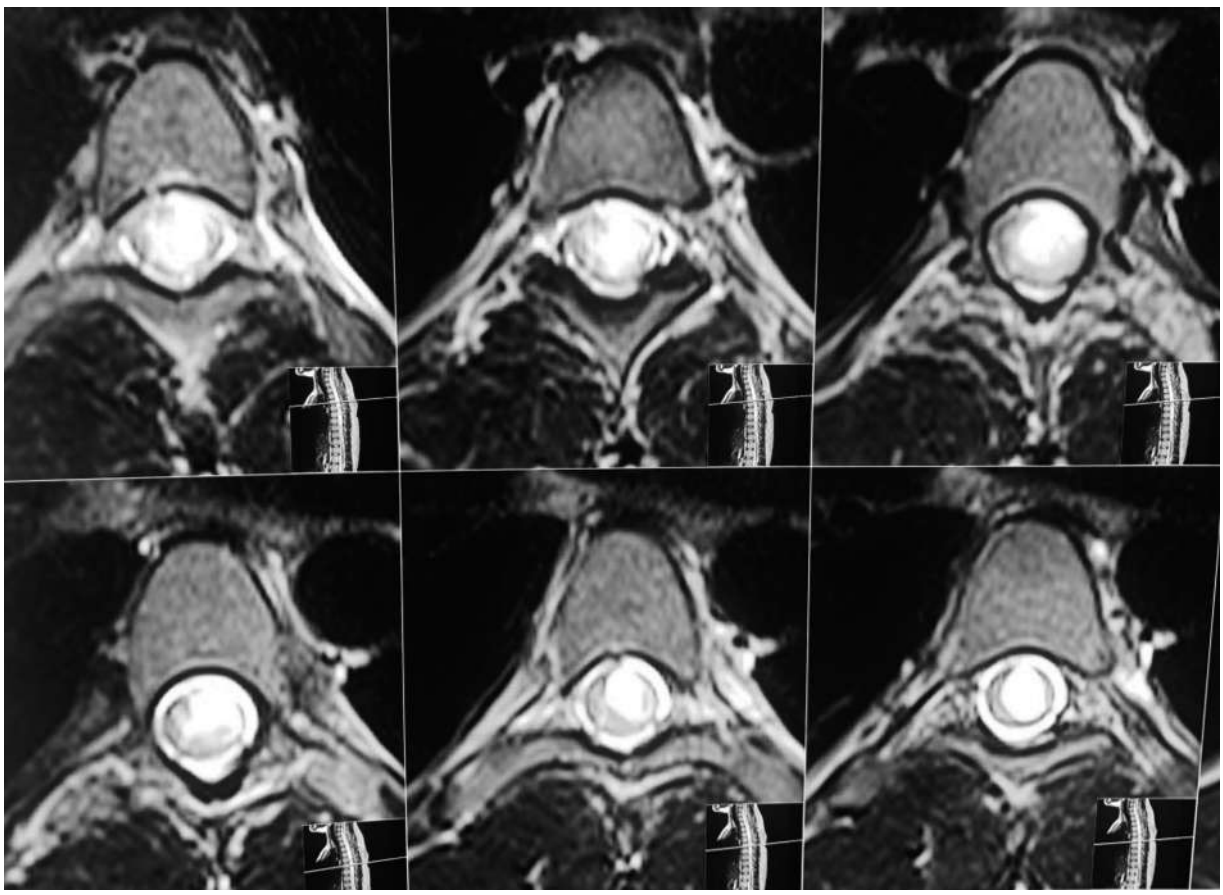

Fig. 2 Preoperative magnetic resonance imaging (MRI) scan of the dorsal spine with contrast showing the intramedullary contrast-enhancing lesion.

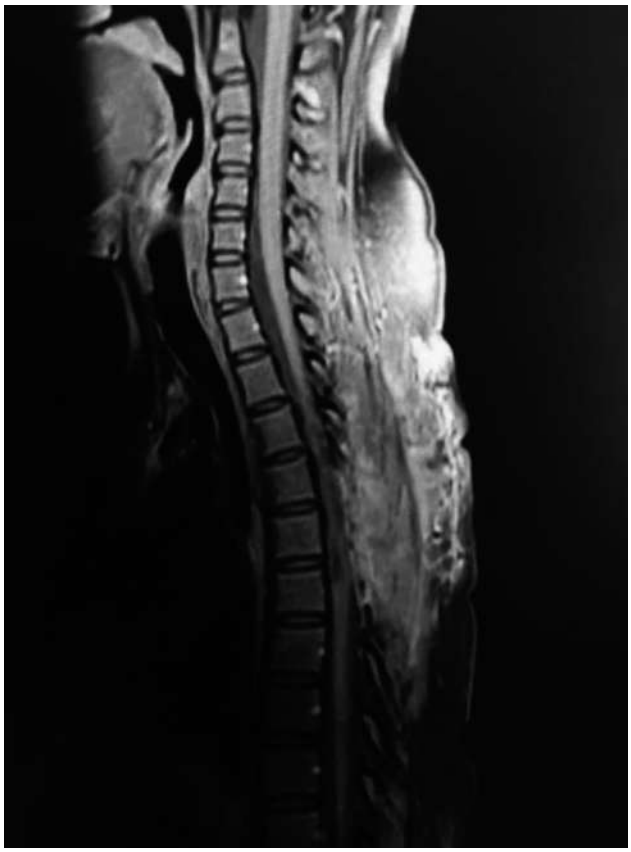

Fig. 4 Intraoperative image showing the lesion within the spinal cord.

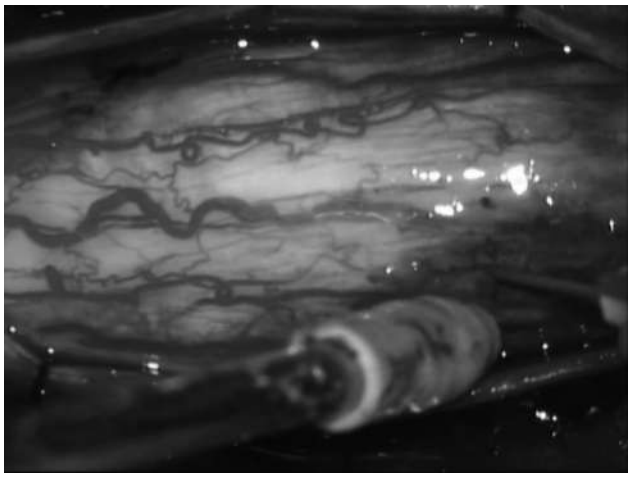

Fig. 5 Intraoperative image showing paramedian myelotomy.

To our surprise, the histopathology was suggestive of spindle-cell tumor with pallisading architecture and intratumoral aggregates of pigments in the hemosiderin-laden macrophages with cystic changes that is, schwanomma (►**Fig. 8**).

Discussion

Spinal schwannomas are the most common primary spinal tumors, accounting for ~ 25% of primary intradural spinal cord tumors in adults. Males and females are equally affected, and the age of onset is usually between 25 and 50 years.

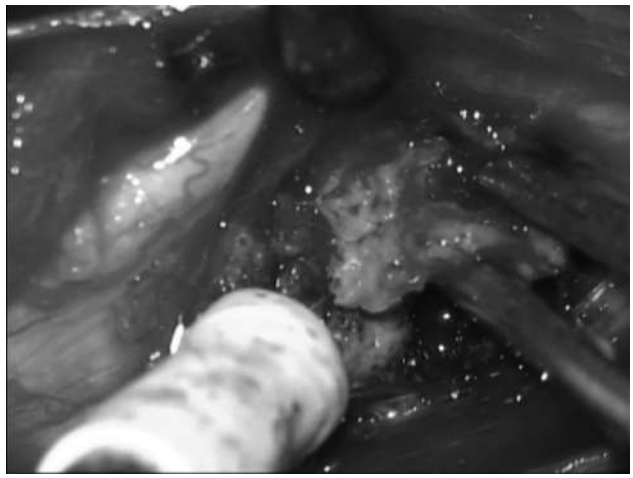

Fig. 6 Intraoperative image showing gradual piecemeal removal of the intramedullary lesion.

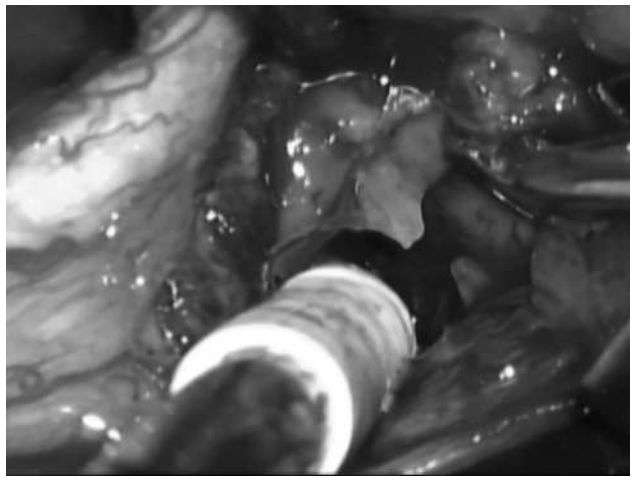

Fig. 7 Intraoperative image after complete removal of the lesion showing the cavity within the cord.

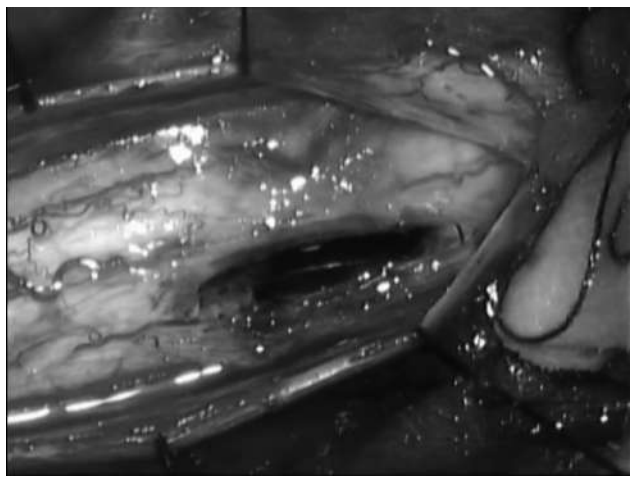

Fig. 8 Postoperative MRI of the dorsal spine showing complete excision of the lesion.

Hirano et al. reported an extended series of 678 spinal cord tumors: schwannomas were the most common histological type, with a slight prevalence of the male sex. The symptoms are related to tumor location and its proximity to the spinal

cord. Most studies report pain as the first symptom, followed by sensory deficits. Motor deficits and sphincter impairment are observed relatively late. The gold standard for the preoperative diagnosis of spinal schwannoma is the MRI. Schwannomas are more commonly observed in the lumbar spine. In the literature, 70% to 80% of spinal schwannomas are reported to be intradural in location, followed by dumbbell tumors, with both intradural and extradural components accounting for another 15%. Surgical resection is considered the gold standard for the treatment of spinal schwannomas.[4,5]

IS was first reported in 1931 by pathologist James Kernohan. However, to date, less than 70 cases of IS have been reported, most of them cervical, with less than 20 in the dorsal region. The most common location of ISs in order of frequency are the cervical spine (63%), and the thoracic (26%) and lumbar (11%) levels. Intramedullary schwanommas are benign but clinically progressive lesions. Early surgical intervention remains the gold standard treatment before the neurological deficits develop.[1]

The intramedullary location is rare, since the origin of the schwanomma is the Schwann cells, which are not normally found within the parenchyma of the brain and spinal cord. This has raised speculations about its pathogenesis, and has led to several theories to explain the origin of these tumors, although none has gained acceptance.[1,3]

The theories regarding the possible genesis that have been postulated[3] are:

- central displacement of Schwann cells during embryonic development;
- Schwann cells ensheathing aberrant intramedullary nerve fibers;
- Schwann cells extending along the intramedullary perivascular nerve plexus;
- possible neoplastic growth from dorsal-root Schwann cells located in a "critical area," as suggested by Mason and Keigher, in which the posterior roots lose their sheaths upon entering the pia mater; and
- transformation of pial cells of neuroectodermal origin into Schwann cells.

Wood et al. made two important observations: first, that schwannomas are usually located posteriorly/posterolaterally, and second, that the tumoral vascular plexus, if observed during surgery, always originates from anterior spinal arteries, never from posterior spinal arteries. A case of dumbbell-shaped neurofibroma with intramedullary and extramedullary components has been reported by Gorman et al., supporting the hypothesis of a "critical area."

The modality of choice for the diagnosis of intraspinal tumors is the MRI. Intramedullary schwannomas usually present with two patterns: solid lesions without a cystic portion; and cystic-solid lesions with associated cyst formation. The solid portion is isointense to hypointense on T1-weighted images; T2-weighted images usually show a hyperintense signal, with occasional isointense or low-signal areas. Segmental fusiform dilation of the cord is common, and peritumoral edema, which is usually present in astrocytoma, is uncommon. Contrast-enhanced T1-weighted images better delineate the lesion and differentiate the solid from the cystic components and edema. After gadolinium administration, variable enhancement can be found, and heterogeneous enhancement is the most common, with a few cases showing homogeneous and circular enhancement. The preoperative diagnosis of an IS purely on radiological grounds is difficult, as it is also difficult to differentiate it from intramedullary gliomas. However, in ISs, the classic dumb-bell appearance is rarely observed.[3,6]

Histologically, schwannomas are composed of an Antoni-A cell areas comprising compact cells in a reticular framework, and Antoni-B cell areas comprising large cells in a loose collagenous background. Intramedullary schwannomas do not have any specific histological feature.[6]

As most of these lesions are well-demarcated, gross total excision of the lesion with minimal damage to the surrounding neural tissue remains the gold standard treatment. However, subtotal resection can be performed if it is adherent to surrounding neural tissue. The use of advanced neurosurgical techniques, surgical microscope and a cavitron ultrasonic suction aspirator (CUSA) have resulted in better removal of intramedullary tumors by reducing tumor volume, with minimal retraction of the spinal cord, yielding better results.[3]

Conclusion

Intramedullary schwanommas are histologically benign tumors, and complete functional recovery can be achieved after early total excision. They are difficult to diagnose preoperatively, as there are no pathognomonic signs that enable its differentiation from other intramedullary tumors. Therefore, IS should be considered in the differential diagnosis of an intramedullary lesion in the thoracic spine.

Conflict of Interests

The authors have no conflict of interests to declare.

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Um cirurgião sob o olhar de Deus

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"Ao trazermos o sagrado para a nossa mesa de trabalho e para as nossas mesas cirúrgicas, elas se tornam um altar."

In this book *Um cirurgião sob o olhar de Deus*[1] (►**Fig. 1**), one of the most influential Brazilian neurosurgeons, Professor Raul Marino Jr. provides us with an insightful and inspirational report of his bright carrier. At the same time correlates it with an introduction for brain/mind sciences and spiritual issues as well. Professor Marino is former Chairman of Neurosurgery and Full Professor of Ethics and Bioethics at the University of Sao Paulo, Brazil.

Aside from tracing each step of his neurosurgical trajectory, this humanistic book may serve as a reflection and a valuable contribution to the true practice of medicine, centered on the human being, which, nowadays, increasingly distances itself from the fundamental human values that created it. This book also enhances the value of the spiritual practice of medicine in general and neurosurgery, in particular. It represents an ignition of a simple spark of *utopia* within our daily outraged practice. Just others *utopias* in the history of humanity, it can one day become a reality and an inextinguishable light to illuminate our steps and paths.

Um cirurgião sob o olhar de Deus, by Professor Raul Marino Jr., is unique and a must-read book for all generations of Brazilian neurosurgeons.

Fig. 1 Um cirurgião sob o olhar de Deus, by Prof. Dr. Raul Marino Jr.

Conflict of Interests

The authors have no conflict of interests to declare.

Reference

1 Marino R Jr. Um cirurgião sob o olhar de Deus. -1 ed – Barueri -SP. Manole, 2020 Conflict of Interest None declared.

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- ***Review:*** review and update synthesis of specific themes, with critical analysis and conclusions. Databases and the period range must be specified.
- ***Case Report:*** presentation, analysis and discussion of cases that present relevant interest.
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1. Title page: article title both in Portuguese and English; full name of all authors; academic or professional affiliation of each author; institutions names where the study took place; running title; corresponding author name, degree, full address, e-mail and phone number; followed by **ICMJE COI forms** (COI forms are available at: http://www.icmje.org/conflicts-of-interest/).

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4. Main text: introduction; casuistry or material and methods; results; discussion; conclusion; acknowledgments.

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Book Chapter

Peerless SJ, Hernesniemi JA, Drake CG. Surgical management of terminal basilar and posterior cerebral artery aneurysms. In: Schmideck HH, Sweet WH, editors. Operative neurosurgical techniques. 3rd ed. Philadelphia: WB Saunders; 1995:1071–86.

Book

Melzack R. The puzzle of pain. New York: Basic Books Inc Publishers; 1973.

Theses and dissertations

Pimenta CAM. Aspectos culturais, afetivos e terapêuticos relacionados à dor no câncer. [thesis]. São Paulo: Escola de Enfermagem da Universidade de São Paulo; 1995.

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Corrêa CF. Tratamento da dor oncológica. In: Corrêa CF, Pimenta CAM, Shibata MK, editores. Arquivos do 7º Congresso Brasileiro e Encontro Internacional sobre Dor; 2005 outubro 19–22; São Paulo, Brasil. São Paulo: Segmento Farma. pp. 110–20.

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Capítulo de livro

Peerless SJ, Hernesniemi JA, Drake CG. Surgical management of terminal basilar and posterior cerebral artery aneurysms. In: Schmideck HH, Sweet WH, editors. Operative neurosurgical techniques. 3rd ed. Philadelphia: WB Saunders; 1995:1071–86.

Livro considerado como todo (quando não há colaboradores de capítulos)

Melzack R. The puzzle of pain. New York: Basic Books Inc Publishers; 1973.

Tese e dissertação

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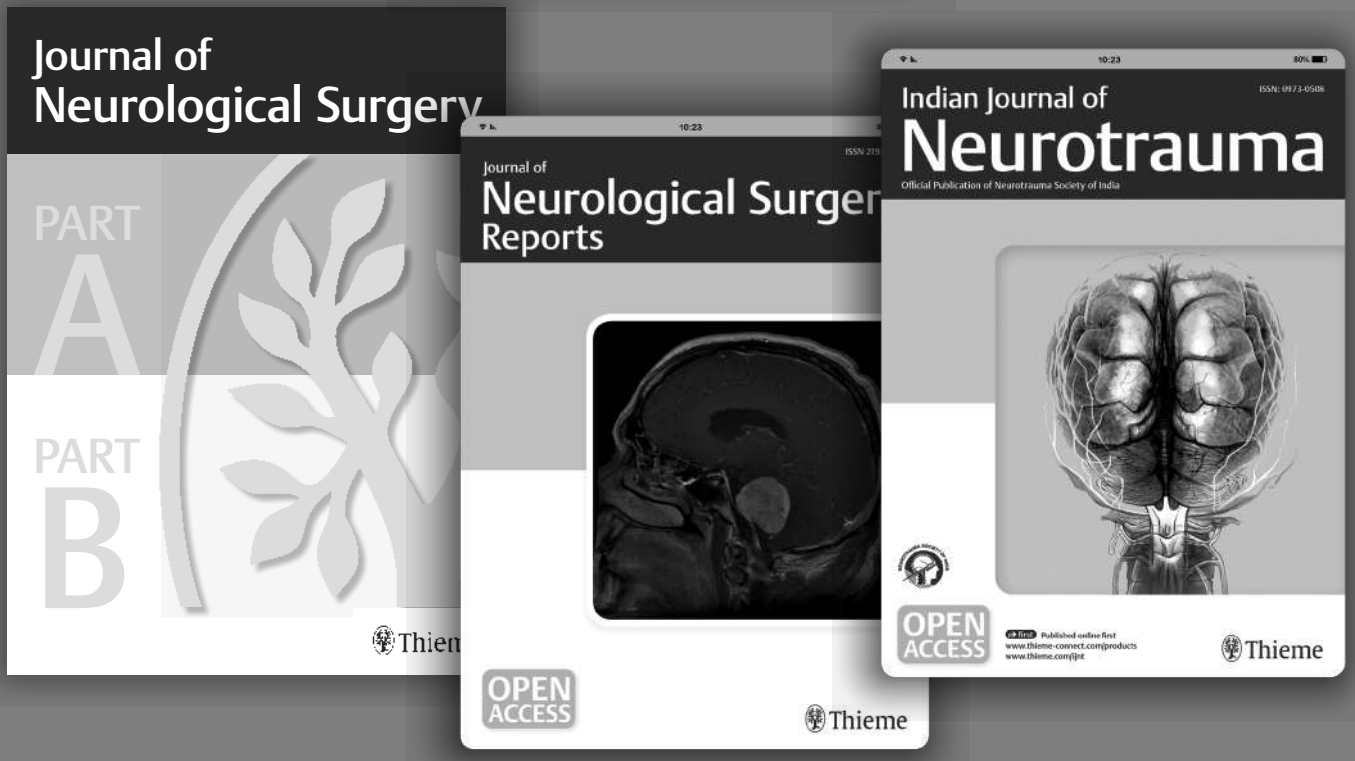

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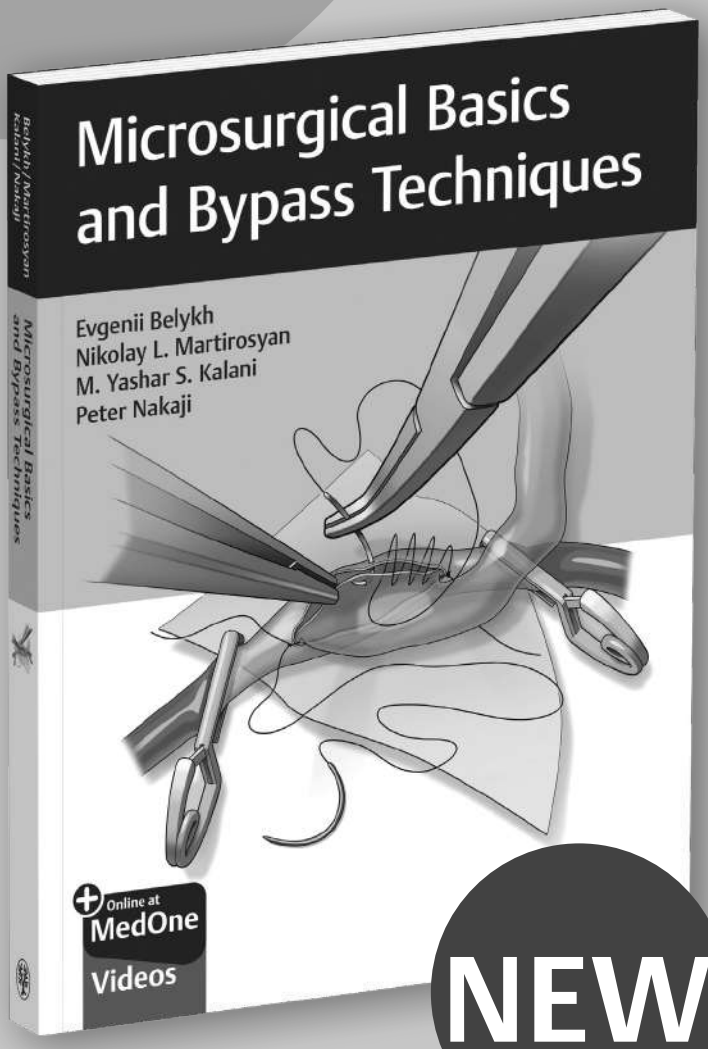

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