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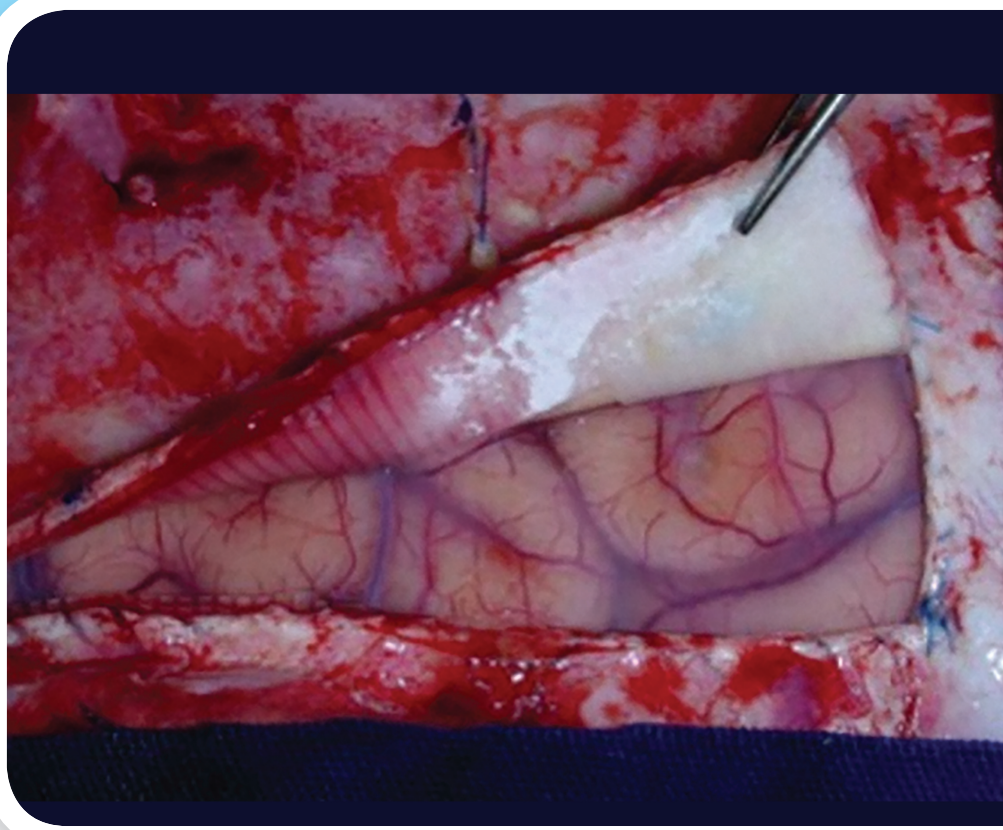

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Angiographic Findings in Refractory Delayed Cerebral Ischemia

Achados angiográficos na isquemia cerebral tardia refratária

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Abstract

Background Delayed cerebral ischemia (DCI) follows a refractory course in a subgroup of patients with aneurysmal subarachnoid hemorrhage (SAH), leading to diffuse ischemic injury. The role of angiographic vasospasm (AV) is unknown. Our goal is to study the angiographic alterations and the clinical profile of refractory DCI patients.

Methods Retrospective study of patients with SAH who presented with DCI treated with medical and endovascular therapy, with a refractory evolution, defined as multiple ischemic infarction and brain death.

Results Out of a cohort of 336 patients, 7 (2%) developed refractory DCI. The median age of the patients was 48 (38–60) years old. Five patients had ruptured anterior communicating artery (ACoA) aneurysms. Four patients were treated with coil embolization, and three with microsurgical clipping. Angiographic vasospasm was classified as severe in 5 cases. Compromise of bilateral circulation was detected in six patients. Distal circulation vasospasm occurred in five cases. Slow circulatory transit times were observed in three patients.

Conclusion Angiographic findings such as bilateral circulatory compromise and distal vasospasm were frequent alterations. Further studies are required to establish the association of these findings with the clinical outcomes.

Keywords
- subarachnoid hemorrhage
- intracranial vasospasm
- brain ischemia
- angioplasty

Resumo

Introdução A isquemia cerebral tardia (ICT) pode seguir um curso refratário em um subgrupo de pacientes com hemorragia subaracnoidea aneurismática (HSA), levando a uma lesão isquêmica difusa. O papel do vasoespasmo angiográfico (VA) ainda é desconhecido. Nosso objetivo é avaliar as alterações angiográficas e o perfil clínico dos pacientes com ICT refratária.

Métodos Estudo retrospectivo de pacientes com HSA que apresentaram ICT tratados com terapia médica e endovascular, com evolução refratária, definida como infarto isquêmico múltiplo e morte cerebral.

Palavras-chave
- hemorragia subaracnoidea
- vasoespasmo intracraniano
- isquemia cerebral
- angioplastia

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Resultados A partir de uma coorte de 336 pacientes, 7 (2%) desenvolveram ICT refratária. A mediana de idade foi de 48 (38–60) anos. Cinco pacientes tiveram ruptura de aneurisma da artéria comunicante anterior (ACoA). Quatro pacientes foram tratados com *coiling* e três com clipagem. O VA foi classificado como grave em cinco casos. Detectou-se acometimento da circulação bilateral em seis pacientes. A circulação distal do vasoespasmo aconteceu em cinco casos. Observou-se tempo de trânsito circulatório lento em três pacientes.

Conclusão Os achados angiográficos, como o acometimento circulatório bilateral e o vasoespasmo distal, foram alterações frequentes. Estudos adicionais serão necessários para confirmar as associações entre os achados angiográficos e os resultados clínicos.

Introduction

Delayed cerebral ischemia (DCI) is an important cause of neurological morbidity in aneurysmal subarachnoid hemorrhage (SAH). The role of angiographic vasospasm (AV) and its contribution to brain injury in this group of patients is controversial.

Angiographic vasospasm is commonly reported in up to 70% of SAH cases, and it is known that only 50% develop neurological deterioration.[1] Clinical presentation of DCI is heterogeneous, in terms of timing of presentation, clinical manifestations, location of spasms in the vasculature,[2] severity of vessel stenosis,[3] and response to treatment. Severe AV is associated with severe ischemia and infarction, but hypoperfusion is also reported in areas without macrovascular vasospasm on computed tomography (CT) perfusion studies.[4,5]

Spreading cortical ischemia, microthrombosis, microcirculatory constriction, and genetic polymorphisms[6] are other mechanisms that could explain why patients without significant angiographic vasospasm develop cerebral infarction.[7,8] Which one of these factors is related to a higher risk of stroke is currently not well understood. The study of angiographic findings from patients with refractory delayed cerebral ischemia might lead to insights into the relationship between AV and brain ischemic injury

We report a series of 7 patients with severe DCI and AV, refractory to full medical and endovascular therapy, that ultimately led to brain death. Our objective is to describe the angiographic alterations in this group of patients with severe DCI.

Methods

This is a retrospective study of patients with aneurysmal SAH, treated with microsurgery or endovascular therapy, during a 3-year period (2014–2016) at Institute of Neurosurgery Asenjo, Santiago, Chile. Inclusion criteria were: diagnosis of DCI according to the current definitions,[9] and absence of medical (i.e., fever, hydroelectrolytic imbalance, and infection) and of other neurological causes of deterioration (hydrocephalus, seizure). Angiographic vasospasm was established by means of digital subtraction angiography (DSA). Refractory DCI was defined as multiple ischemic infarctions leading to diffuse brain injury in spite of full medical therapy, translating into a hypodense brain parenchyma on CT.

Clinical charts, neuroimaging studies, endovascular and surgical protocols were reviewed. The modified Fisher scale[10] and World Federation of Neurosurgical Societies (WFNS) scale[11] were used to grade SAHs. The surgical techniques included cisternal cleansing therapy[12] and lamina terminalis[13] fenestration. Hydrocephalus was treated with the installation of an external ventricular drain (EVD).

Oral nimodipine was indicated for all patients on admission.[14] Delayed cerebral ischemia monitoring included serial clinical examination and transcranial Doppler (TCD) imaging.[15] Mainstay therapy included fluid resuscitation and induced hypertension, according to the current guidelines.[16,17] Hypervolemia and hemodilution were not indicated. Computed tomography angiography (CTA) was indicated when clinical deterioration persisted after first tier medical therapy. If AV was diagnosed, DSA was performed by an experienced neuroradiologist, and the severity of the AV was classified as mild, moderate, or severe, according to vessel stenosis (0–33%, 34–66%, and $>$ 67% decrease in arterial diameter, respectively). Additional angiographic evaluation included slowing of circulatory times after contrast injection, and distal circulation (minor caliber cortical branches) compromise. Method of endovascular therapy (balloon or pharmacological angioplasty) was decided by the endovascular specialist. Nimodipine was used as pharmacological agent for intra-arterial use. Patients with intracranial pressure (ICP) monitoring with an ICP $>$ 20 mmHg were treated with first (deep sedation, drainage of cerebrospinal fluid [CSF]), second (hypertonic saline, moderate hyperventilation), and third tier therapies (therapeutic hypothermia, decompressive craniectomy).

Results

During the study period, a total of 336 patients with SAH were treated at our institution. Seven patients developed refractory DCI (2%).

The median age of the patients was 48 (38–60) years old. There were five female and two male patients. The characteristics of the patients are resumed in ►**Table 1**. All of the

Table 1 Patient data

Patient	Age	Gender	Medical History	Fisher scale	WFNS scale	Aneurysm	Treatment
1	43	F	HT	IV	3	ACoA	Coils
2	48	F	CHD	IV	2	ACoA	Clip
3	58	F	HT	IV	2	Opht	Clip
4	43	M	CKD, HT	IV	4	ACoA	Coils
5	38	F	HT	IV	2	Opht	Clip
6	60	F	HT	IV	2	ACoA	Coils
7	49	M	ARF	IV	4	ACoA	Coils

Abbreviations: ACoA, anterior communicating artery; ARF, acute renal failure; CHD, coronary heart disease; CKD, chronic kidney disease; F, female, HT, arterial hypertension; M, male, Opht, Ophthalmic artery; WFNS, World Federation of Neurosurgical Societies.

patients had anterior circulation aneurysms; five were ruptured anterior communicating artery (ACoA) aneurysms (see ►**Figs. 1**, **2**, **3**, **4** for clinical examples), and 2 were ruptured paraclinoid aneurysms. Four patients were treated with endovascular coiling, and three with surgical clipping.

Two patients had aneurysm rebleeding prior to exclusion. The median time to aneurysm treatment was 1 day (range: 0–8 days). Two patients developed hydrocephalus, requiring external ventricular drainage.

The most frequent clinical manifestation of DCI was consciousness impairment (six patients). Only one patient presented with a new focal neurological deficit (aphasia and hemiparesis).

All patients were treated with endovascular angioplasty. Median time from aneurysm bleeding to angioplasty was 8 days (range: 4–8 days). Median number of angioplasties per patient was 1 (range: 1–2). Three patients were treated with mixed balloon and pharmacological angioplasty, and four with pharmacological angioplasty only. Improvement of vessel stenosis was reported on all of the procedures (►**Figs. 2** and **3**).

Angiographic findings are resumed on ►**Table 2**. DSA revealed early vasospasm (occurring in the 1st 72 hours after bleeding) in 2 patients. Angiographic vasospasm was reported in all patients, and vessel stenosis was classified as follows: severe (> 67% stenosis) vasospasm in 5 patients, moderate (34–66%) in 1 patient, and mild (< 33%) in 1 patient. Compromise of bilateral anterior circulation was detected in six patients. One patient with a left paraclinoid aneurysm presented with focal angiographic vasospasm of the left anterior circulation (anterior cerebral and middle cerebral artery). Posterior circulation (vertebrobasilar) compromise was reported in one patient (►**Fig. 4**). Distal vasospasm of cortical branches was reported in five patients. Slow circulatory times were observed in three patients.

Case 1

►**Fig. 1A:** A 43–year-old female presented with thunderclap headache. WFNS scale was graded as 3. A CT of the brain revealed a diffuse SAH (modified Fisher scale IV) and hydrocephalus. An EVD was installed.

►**Fig. 1B:** DSA confirmed a ruptured ACoA aneurysm, bilateral unruptured middle cerebral artery (MCA) aneurysms, and moderate left A1 vasospasm. Endovascular coil embolization was performed the day after the bleeding.

►**Fig. 1C:** At 9 days postprocedure, the patient developed consciousness impairment. DSA reported severe anterior circulation and moderate posterior circulation vasospasm. Endovascular treatment was indicated with bilateral internal carotid artery (ICA) and proximal MCA balloon angioplasty.

►**Fig. 1D:** After initial improvement, the patient deteriorated with multiple ischemic infarcts. Refractory intracranial hypertension developed and in spite of intensive care treatment. Brain death was established 11 days after the rupture of the aneurysm. A CT scan revealed a diffuse ischemic injury.

Case 2

►**Fig. 2A:** A 48-year-old male was evaluated at our institution for thunderclap headache. Subarachnoid hemorrhage was observed on CT. DSA revealed an ACoA aneurysm that was treated with surgical clipping.

►**Fig. 2B:** DSA right ICA artery injection reveals normal vessel caliber at admission.

►**Fig. 2C:** Seven days after the rupture of the aneurysm, the patient developed aphasia and hemiparesis. DSA revealed severe vasospasm of the ICA, of the A1 and of the M1, and moderate MCA distal vasospasm. The rest of the study confirmed bilateral compromise with slow transit times.

►**Fig. 2D:** Postangioplasty DSA. Bilateral ICA and M1 balloon angioplasty with intra-arterial nimodipine instillation was performed with marked improvement of vessel stenosis.

Case 3

►**Fig. 3A:** A 43-year-old male with a history of renal failure presented with WFNS 4, modified Fisher IV SAH, a left frontobasal intraparenchymal hematoma, and hydrocephalus. An EVD was installed.

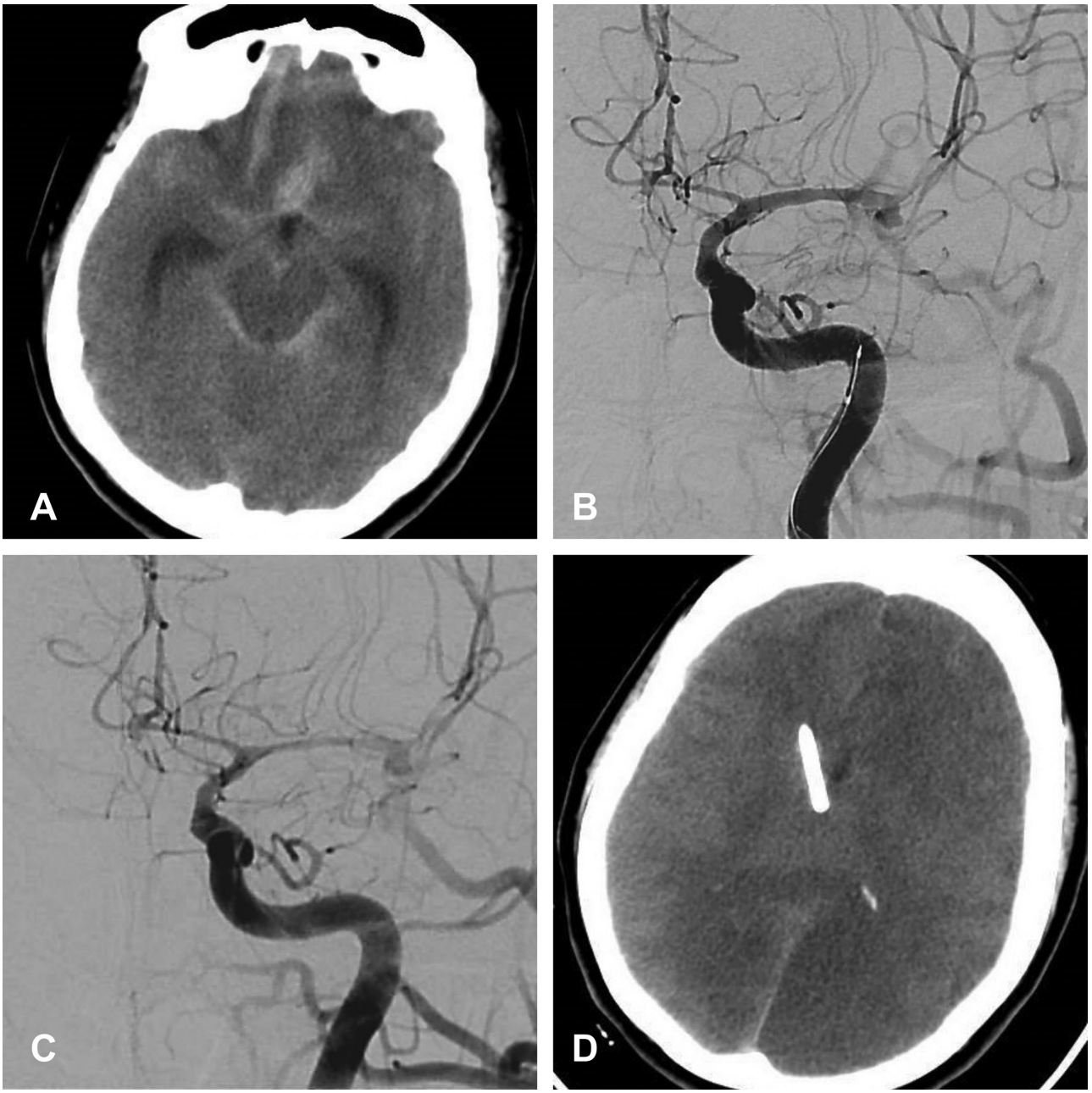

Fig. 1 Case 1. Ruptured AcoA aneurysm with hydrocephalus. Refractory DCI with severe vasospasm of anterior circulation. See text for description.

►**Fig. 3B:** DSA revealed a ruptured ACoA aneurysm that was treated with coil embolization.

►**Fig. 3C:** Serial TCD monitoring revealed increased MCA velocities. DSA informed bilateral supraclinoid ICA, M1 segment and pericallosal arteries vasospasm.

►**Fig. 3D:** Balloon and pharmacological angioplasty were performed 8 days after the initial bleeding. Additionally, two pharmacological angioplasties were indicated for persistent vasospasm. The patient deteriorated and multiple infarcts were observed on CT, with signs of intracranial hypertension. An ICP monitor was installed, and therapeutic hypothermia was started. The patient had an unfavorable evolution and brain death was established 12 days after the rupture of the aneurysm.

Case 4

►**Fig. 4A:** A 49-year-old male with a history of alcohol abuse was found by relatives with consciousness impairment. Initial laboratory tests informed acute renal failure. A CT of the brain revealed a modified Fisher IV SAH with an associated frontal interhemispheric hematoma.

►**Fig. 4A 4B**, **4C:** When the renal compromise improved, a DSA was performed, revealing a ruptured ACoA aneurysm with severe anterior and posterior circulation vasospasm. Coil embolization and pharmacological angioplasty were performed. Serial CT imaging revealed hypodensities in multiple arterial territories. Brain death was confirmed 10 days after the initial bleeding.

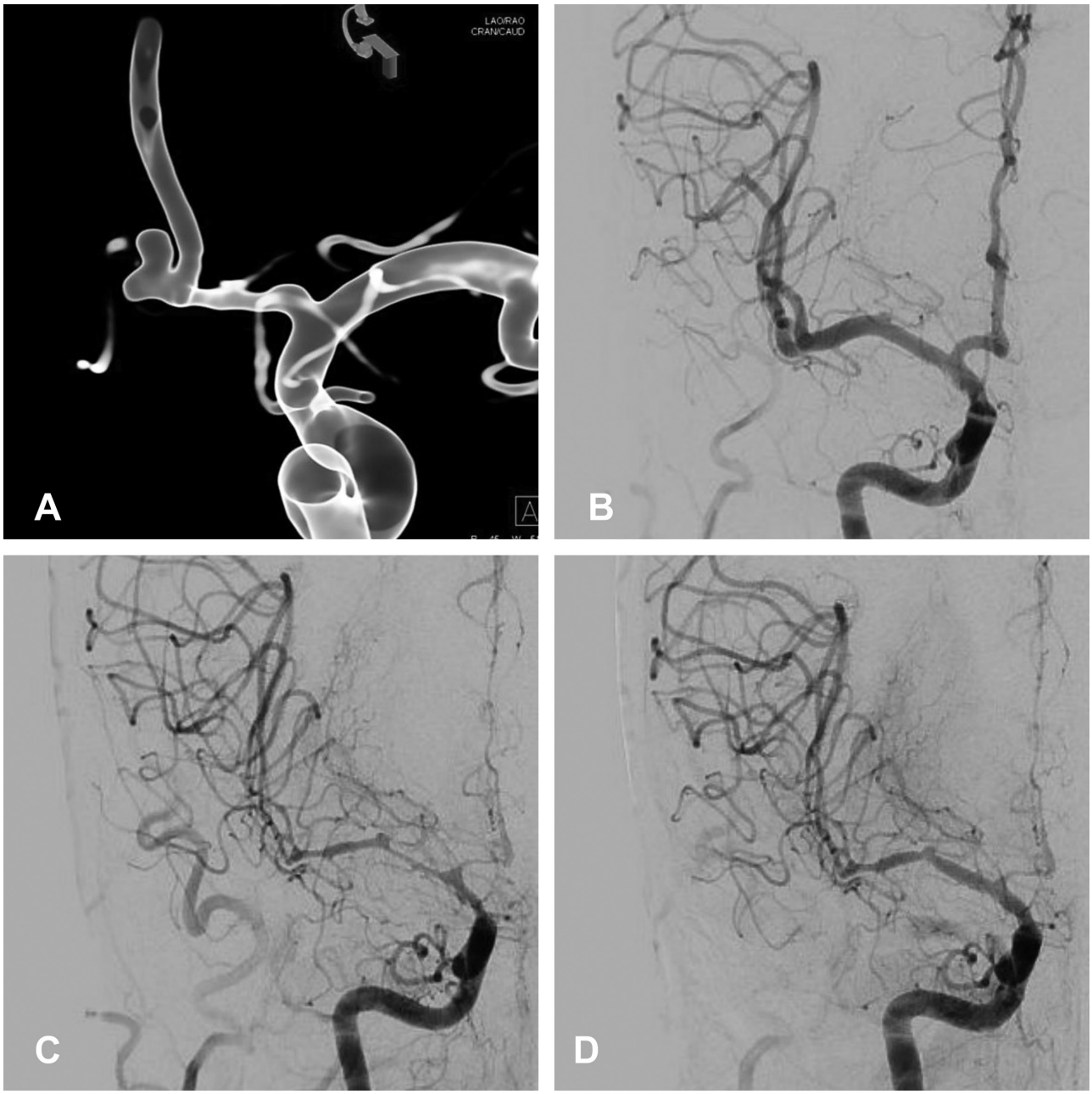

Fig. 2 Case 2. Ruptured AcoA aneurysm. Severe vasospasm of anterior circulation treated with balloon angioplasty. See text for description.

Discussion

It is known that AV occurs in up to 70% of the patients with SAH, and that only 30% of these patients develop DCI that is related to a poor neurological outcome.[9] The relationship between AV and cerebral infarction is not well-established.[18]

Infarction may develop in territories without significant AV, most likely in watershed areas.[19] Severe AV, on the other side, is a well-known predictor of cerebral infarction,[20] and is correlated with perfusion deficits on CT perfusion studies.[18]

In our series, 7 (2%) out of 336 patients developed this catastrophic complication of SAH. Digital subtraction angiography exams revealed severe vasospasm in five out of seven patients; two were classified as moderate and mild. As such, intracranial vasospasm must be understood as a dynamic event, and even patients with mild or moderate vessel stenosis reported on the initial DSA may develop DCI with a refractory evolution. Bilateral compromise of the anterior circulation was observed in six patients, indicating a diffuse macrovascular compromise. Distal circulation compromise and slow transit times were frequent findings. A hypothesis could be that these angiographic findings may be red flags of circulatory hemodynamic failure, but we cannot prove this with the design of our study. It is not the goal of the present study to establish causality between this angiographic phenomena and DCI. We can say, however, that the angiographic findings in our cohort of patients with refractory DCI were dynamic, and not restricted only to vessel stenosis. Ultra-early AV, for example, has been associated with refractory DCI in other studies.[21–23] A common misconception is to

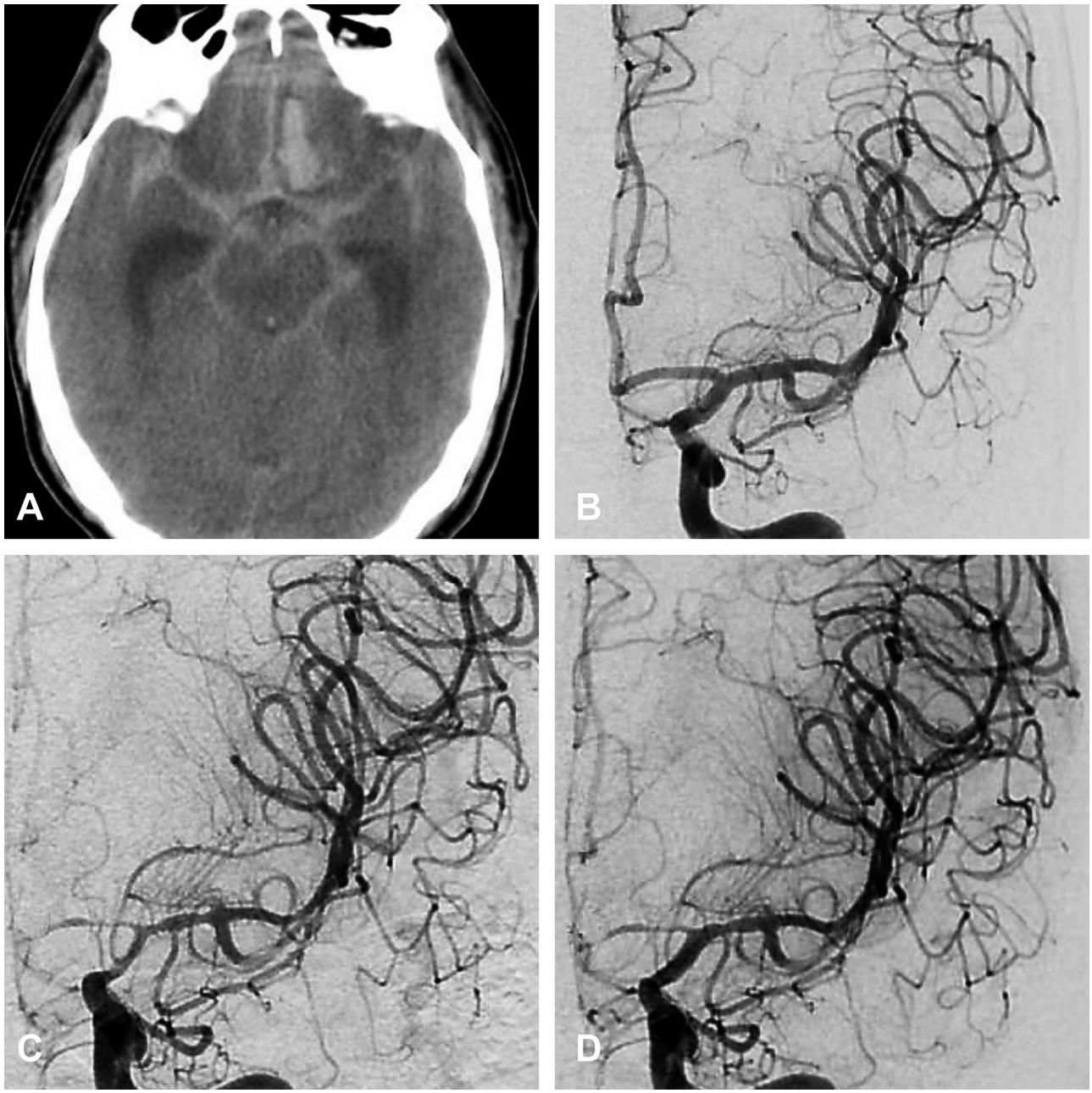

Fig. 3 Case 3. Ruptured AcoA aneurysm with left frontobasal hematoma. Persistent vasospasm after balloon angioplasty. See text for description.

confuse "mild vasospasm severity" in the angiography report as a predictor of "mild" evolution with no risk of brain injury.

Anterior communicating artery aneurysms were the most frequent in our cohort of patients; most of them (80%) were treated with coil embolization. Injury to hypothalamic structures after bleeding or/and ischemic injury may be a factor associated with a refractory evolution. Microsurgical blood clot removal[12] in this region may be beneficial in order to avoid irritation of hypothalamic perforators, but further studies are needed to confirm this hypothesis.

The relationship between the location of the aneurysm and DCI was studied by Abla et al.[24] The authors found that ruptured pericallosal aneurysms were associated with a low clot burden, but with a higher risk of DCI in comparison with other locations.

The most frequent clinical manifestation of DCI was consciousness impairment, a finding that is common in SAH patients in the intensive care unit (ICU), which may also be explained by other medical factors (fever, infections, metabolic disturbances, among others).

Endovascular therapy for symptomatic DCI was indicated for all patients, usually on the most critical period (between the 4th and 8th days). Intra-arterial vasodilator therapy and balloon angioplasty are treatment modalities well-described in the literature,[25–27] but angiographic improvement is not always associated with clinical improvement, with up to 69% of reported postprocedural ischemia.[28] Other mechanisms

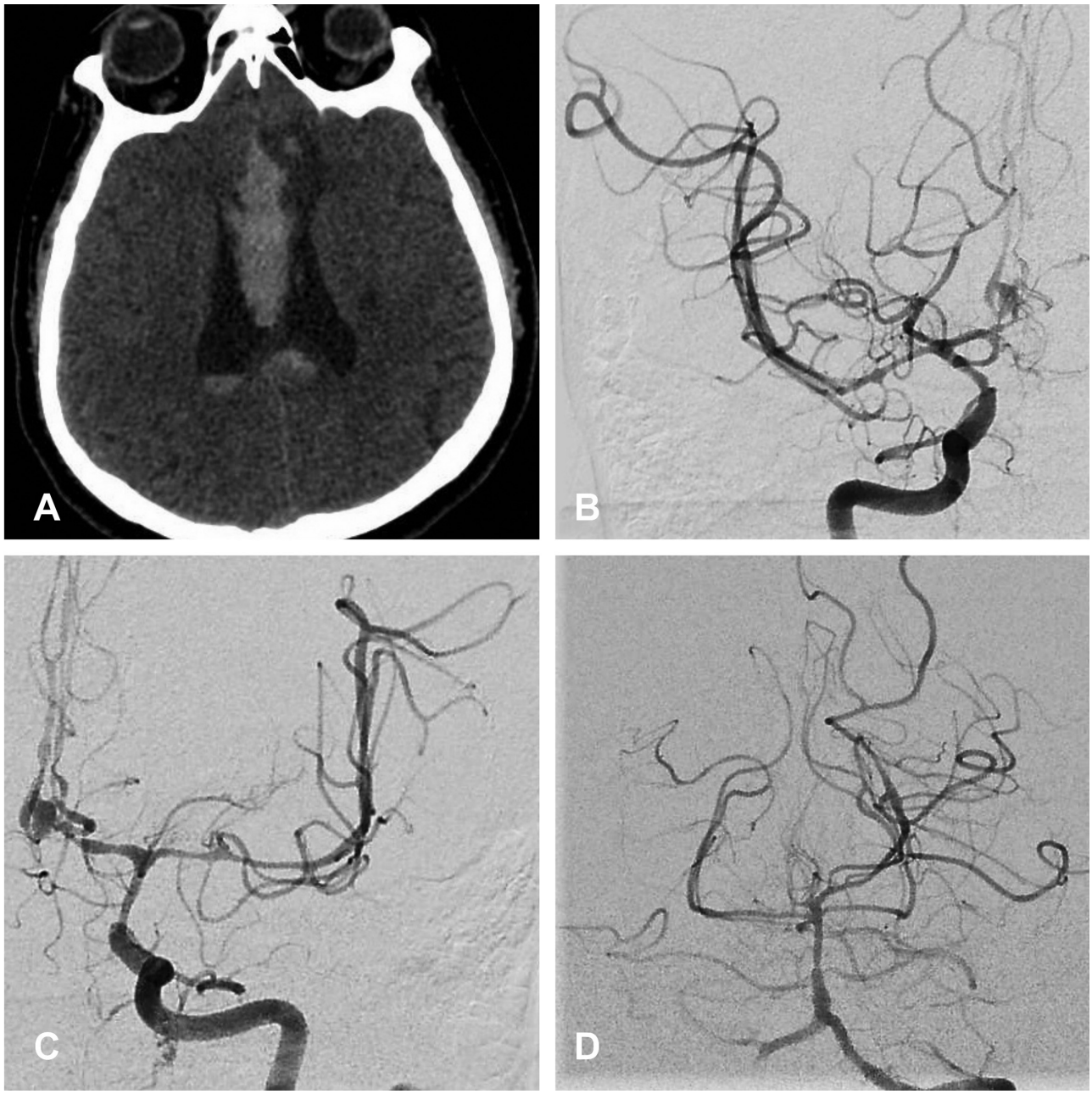

Fig. 4 Case 4. Ruptured AcoA aneurysm with intraventricular hemorrage. Bilateral vasospasm of anterior and posterior circulation. See text for description.

for ischemia are described in this subgroup of patients, such as spreading cortical ischemia, microcirculatory constriction, and microthrombosis.[1] Angiographic improvement after angioplasty must not be considered an endpoint to decide the withdrawal of hemodynamic intensive care therapy, as improvement of intracranial vessel stenosis was reported in all of our patients after the procedure.

No patient in our series was treated with decompressive craniectomy (DC). Tuzgen et al reported a series of 6 patients(4 MCA and 2 ACoA) with malignant vasospasm and proven intracranial hypertension treated with DC, reporting a favorable neurological outcome in $<$ 50% of the patients (modified Rankin scale $\leq$ 3).[29] DC was not indicated because severe ischemic injury made the surgery futile to the attending multidisciplinary team. One patient in our series was treated with therapeutic hypothermia, which produced favorable control of the ICP, but could not prevent cerebral infarction. Other treatment modalities described in the literature are anesthesia of the stellate ganglion,[30] aortic balloon,[31] immunosuppressants,[32] continuous intra-arterial nimodipine,[33] and ketamine,[34] but further studies are required.[35]

Limitations of the present study are its small sample size and its retrospective design. In the literature, several series describe outcomes of patients with DCI, but our study is, to our knowledge, the first detailed angiographic description of patients with refractory DCI, reporting other findings besides severe AV, as potential angiographic predictors for further studies.

Table 2 Angiographic findings

Patient	Clinical presentation	Timing to angioplasty	AV severity	Bilateral AV	Posterior circulation AV	Distal AV	Slow Circulatory times	Number of angioplasties	Angioplasty type
1	CI	9	Severe	Yes	Yes	Yes	No	1	B
2	Aphasia, Hemiparesis	8	Severe	Yes	No	Yes	Yes	1	B
3	CI	7	Severe	Yes	No	No	No	1	P
4	CI	8	Severe	Yes	No	Yes	Yes	3	B(1), P(2)
5	CI	6	Moderate	No	No	No	Yes	2	P(2)
6	CI	4	Mild	Yes	No	Yes	No	1	P
7	CI	8	Severe	Yes	Yes	Yes	No	1	P

Abbreviation: AV, angiographic vasospasm; B, balloon angioplasty; CI, consciousness impairment; P, pharmacological angioplasty.

Conclusion

Common angiographic findings in refractory DCI were severe vessel stenosis, slow circulatory times, distal cortical stenosis, and bilateral circulatory compromise. More studies are needed to establish an association between individual angiographic findings and clinical outcome in SAH patients.

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None.

Disclosure
None.

Conflicts of Interests
The authors have no conflicts of interests to declare

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Use of Models of Finite Elements in the Biomechanics of the Lumbar Spine

Uso de modelos de elementos finitos na biomecânica da coluna lombar

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Abstract

The same correspondence between general mechanics and civil engineering is true for biomechanics and surgical implants. Currently, numerous mechanical processes are required until a prosthesis is offered to its target audience. These processes typically require human or animal vertebrae, as well as all the complexity involving such tissues, for example, an ethics committee, the availability of materials, etc. Thus, finite element models (FEMs) have become a great option to carry out biomechanical tests independently from anatomical specimens, and, at the same time, to obtain mathematical data to assist in the general physical understanding. The present review discusses the mechanical principles involved in bioengineering, clarifies the steps for the development of FEMs, and shows application scenarios for these models. To the knowledge of the authors, the present paper is the first review study in Portuguese aimed to health care professionals in a language accessible to them.

Keywords
- spine
- finite elements
- biomechanics
- pedicle screw

Resumo

A mesma relação de correspondência que existe entre mecânica geral e construção civil ocorre entre biomecânica e implantes cirúrgicos. Atualmente, existem inúmeros processos mecânicos que são necessários até que uma prótese seja oferecida ao público alvo. Estes processos, normalmente, exigem a presença de vértebras humanas, ou mesmo de animais, e têm toda a complexidade que envolve o uso destes tecidos, como comissão de ética, disponibilidade de material, etc. Desta forma, os modelos de elementos finitos (MEFs) passaram a ser uma ótima opção, como meio de realizar testes biomecânicos e de obter independência de peças anatômicas e, ao mesmo tempo, de obter dados matemáticos que auxiliarão no entendimento geral físico. A presente revisão discute os princípios mecânicos que envolvem a bioengenharia; ademais, clarifica os passos para o desenvolvimento dos MEFs, e finaliza mostrando cenários de aplicação destes modelos. Ao conhecimento dos autores, este artigo é o primeiro estudo de revisão em português voltado para profissionais da saúde, com uma linguagem acessível para o meio médico.

Palavras-chave
- medula
- elementos finitos
- biomecânica
- parafuso pedicular

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Introduction

In any study involving spinal biomechanics, the researcher can choose between two methods: (1) an experimental study, using vertebrae or bone structure-simulating synthetic materials and applying any mechanical factor directly or through an implant of interest; or (2) an analytical study (mathematical model), transforming study units into virtual models, and using them in virtual physical tests (finite element models [FEMs]). It is worth noting that one form does not exclude the other, and that experimental studies are indeed used in many biomechanical papers.[1]

The mathematical model is considered a substitute experiment that can be repeated as many times as necessary only by varying one or more parameters, resulting in different outcomes at each change. In addition, compared to experimental studies, it estimates parameters that cannot be easily measured, such as the internal stress of an object.[2]

Numerous purposes can be created for the biomechanical study of the spine, and some investigate the interactions between spinal parts (the relationship of the biomechanical variations of the intervertebral disc with ligaments or articular facets, for instance).[3,4] It is possible to evaluate in pathological processes, such as in curvature dysfunctions, osteoporosis, etc.[5,6] In addition, more recently, FEMs have served as an initial research tool for new surgical or instrumental spinal techniques.[7]

In the present review, the authors aim to provide specialized health care professionals with the knowledge of terms used in vertebral biomechanics and the principle behind finite elements (FEs), in addition to presenting studies about mathematical mechanical tests for implant simulations.

Methods

The methodology used in the present review focused on papers and books about spinal biomechanical tests using FEMs, without specifying the date of publication. The tools used were PubMed, as a way of retrieving scientific papers, and HOLLIS+ (a research tool from Harvard University) to search for textbooks. In both, the following terms were inserted: *finite element models*, *spine biomechanics*, and *biomechanical tests*. We have selected papers and books that were relevant to the present review, and presented data to achieve the proposed objectives

Biomechanics

To better understand the FEM principle, the researcher needs to know some general concepts of material mechanics, such as elastic modulus (E), stress (σ), strain (ε), and von Mises stress, as well as other terms, such as elastic and plastic deformation, and variations in material tropism.

Stress/Strain

One needs to understand how a material will deform according to a specific load imposed on it. This knowledge is required to prevent failure in any organic or inorganic compound. This behavior will depend on the dimensions of the study material (area and length), as well as on the load to which it is exposed. ►**Fig. 1** shows that the strain variation (δ or D) – or, in other words, the final strain (L) minus the initial strain (Lo) – is directly proportional to the area increase and inversely proportional to the length increase.

However, this proportional behavior is linear only until the beginning of the intermolecular failure process; from this point on, the direct (linear) correlation will no longer be the same, and the strain may triple or quadruple at each unit increase in the load (►**Fig. 2**).

Stress (σ) will depend on the load (P) exerted on a certain area (A), according to equation 1:

$$\sigma = \text{(EQ1)}$$

The term stress, not load, should be applied, since it configures the amount of weight applied per unit area in greater detail.

The deformity that the object undergoes under stress depends on the strain variation (δ) and on the initial length, according to equation 2.

$$\varepsilon = \text{(EQ2)}$$

When stress (σ) is plotted against strain (ε), it is possible to identify a characteristic curve for each material, regardless of the dimensions of the studied part. This curve is called a stress-strain diagram (►**Fig. 3**). This graph varies a lot from one structure to another and within the same material, depending on the temperature of the specimen and on the load rate applied.

As the sample is subjected to an increasing load, its length increases linearly. Thus, the initial portion of the diagram is a straight line that ascends steeply. However, after reaching a critical stress value (σγ), also known as yield stress, the deformation process starts, and a smaller load is required to achieve the same deformation. After reaching a maximum stress value, the sample fails (green line in ►**Fig. 3**).

It is worth mentioning that, during the linear phase, if the applied stress is completely withdrawn, the length of the material returns to baseline, without any resulting deformity (elastic phase). However, after the yield stress point, the object remains deformed even if no stress is present (plastic phase), in a process called plastic deformation.

This behavior distinguishes two types of materials: malleable and rigid materials. The former resembles the one previously described, with distinct phases; the rigid ones do not present a plastic phase, since they go from an elastic phase directly to failure. The first group is represented by steel and iron; the second one, by glass and ceramics (►**Fig. 4**).

Elastic Modulus

Most materials used in real practice are developed to withstand relative strain, that is, variations only in the linear area of the stress-strain diagram, in which stress (σ) is directly proportional to strain (ε). The graphical slope of this relationship is described by the elastic modulus or Young modulus (*E*). It is a mechanical parameter that measures

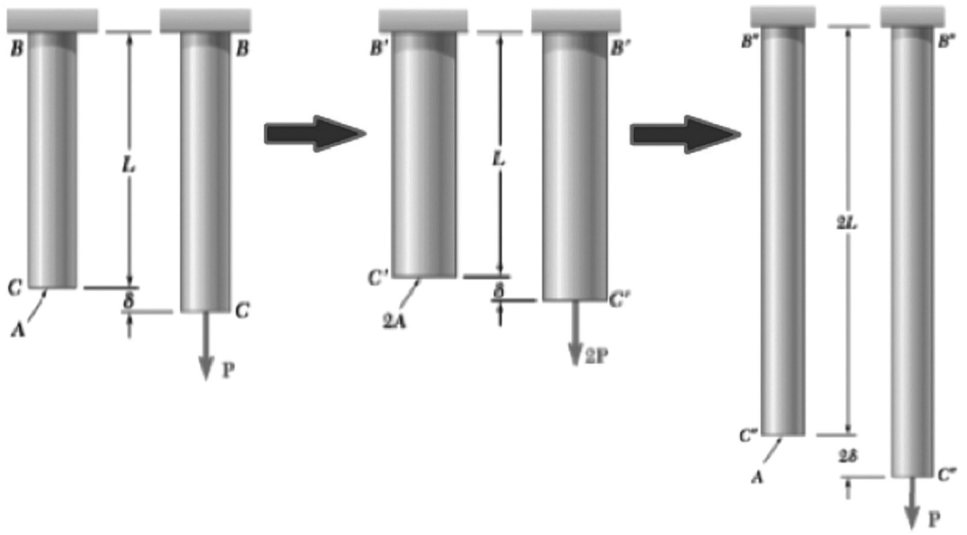

Fig. 1 A bar (BC) of size L and area A suffers a load P in the direction opposite to its fixation, thus exhibiting a variation of size D. However, as shown in the second figure, increasing the area to 2A, in order to achieve the same size variation D, the load exerted should be 2P. In the last example, a bar of size 2L with the same load P will suffer a variation of 2 x D.

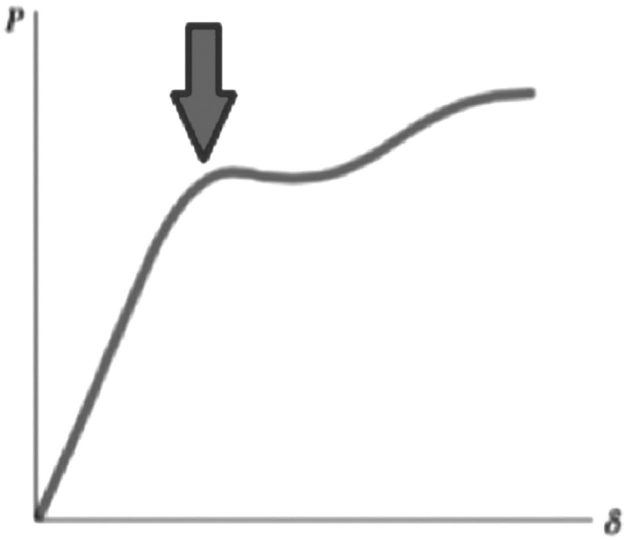

Fig. 2 Image showing that a load (P) increase is directly related to a strain (δ) increase up to the point (indicated by the arrow) in which the object distends differently to a unitary load increase.

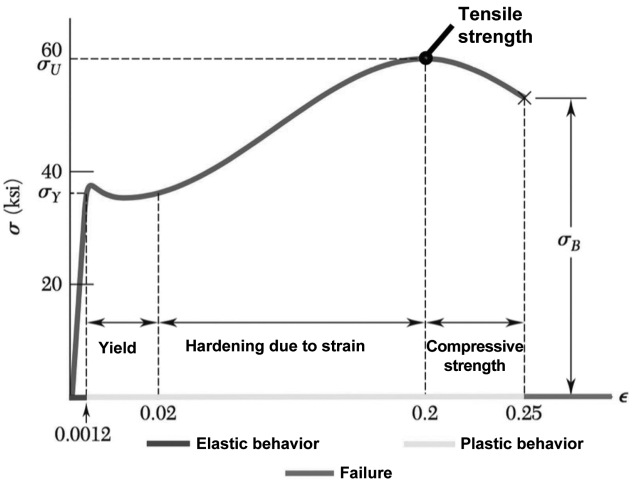

Fig. 3 Stress-strain diagram of a given material (σ = stress measured in ksi – pound force per square inch) showing its yield (γ), maximum (U), and failure (B) points. The elastic or linear behavior and the plastic behavior can also be seen. Source: personal archive.

the rigidity of a solid material, and it originates from the energy binding the atoms of the material. This modulus roughly divides materials in two major classes: flexible and rigid materials. A material with a high Young modulus is rigid;[8] therefore, if a material has a steeper slope, it is said to be rigid; otherwise, it is described as malleable.

Von Mises Stress

Von Mises stress is a mechanical parameter widely used to determine if the design will withstand a certain loading condition.[9] With this information, an engineer can tell whether the design will fail.

It represents the maximum load that the structure will withstand before going into the plastic phase, through a strain ratio up to the yield stress.[10] In mathematical FE models, it is said that when an object deforms > 3% of its initial size, it will exit the elastic phase, and any additional load will deform it in a definitive way.

Poisson Coefficient

A tensile stress exerted on a piece of any material results in longitudinal deformation, proportional to the applied force, and determined by its elastic or Young modulus.

The Young modulus is defined only by longitudinal deformation; however, any "stretched" elastic material also undergoes a transverse deformation, which is proportional to the longitudinal strain applied. These two strain types can be seen by stretching a piece of rubber with enough malleability.[11]

The ratio of transverse to longitudinal strain in the direction of the tensile stress is called the Poisson coefficient (or ratio) (ν).[11]

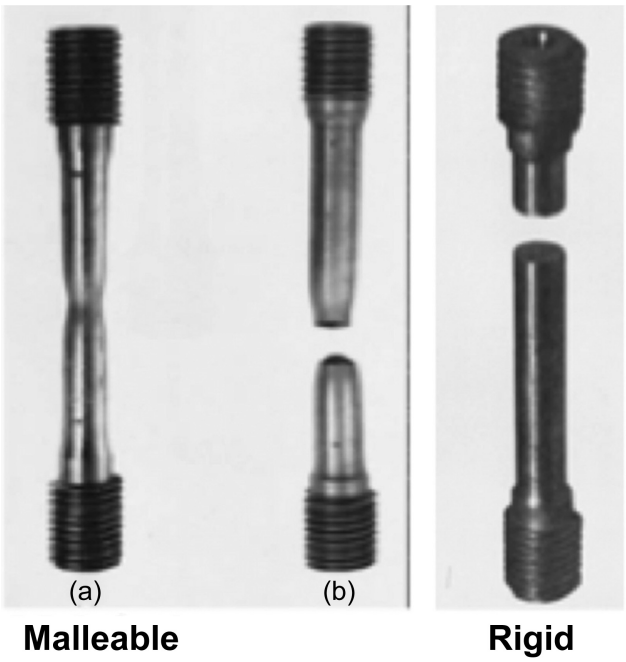

Fig. 4 Behavior of samples of materials: rigid (glass) and malleable (steel). Note the existing deformation in one material and its absence in the other. Source: personal archive.

Isotropic and Anisotropic Materials

In isotropic materials, their physical characteristics – including elastic modulus and von Mises stress – are the same in every loading direction. In anisotropic materials, these physical parameters vary depending on the position in which tension is exerted. The vertebral bone is an anisotropic material, since its trabecular and cortical orientations are not the same in the laterolateral, anteroposterior, or craniocaudal directions.[11]

Finite Elements

Nowadays, digital tools such as FEs or FEMs are widespread in analytical engineering, as well as in medicine.[12] These tools are extensively used to analyze solid materials, structures, heat transfers, and so on.[13] At the spine, Brekelmans et al[14] were the first to use mathematical models to represent bone tissue. Later, several studies regarding the spine were performed.[15]

Finite element models were created to aid the understanding of certain physical-mechanical structural behaviors, due to variations in weight, stress, or even in the dimensions of these structures. It was soon recognized that their use could avoid unnecessary expenditures with actual mechanical tests.

It is important to understand that FEMs deal with physical problems, and, to that end, mathematical equations must be created to simulate problems and solutions. It is worth mentioning that FEMs will only answer questions with the information inserted in the software, and that they will never be able to solve more than what is contained in this database.[13,16]

Many studies use FEMs to analyze normal vertebrae under various stress situations, including flexion, extension, and going from a sitting to a standing position.[17] Some focus their attention on models in which a pre-existing pathology requires surgical correction or the implantation of metallic prostheses. Finite element models have been recently more explored in these cases.[6,18–22]

Both in engineering and in biomechanics, the construction and processing of FEMs begin with the identification of the studied object; next, constraints and stresses are imputed to the model, resulting in postprocessing.

In physiological studies, the models created contemplate the entire structure of the functional vertebral unit, that is, models from two[16,23–25] or more articular levels are based on images obtained through computed tomography (CT) scans or magnetic resonance imaging (MRI) (e.g., stereolithography [STL] – a 3D format).[3] These models can represent the vertebra, the intervertebral disc, the articular facets, and all of the ligaments with their own meshes.[26]

In pathological models, the studied material may have several shapes (square, cylindrical) to simplify the model. Thus, in the first case, the appearance of the testing model will be very similar to the spine.[3] In the second case, it will depend on the format stipulated by the researcher (►**Fig. 5**).[18,27]

After the creation of the models, or meshes, as described in mechanical language, physical rules are stipulated for each portion. For instance, one part may be fixed, and another movable in one or more directions. In addition, it is possible to stipulate at which point a load will be inserted, if any. Moreover, each structure needs to be classified as isotropic or anisotropic, more or less rigid (elastic modulus), and its behavior (plastic and/or elastic phase), as well as when such behavior(s) will begin (von Mises stress) must be determined.

Kurutz et al[4] reviewed the values imposed on vertebral structures and demonstrated their enormous variability. For example, some authors have stipulated an elastic modulus of 5,000 Mpa for the cortical bone, and of 50 MPa for the trabecular bone;[17] however, for other researchers, these values are 22,000 MPa and 10 MPa, respectively.[28] This means that there is not a standard form to mathematically define each structure. This difficulty results from two

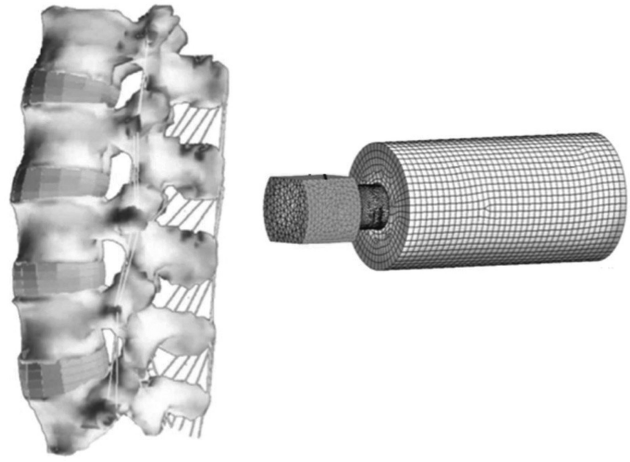

Fig. 5 Different ways of drawing the object under study that will be the basis for the FEM. Source: adapted from Amaritsakul et al[18] and Dreischarf et al.[3] (with permission from GB publisher 494 6272 12).

aspects: (1) the choice of the method used to measure the physical characteristics of the two bone types;[29] and (2) the disparity between the characteristics of the samples that significatively influence the results.[30]

Lastly, there are the results from the so-called postprocessing phase. This occurs primarily in two forms: the stress in a certain structure and its strain, both under the effect of a load or of a movement. That is, whenever a model is created and situations are stipulated, some structural data are sought under these two variables. In a physiological model, stress and displacement are seen in one vertebra over another, in a ligament, or even in an intervertebral disc.[3] In a pathological model with implants, it is evaluated whether it will carry the proposed load, or how much movement there will be within the supposed bone tissue.[12,18–20,27]

In summary, FEMs serve a range of contexts and greatly facilitate the understanding of how each structure will behave in a given situation. In addition, they do not need physical structures and complex machinery, since they are based on mathematical models. And, lastly, they do not require the difficult and time-consuming approval by ethics committee groups.

Applications

Lately, spinal FEMs have been used for a better understanding of the mechanics of vertebral implants. However, in the past, when this tool began to be used in the spine, most studies proposed a better understanding of the functionality and of the absorption of loads that are inherent to the body. In the present review, the focus is on studies meaningful for these applications.

Finite Element Models in Implants

Amaritsakul et al, in order to analyze pedicle screws failures, such as breaking, loosening or bending, studied five types of screws in an FE study.[18] Their work aimed to evaluate which screw would have the best fixation and the lower failure rate. An FEM was created in a 3D cylindrical mould, simulating the bone space in which the screw would be inserted. The screw mesh had 10-node tetrahedral elements; the bone (cylinder) had a mesh of 20-node tetrahedral elements, both at a distance of 1.2 mm. The contact surface between the two elements (bone and screw) was stipulated as frictionless; furthermore, axial rotational movement was not allowed.

To evaluate its capacity, the screw was folded into a 20 mm diameter cylinder, with an elastic modulus (E) of 20 GPa, and with a Poisson coefficient (v) of 0.3. A 225 N load was applied transversely to the screw (►**Fig. 6a**). The result was measured by the maximum stress at the screw surface, representing the resistance to bending.

To simulate the pullout, the cylinder diameter was increased to 30 mm, and E was decreased to 137.5 MPa ($v = 0.3$) to mimic an osteoporotic bone (►**Fig. 6b**). In addition, it was predicted that, at the insertion of the screw, the bone would be compacted (bone debris) around it. This process was carried out from the mathematical point of view through an adjustment in the elastic modulus, with a function of the change of the density squared, as described by other authors.[31] As a traction simulator, a displacement of 0.01 mm was applied to the screw, and the structures around it were set so as to not allow any movement.

In the paper, the authors discuss the results of each screw, concluding that the FEs were adequate to obtain mechanical responses; in addition, they could generate multiple response parameters (bending and pullout) in the same model by data interpolation.

Macedo et al tried to validate a virtual model for the study of double-threaded and cylindrical screws in order to evaluate how much the geometry would influence their mechanical behavior and anchoring, as well as to determine which one would have the best long-term performance.[20] All of the components were considered homogeneous and isotropic. The simulation used a polyurethane block (representing the bone) with an E of 0.023 GPa and a v of 0.30, and a screw with an E of 114 GPa and a v of 0.30, as previously described by other researchers.[31] A force of 50 N in the (pulling) direction,

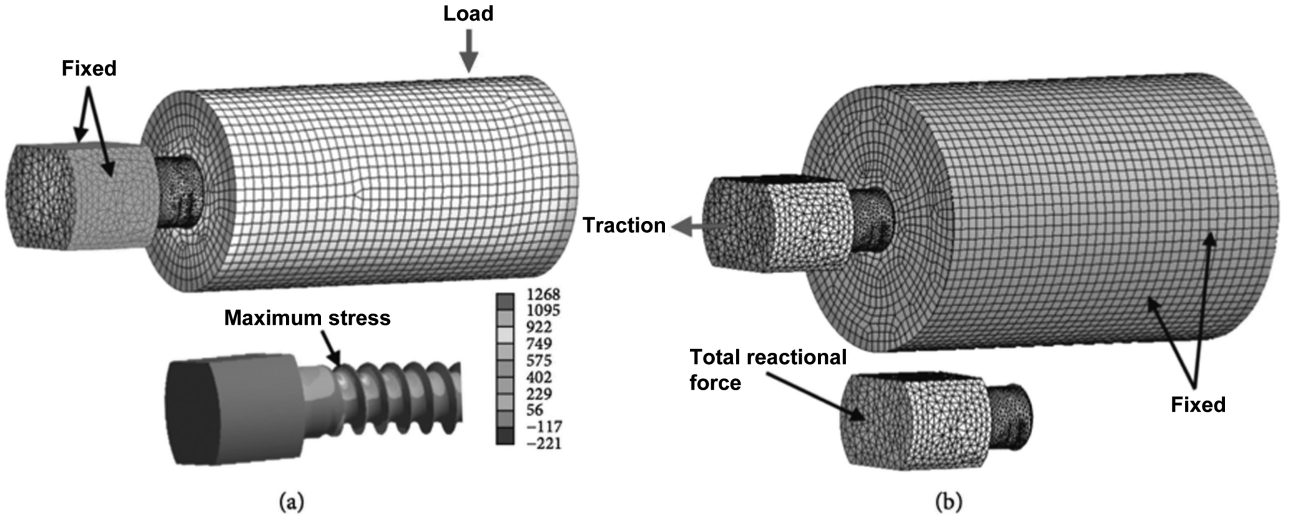

Fig. 6 Screw FEM; (a) bending and (b) pullout. The cylinders represent the bone with the rigid and movable (stressed) regions. Source: adapted from Amaritsakul et al.[18]

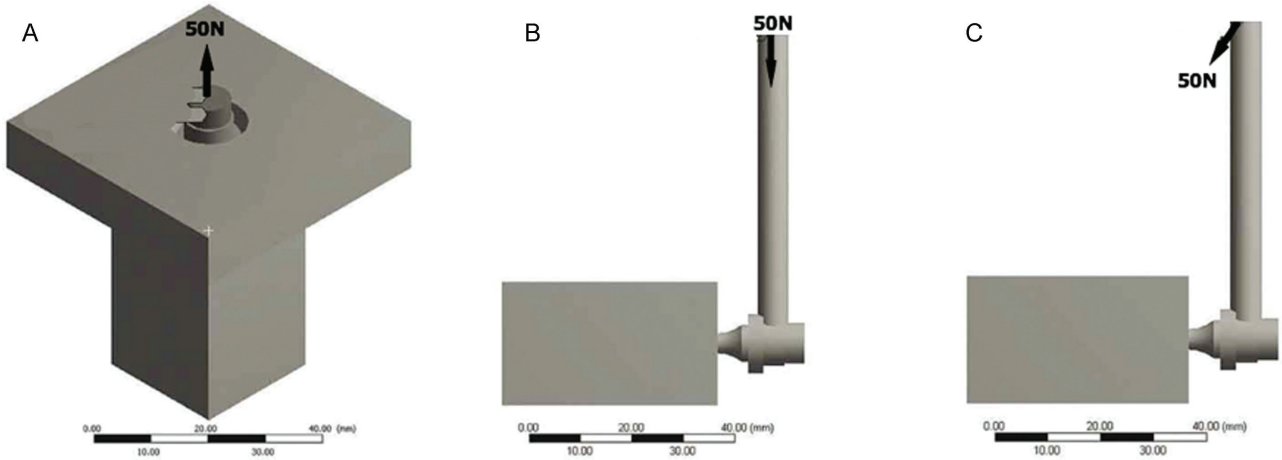

Fig. 7 Loading simulation conditions (50 N) on the screw: A, along; B, transversely; and C, obliquely (45°).

transversely and obliquely to the screw, was created (►**Fig. 7**). The von Mises stress distribution was evaluated in the vicinity of the screw at 13 points, 6 mm apart. The stresses generated along the internal diameter and the upper, central, and lower region of the screws were evaluated in 30 points each (►**Fig. 8**).

This study, simple in facts, shows the presence of other loading forms in addition to pullout, such as transverse and oblique loads. However, to perform this analysis, the bone must not be considered an isotropic material, but presenting different mechanical characteristics at different planes. As such, the FEM would be more convincing if it contemplated an anisotropic pattern, or at least, a transversely isotropic pattern.[28,32,33]

Physiological Finite Element Models

Dreischarf et al,[34] assuming that in vivo tests are unable to establish the compression force (CF) to which the intervertebral disc (IVD) is exposed, declared, aided by other studies,[35,36] that an approximate CF value can be estimated from the intradiscal pressure (IP) in the disc area (A), and that the individual correction factor for human vertebrae was defined as 0.66. In this situation, in a person standing up, the load over the disc would be of ~ 500 N. However, because this correction factor is not always adequate for each individual person, the authors propose calculating the CF using FEMs. To do so, they constructed an intact model of the lumbosacral spine with all of its ligaments. As a reference for IPs, using the literature, they have established that the IVD is in a non-compression situation. Fibrous annulus fibers were described with 14 bands and a crisscross pattern. The articular facets were designed as containing a frictionless cartilaginous layer, but with a squared increase according to the decreased IVD height.

The mechanical properties of the virtual spine components were taken from the literature and are shown in ►**Fig. 9**.

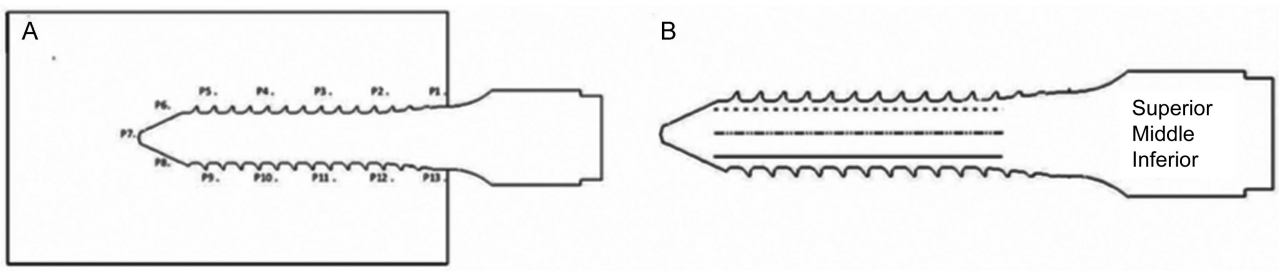

Fig. 8 Points analyzed on polyurethane foam (von Mises stress) and screw.

Component	Elastic modulus	Poisson coefficient
Cortical bone	10,000	0.30
Cancellous bone	200/140	0.45/0.315
Posterior bone elements	3,500	0.25
Fibrous annulus ground substance	Hyperelastic, neo Hookean C10= 0.3448, D1= 0.3	-
Fibrous annulus fibers	Nonlinear and depending on the distance from the center of the disk	-
Ligaments	Nonlinear	-
Articular facet cartilage	Smooth contact	-

Fig. 9 Mechanical properties of different materials. Source: adapted from Dreischarf et al[34] (reproduction permission by Elsevier 3940280612680).

Body position	Continuous loading	Initial momentum
Standing up	500 N	-
Flexion	1,175 N	7.5 Nm
Extension	500 N	7.5 Nm
Lateral flexion	700 N	7.8 Nm
Axial rotation	720 N	5.5 Nm

Fig. 10 Loading values for simulations in different body positions. Source: adapted from Dreischarf et al.[34]

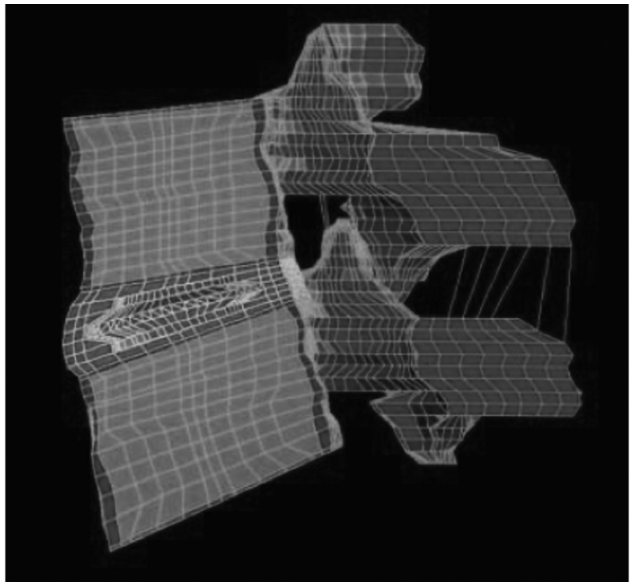

Fig. 11 Image of the three-dimensional mesh of the 4th and 5th lumbar vertebrae. Source: adapted from Goto et al.[38]

The present study focused on the L4-L5 level to facilitate the understanding of such a complex system. The loads applied according to different positions can be seen in ►**Fig. 10**.

The authors used several indicators to measure the CF, but PI alone was not enough to understand the real situation of CF over IVD.

Another very representative paper is the work by Fagan et al, who reviewed the studies to date, with basic modeling concepts and stipulated values. This study confirms FEMs as an excellent method for studying spinal biomechanics, reducing the use of human vertebrae and the reliance on animal studies.[37]

Goto et al, using FEMs, proposed to elucidate the damage that IVD, articular facets, and endplates undergo in pathological situations.[38] Meshes were prepared based on CT scan images of a 29-year-old man without any vertebral pathology between the 4th and 5th lumbar vertebrae (►**Fig. 11**).

The application of the properties was stipulated according to ►**Fig. 12**. A nonlinear pattern was attributed to the ligaments; for the facets, frictionless spaces were created. An IVD was created with a ratio of 3:7 between the nucleus pulposus and the fibrous annulus, respectively, with an intradiscal pressure of 1.32 MPa at the flexural and the upright posture, and of 0.6 MPa at extension. A 294 N load was applied gradually, and the flexion/extension stress of 15 N-m was inserted in 15 steps. The postprocessing intended to evaluate the von Mises stress (failure stress) in several disc areas.

The study demonstrated an increase in the von Mises stress in the posterior portion of the fibrous annulus. This stress was 1.5 times higher in flexion compared to other positions (►**Fig. 13**).

Conclusions

In the present review, the authors were able to introduce to health care professionals, especially to spine specialists, the basic concepts of general and vertebral biomechanics, to demystify the complexities involving finite models and to show their usefulness in anatomy/physiology studies and in the simulation of scenarios with implants.

Material	Element type	Young modulus (E : Mpa)	Poisson coefficient (v)
Cortical bone	8-solid node	12,000	0.3
Cancellous bone	8-solid node	100	0.2
Endplate	8-solid node	23.8	0.4
Ground ring	8-solid node	4.2	0.45
Intradiscal pressure	-	-	-
Flexion	-	1.32	-
Vertical	-	0.54	-
Extension	-	0.59	-
Fibrous annulus	2-solid node	Nonlinear	-
Ligaments	2-solid node	Nonlinear	Area (mm2)
Anterior	-	-	75.9
Posterior	-	-	51.8
Interspinal	-	-	36.3
Supraspinal	-	-	75.7
Intertransverse	-	-	2
Facet	Gap	-	-

Fig. 12 Properties and values of materials and their types. Source: adapted from Goto et al.[38]

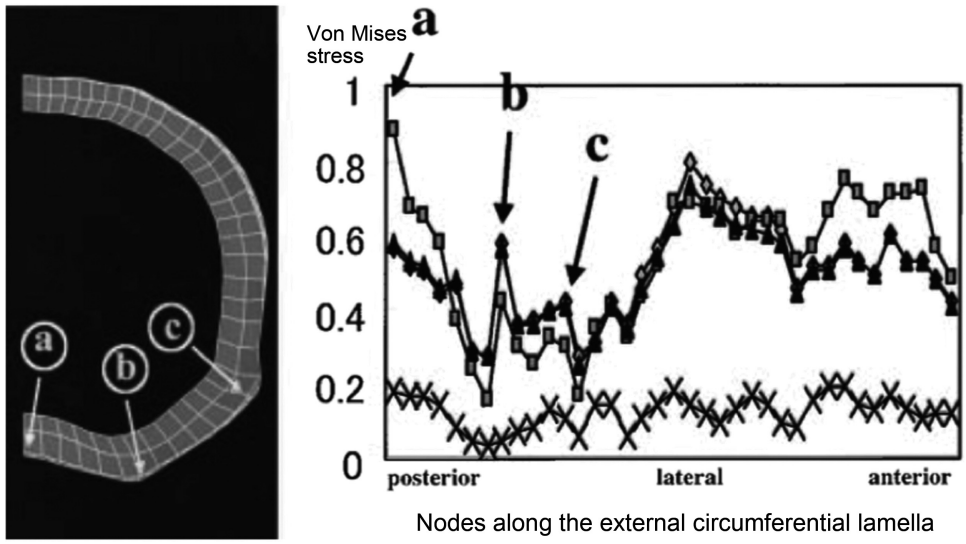

Fig. 13 Von Mises stress in different structures of the disc fibrous annulus in flexed position. Source: adapted from Goto et al.[38]

There is a vast of literature on the subjects discussed here, but few in Portuguese. The idea is to stimulate Brazilian researchers to perform more biomechanical and FEM work involving the spine.

Conflicts of Interests

The authors have no conflicts of interests to declare.

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Deep Brain Stimulation as a Treatment Approach for Anorexia Nervosa: a Systematic Literature Review

Estimulação cerebral profunda como uma abordagem de tratamento para anorexia nervosa: Uma revisão sistemática de literatura

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Abstract

Anorexia nervosa is a psychiatric disorder characterized by distortions of body size, weight, and shape perception, as well as by food restriction and/or binge and purging behaviors. It mostly affects young women and causes severe negative impacts on their physical, psychological, and social health. Recent studies have analyzed deep brain stimulation (DBS), a neurosurgical procedure that involves electrode implantation in strategical brain areas, to obtain remission of the symptoms of anorexia nervosa. The results showed that the stimulation of areas associated to the neurocircuitry of anorexia nervosa, such as nucleus accumbens, anterior cingulate cortex, ventral striatum, and bed nucleus of the stria terminalis, provokes beneficial responses in terms of body mass index, quality of life, social functioning, and psychiatric comorbidities. Nevertheless, broader investigations are needed to endorse the clinical usage of DBS in the management of anorexia nervosa.

Keywords
- anorexia nervosa
- eating disorder
- deep brain stimulation
- neuromodulation

Resumo

A anorexia nervosa é uma desordem psiquiátrica caracterizada pela distorção da percepção de tamanho, peso e formas corporais, bem como por restrição alimentar e/ou comportamentos excessivos e purgativos. Afeta principalmente mulheres jovens e causa grande impacto negativo sobre a sua saúde física, psicológica e social. Estudos recentes analisaram a estimulação cerebral profunda (ECP), um procedimento neurocirúrgico que envolve a implantação de eletrodos em áreas cerebrais estratégicas, como forma de obter remissão dos sintomas da anorexia nervosa. Os resultados demonstraram que a estimulação de regiões que participam da neurocircuitaria da anorexia nervosa, como núcleo accumbens, córtex do cíngulo anterior, estriato e núcleo da estria terminal, provocou respostas benéficas em termos de índice de massa corporal, qualidade de vida, funcionamento social e comorbidades psiquiátricas. No entanto, investigações mais amplas são necessárias para se recomendar a aplicação clínica da ECP no manejo da anorexia nervosa.

Palavras-chave
- anorexia nervosa
- desordem alimentar
- estimulação cerebral profunda
- neuromodulação

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Introduction

Anorexia nervosa is a debilitating and challenging condition with the highest mortality rate among all the psychiatric disorders, ranging from 6 to 11%.[1,2] It is characterized by intense fear of putting on weight, persistent and severe restriction of food intake, adoption of behaviors that interfere with weight gain, and disturbed perception of the body weight, size, and shape.[2,3]

The disorder affects 0.7% of the world population, mainly women (ratio of male to female = 10:1), and, among them, especially teenage girls. The age at onset of anorexia nervosa ranges from 15 to 19 years old in 40% of the cases.[2]

The etiology of anorexia nervosa is complex and multifactorial. Genetic predisposition and personality traits play important roles on the genesis and perpetuation of the disease. Additionally, environmental features such as cultural pressure for thinness and standardized beauty models may trigger the disorder.[4]

It is widely known that anorexia nervosa can have profound effects on people's health. One of the main consequences of the disease, chronic malnutrition, may lead to severe physical complications, including hydroelectrolytic, gastrointestinal, hepatic, and cardiac disorders, and bone lesions.[5,6] Furthermore, other psychiatric disorders, such as major depression, generalized anxiety, obsessive compulsive disorder (OCD), and personality disorders, often accompany anorexia nervosa.[7] Also, anorexic patients have a higher risk of eventually becoming addicted to alcohol and drugs.[8]

In spite of all these impairments caused by anorexia nervosa, the evidences that demonstrate the efficacy of the current therapies to treat this disorder are weak.[9,10] So far, conventional therapeutic approaches have failed to elicit disease remission in nearly 50% of the patients.[11]

Deep brain stimulation (DBS) is a neurosurgical procedure that has been used for almost 30 years to adjust the activity of dysfunctional brain circuits. It exerts effects not only locally, but also on distant targets, through mono and polysynaptic connections. The DBS technique is considered safe and effective for the treatment of Parkinson's disease and essential tremor. Its use has also been recently extended to some psychiatric disorders, such as major depression, OCD, Tourette syndrome, and Alzheimer disease.[2]

Currently, DBS has been explored as a novel treatment modality for anorexia nervosa. Several studies have shown the use of DBS for the treatment of anorexic patients in experimental trials with promising results.[2,12]

This study aimed to perform a systematic review of the literature to identify and discuss the indications, outcomes, and side effects of DBS as a treatment approach for patients with anorexia nervosa.

Methods

A systematic literature review was performed aiming to identify the use of DBS for the treatment of people with anorexia nervosa. The search was performed by two independent researchers and followed the steps proposed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.[13]

The databases searched for this study were: Medical Literature, Analysis, and Retrieval System Online (MEDLINE), Cochrane Central Register of Controlled Trials (CENTRAL), Latin American and Caribbean Health Sciences Literature (LILACS), Web of Science, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Health Technology Assessment (HTA), PsycINFO, The Digital Library of Theses and Dissertations of the Universidade de São Paulo (Digital Library USP), Portal de Periódicos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior do Ministério da Educação (CAPES/MEC), Instituto Brasileiro de Informação em Ciência e Tecnologia (IBICT), ProQuest Dissertations & Theses (PQDT) Global, ClinicalTrials.gov, Registro Brasileiro de Ensaios Clínicos (ReBec), World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), International Standard Randomized Controlled Trials Number (ISRCTN), Australian New Zealand Clinical Trials Registry (ANZCTR), and Deutschen Register Klinischer Studien (DRKS).

The descriptors selected around Boolean operators were: *anorexia*, OR *anorexia nervosa*, OR "*eating disorder*, OR *binge eating*, AND *deep brain stimulation*, OR *DBS*, OR *neurofunctional surgery*, OR *electrode implantation*, OR *neurostimulation*, OR *neuromodulation*, OR *psychiatric surgery*, and their equivalents in Portuguese, Spanish, German, and French. The terms were searched in all fields of the databases.

The following inclusion criteria were applied for the selection of the studies: 1. articles correlating anorexia nervosa and DBS as a treatment strategy; 2. articles published from 2008 to 2018; 3. articles in English, Portuguese, Spanish, German, and French; 4. articles involving human experimental studies, case reports, and review studies.

The exclusion criteria selected for this review were: 1. duplicate articles; 2. studies involving animal experimentation; 3. articles involving the philosophical and existential implications of DBS. Along the search process in the databases, the keywords *deep brain stimulation* = ; *DBS*; *neurofunctional surgery*; *electrode implantation*; *neurostimulation*; *neuromodulation* and *psychiatric surgery* have resulted in a considerable amount of studies whose main purpose was to approach existential, ethical and philosophical limitations of the DBS procedure. However, often in the search results, these studies have shown to escape the scope of the present review and were, therefore, excluded; 4. editorials, authors' comments, or debates; 5. articles addressing any psychiatric disorders other than anorexia nervosa; 6. articles reporting any neurosurgical interventions other than DBS.

The data obtained during this systematic literature review are shown in ►**Fig. 1**.

A total of 74 finished studies were used to perform the review. Nevertheless, we described in the results section only the eight existent experimental studies that applied DBS on patients with anorexia nervosa. The remaining 66 studies were used to compose others sections of this paper, such as introduction, discussion and conclusion, once they were constituted by reviews studies and represent a compilation of the data obtained on the experimental studies.

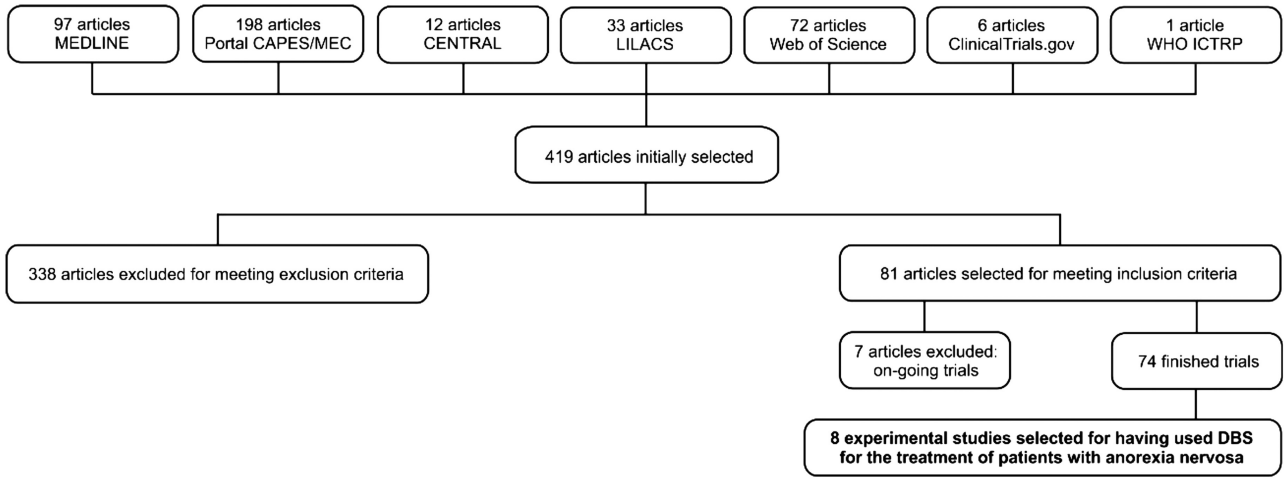

Fig. 1 Data obtained during this systematic literature review

Results

In this systematic literature review, eight experimental studies were selected for having used DBS for the treatment of patients with anorexia nervosa. Nucleus accumbens (NAc) plays a central role in the reward circuitry. Therefore, it has been used as a target in several studies that aimed to apply a neurosurgical treatment to anorexia nervosa.[1–3]

Bilateral NAc DBS (stimulation frequency: 180 Hz; pulse width: 90 µs; stimulation voltage: 1–8 V) was performed in 4 female teenagers diagnosed with anorexia nervosa, refractory to conventional treatment. Before surgery, the mean age of the patients was 16.5 years, and the average duration of this disorder was 18.5 months. At the beginning of the study, all the patients had some psychiatric comorbidities, and none of them was attending school due to physical or psychiatric limitations. The patients underwent this neurosurgical procedure between 2007 and 2011, with a mean follow-up period of 38 months (9–50 months) after the surgery. A considerable improvement was observed in the medical conditions of the patients. Their average body mass index (BMI) increased from 11.9 kg/m^2 at baseline to 19.6 kg/m^2 at the last follow-up, that is, a 65% increase, no longer meeting the diagnostic criteria for anorexia nervosa.[1] Their menstrual cycles became regular in an average period of 6.8 months after the surgery, and the symptoms and comorbidities had a decrease. The average score in the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) reduced from 29 to 1.7 and so did the average score in the Hamilton Rating Scale for Anxiety (HAMA), decreasing from 19 to 2. At the end of the study, three out of the four patients returned to school.[14]

Similar results were found in an independent study that involved eight women with anorexia nervosa, six of whom underwent bilateral stereotactic radiofrequency ablation, and two, bilateral DBS (135–185 Hz; 120–210 µs; 2.5–3.8 V), both procedures having NAc as the target area. At baseline, the vital signs of the patients, such as blood pressure, heart rate, and temperature, were low; after the interventions, all of them increased and became normal 1 year after the surgery. The BMI significantly increased ($p < 0.001$) 6 months and 1 year after the procedures. The mean BMI of the patients did not reach the normal range, but it came close to its inferior value of normality. The menstrual cycle became normal in all the patients in a mean period of 4.63 months.[15]

In both studies, a significant increase regarding intelligence, memory, quality of life, and social functioning, and a significant decrease in nervosity, psychoticism, and tendency to lie were noted. Yale-Brown obsessive-compulsive scale, HAMA, and Hamilton Depression Scale (HAMD) significantly decreased 1 week after the surgeries. No long-lasting adverse events or complications of the procedures were reported.[14,15]

The glucose metabolism of 6 patients diagnosed with anorexia nervosa and 12 age-matched healthy controls were analyzed using fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET). Certain cerebral areas of patients with anorexia nervosa showed hypermetabolism in comparison to healthy controls, namely the frontal lobe, lentiform nucleus, and hippocampus. Bilateral NAc DBS was performed in four of the patients with anorexia nervosa. After the surgical procedure, the cerebral areas with hypermetabolism had a decrease in their metabolism. It was hypothesized that the frontal lobe, the lentiform nucleus, and the hippocampus are responsible for the obsessive symptoms and eating disorders that characterize anorexia nervosa. Nevertheless, larger randomized controlled trials are needed to confirm this evidence.[16]

A Canadian group focused on the subcallosal cingulate (SCC) as a DBS target for the treatment of anorexia nervosa. In their first study, 6 anorexia nervosa patients underwent bilateral SCC DBS (130 Hz; 90 µs; 3.5 V). At the beginning of the study, the mean age of the patients was 38.3 years, while the average duration of this disease was 18.3 years. A 9-month follow-up after DBS pointed to improvements on the psychiatric condition and quality of life of the patients, with decreases in HAMD (17.8 at baseline versus 10.7 at the end of the study), Beck Depression Inventory (BDI) (38.8 versus 20.2), Y-BOCS (25.0 versus 13.2), and Beck Anxiety Inventory (BAI) (31.2 versus 21.7) scores, and an increase from an average of 57.3 at baseline to 65.8 at the end of the study in the Quality of Life Scale (QOLS or Flanagan score). At

the final follow-up, three patients had gained weight and three remained with the same BMI of the pre-surgery phase.[3]

In the second study of the same Canadian group, the investigation was expanded, enrolling 16 anorexia nervosa patients that were followed for 12 months after SCC DBS (130 Hz; 90 µs; 5–6.5 V). The results point to a significant increase in BMI (13.83 kg/m^2 at baseline versus 17.34 kg/m^2 at the final follow-up, $p = 0.0009$), as well as a significant decrease in depression, obsession, compulsion, and anxiety symptoms after 12 months. These outcomes show that the benefits of DBS can be better evaluated with a longer follow-up period.[2] Some adverse events, such as pancreatitis, seizure, QT prolongation, hypophosphatemia, refeeding delirium, and worsening of mood, were reported after the procedure. Nevertheless, these events were related to the fragility caused by anorexia nervosa rather than to the DBS procedure.[2]

Deep brain stimulation has also been used in single-patient studies to treat anorexia nervosa associated with other psychiatric disorders.[17–19] A 56-year-old female patient diagnosed with recurrent depression and anorexia nervosa in adolescence underwent DBS in the subgenual cingulate area (intermittent stimulation: 2 minutes on, 1 minute off; 5 mA; 91 µs). Three years after the surgery, her BMI increased from 14.1 to 19.1 and the Eating Attitudes Test (EAT-26) score decreased from 40.56 to 1.0. Even after a depressive episode because of the suicide of a friend, the symptoms of the eating disorder have been under control.[17]

A 52-year-old female patient with severe OCD since childhood and several comorbidities such as depression, anorexia nervosa, generalized anxiety disorder, and attention-deficit/hyperactivity disorder underwent bilateral ventral striatum DBS (120 Hz; 120 µs; 7.5 V). Her BMI increased from 18.5 kg/m^2 at baseline to 19.6 kg/m^2 at follow-up. In addition, the patient revealed to be more comfortable with food after implantation.[18]

More recently, a 60-year-old female patient with a diagnosis of childhood onset of anxiety and anorexia nervosa presented with symptoms of anxiety connected to food intake, restricted eating, purging, major depressive disorder leading to suicidal ideations and attempts. After years of psychotherapy, several different classes of medication, electroconvulsive therapy, and commitment to a closed psychiatric ward with no improvement whatsoever, she underwent implantation of two DBS electrodes in the medial forebrain bundle (130 Hz; 60 µs; 2.8–3.0 V) with excellent results. However, due to neurological adverse events, the patient was subjected to reoperation 2 years after the first surgery. In the second procedure, bilateral electrodes (130 Hz; 120 µs; 4.3 V) were implanted in the bed nucleus of the stria terminalis (BNST). Although no improvements regarding BMI were observed after the second implantation, her food intake became more stable, the purging episodes disappeared, tube feeding could be discontinued, she was released from the psychiatric ward, and is now living at home with her family.[19]

All the details about the patients, comorbidities, DBS targets, and outcomes after the procedures in the eight studies selected are summarized in ►**Table 1**.

Discussion

The 29 patients diagnosed with anorexia nervosa that underwent DBS selected in this systematic literature review were female, with mean age of 30.9 ± 13.1 years at baseline, ranging from 16 to 60 years old.

The targets for DBS implantation were: SCC, NAc, subgenual cingulate cortex, ventral striatum, medial forebrain bundle and BNST. All these areas and structures participate in the pathological circuit of anorexia nervosa.[2,3,14–19] Although all the studies selected reported a beneficial effect of DBS in the clinical presentation of anorexia nervosa, it is still not possible to determine which target was the most effective, due to the great diversity of the subjects treated.

Deep brain stimulation increased the BMI in all patients, except one.[19] Additionally, consequences of the disease such as food aversion and psychiatric comorbidities greatly decreased in all studies after DBS intervention. Improvements were achieved in physical and psychiatric aspects of the subjects that underwent this type of treatment, with few or no long-lasting adverse effects resulting from the procedure.[2,3,14–19]

However, the broad and clinical use of DBS for the treatment of anorexia nervosa symptoms cannot be endorsed yet, because of lack of evidence obtained from standardized, systematic, double-blind, placebo-controlled trials.[2,3,6,17] Nonetheless, the perspective for the near future is optimistic, once consolidated clinical trials with the use of sham stimulation and double-blind crossover approach,[20] as well as comparing DBS to clinical therapy,[21] have been designed.

This systematic literature review had certain limitations due to the small number of studies and patients involved, as well as the lack of standardized inclusion criteria for patients with anorexia nervosa that could benefit from DBS treatment. A well-established definition of anorexia nervosa refractory to clinical treatment is a critical concept that is yet to be determined.

In 2017, a framework was presented to guide researchers through the ethical implications involving the treatment of severe and enduring anorexia nervosa using DBS. It includes steps such as assessing individual needs and possible risks and benefits, considering issues of mental capacity and informed consent, and considering future care after participation in the research.[22] Similarly, broader frameworks, involving the clinical, psychological, and social aspects of patients diagnosed with anorexia nervosa should be designed to better guide the patient selection process.

Since the factors involved in the pathophysiology of anorexia nervosa are rather complex and multifaceted, the exact neurocircuitry of this disorder has not been completely elucidated yet.[10,14] To this moment, it has not been possible to isolate one single structure or pathway responsible for triggering the symptoms of the disease. Therefore, a model involving multiple circuits has been indicated as the most plausible explanation for the occurrence of the disease.[23]

Studies conducted to investigate the neurocircuitry of anorexia nervosa often rely on important neuronal targets, whose functions and dysfunctions underly the clinical manifestations of the disease, such as pathologic humor, anxiety,

Table 1 Clinical profiles, comorbidities, stimulation targets, and outcomes of patients diagnosed with anorexia nervosa that underwent deep brain stimulation (DBS) in eight studies selected in this systematic literature review

Patients (n)	Clinical profile	Comorbidity	DBS target	Outcome	Reference
4	**1.** 16 years old; female; AN duration: 28 months; amenorrhea duration: 11 months; suspension from school: 5 months; BMI at baseline: 12.2 kg/m^2; medication: SSRI; olanzapine	OCD	NAc	After a mean follow-up of 38 months – average BMI: 19.6 kg/m^2 (increased by 65%); Y-BOCS decreased from 29 to 1.7; HAMA decreased from 19 to 2; menses returned within an average period of 6.8 months; three patients returned to school	14
	2. 16 years old; female; AN duration: 18 months; amenorrhea duration: 15 months; suspension from school: 3 months; BMI at baseline: 13.3 kg/m$^{2;}$ medication: SSRI; olanzapine	OCD	NAc		
	3. 17 years old; female; AN duration: 15 months; amenorrhea duration: 9 months; suspension from school: 10 months; BMI at baseline: 12 kg/m^2; medication: SSRI; olanzapine	GAD	NAc		
	4. 16 years old; female; AN duration: 13 months; amenorrhea duration: 9 months; suspension from school: 6 months; BMI at baseline: 10 kg/m^2; medication: SSRI	OCD	NAc		
2	**1.** 28 years old; female; AN duration: 2 years; BMI at baseline: 13.3 kg/m^2; vital signs at baseline – temperature: 35.5°C; heart rate: 47 bpm; blood pressure: 91 × 60 mm Hg; HAMD: 24; HAMA: 35	Not reported	NAc	1 year after surgery – BMI: 18 kg/m^2; temperature: 36.4°C; heart rate: 71 bpm; blood pressure: 107 × 71 mm Hg; HAMD: 9; HAMA: 8	15
	2. 18 years old; female; AN duration: 3 years; BMI at baseline: 12.9 kg/m^2; vital signs at baseline – temperature: 35.6°C; heart rate: 48 bpm; blood pressure: 82 × 60 mm Hg; HAMD: 20; HAMA: 24	Not reported	NAc	1 year after surgery—BMI: 20.8 kg/m^2; temperature: 36.3°C; heart rate: 69 bpm; blood pressure: 96 × 66 mm Hg; HAMD: 9; HAMA: 7	
4	**1.** 18 years old; female; AN duration: 13 months; amenorrhea duration: 4 months; suspension from school: 2 months; BMI at baseline: 11.8 kg/m^2; medication: SSRI	Not reported	NAc	1 month after surgery—BMI: 17.9 kg/m^2; no medication	16
	2. 16 years old; female; AN duration: 28 months; amenorrhea duration: 11 months; suspension from school: 5 months; BMI at baseline: 11.2 kg/m^2; medication: SSRI, olanzapine	Not reported	NAc	1 month after surgery – BMI: 13.1 kg/m^2; no medication	

(*Continued*)

Table 1 (*Continued*)

Patients (n)	Clinical profile	Comorbidity	DBS target	Outcome	Reference
	3. 16 years old; female; AN duration: 18 months; amenorrhea duration: 15 months; suspension from school: 3 months; BMI at baseline: 13.3 kg/m^2; medication: SSRI, olanzapine	Not reported	NAc	1 month after surgery—BMI: 14.5 kg/m^2; no medication	
	4. 16 years old; female; AN duration: 42 months; amenorrhea duration: 24 months; suspension from school: 12 months; BMI at baseline: 12.2 kg/m^2; medication: SSRI	Not reported	NAc	1 month after surgery—BMI: 17.1 kg/m^2; no medication	
16	**1.** 24 years old; female; AN duration: 10 years; lowest BMI: 11 kg/m^2	MDD; anxiety	SCC	Significant increase in BMI ($p = 0.0009$) and QOLS ($p = 0.021$); significant decrease in Y-BOCS ($p = 0.023$), HAMD ($p = 0.00015$), BDI ($p = 0.0022$), BAI ($p = 0.035$), DERS ($p = 0.019$), YBC-EDS-p ($p = 0.0025$), and YBC-EDS-r ($p = 0.0013$) scores	2,3
	2. 38 years old; female; AN duration: 21 years; lowest BMI: 11.9 kg/m^2	MDD; PTSD; SUD; OCD	SCC		
	3. 35 years old; female; AN duration: 15 years; lowest BMI: 12.4 kg/m^2	MDD; PTSD	SCC		
	4. 40 years old; female; AN duration: 10 years; lowest BMI: 13.1 kg/m^2	MDD; PTSD	SCC		
	5. 35 years old female; AN duration: 19 years; lowest BMI: 13.5 kg/m^2	MDD; PTSD; GAD	SCC		
	6. 57 years old; female; AN duration: 27 years; lowest BMI: 13.0 kg/m^2	None	SCC		
	7. 21 years old; female; AN duration: 9 years; lowest BMI: 11.2 kg/m^2	MDD; OCD; GAD; BPD	SCC		
	8. 32 years old; female; AN duration: 19 years; lowest BMI: 12.9 kg/m^2	MDD; PTSD	SCC		
	9. 26 years old; female; AN duration: 14 years; lowest BMI: 14.8 kg/m^2	PTSD	SCC		
	10. 30 years old; female; AN duration: 19 years; lowest BMI: 10.6 kg/m^2	MDD; OCD	SCC		
	11. 39 years old; female; AN duration: 24 years; lowest BMI: 10.3 kg/m^2	MDD, PTSD; OCD	SCC		
	12. 39 years old female; AN duration: 29 years; lowest BMI: 7.2 kg/m^2	PTSD; GAD	SCC		
	13. 32 years old; female; AN duration: 20 years; lowest BMI: 11.4 kg/m^2	MDD; PTSD; OCD	SCC		
	14. 34 years old; female; AN duration: 19 years; lowest BMI: 15.1 kg/m^2	MDD; anxiety; PTSD	SCC		

Table 1 (*Continued*)

Patients (n)	Clinical profile	Comorbidity	DBS target	Outcome	Reference
	15. 34 years old; female; AN duration: 21 years; lowest BMI: 10 kg/m^2	MDD; OCD; BPD	SCC		
	16. 34 years old; female; AN duration: 11 years; lowest BMI: 13.7 kg/m^2	None	SCC		
1	56 years old; female; AN duration: 35 years; BMI at baseline: 14.1 kg/m^2; relapses of AN precipitated by depression episodes; EAT-26 at baseline: 40.56	Severe refractory depression	Subgenual cingulate cortex	Remission of AN symptoms; 2 years after surgery – BMI: 19.1 kg/m^2; 3 years after surgery – EAT-26: 1.0; medication after DBS: escitalopram, trazodone, triptophan, clonazepam	17
1	52 years old; female; BMI at baseline: 18.5 kg/m^2; long-term concern over weight gain; avoided social events involving food; restricted portion size	MDD; OCD; GAD; ADHD	Ventral striatum	After DBS: patient more comfortable with food, eating higher amounts and variety, and accepting going out to eat; BMI at follow up: 19.6 kg/m^2	18
1	60 years old; female; BMI at baseline: 16.6 kg/m^2; childhood onset anorexia nervosa; committed to psychiatric ward; MADRS: 43, HAMD: 22, HAMA: 22	MDD; anxiety	First procedure: electrode implantation in medial forebrain bundle, with collateral effect: blurred vision; second procedure: electrode implantation in BNST	9 months after second procedure—released from psychiatric ward; 12 months after second procedure—depression and anxiety scores improved dramatically, MADRS: 13; HAMD: 6; HAMA: 5; neither procedure had significant impact on BMI; anxiety involving food disappeared; food intake became more stable; tube feeding was discontinued	19

Abbreviations: ADHD, attention deficit/hyperactivity disorder; AN, anorexia nervosa; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BMI, body mass index; BNST, bed nucleus of the stria terminalis; BPD, borderline personality disorder; bpm, beats per minute; DERS, Dysfunction in Emotional Regulation Scale; EAT-26, Eating Attitudes Test; GAD, generalized anxiety disorder; HAMA, Hamilton Rating Scale for Anxiety; HAMD, Hamilton Depression Scale; MADRS, Montgomery-Åsberg Depression Rating; MDD, major depressive disorder; NAc: nucleus accumbens; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; QOLS, Quality of Life Score; SCC, subcallosal cingulate; SSRI, serotonin selective reuptake inhibitors; SUD, substance use disorder; YBC-EDS-p, Yale-Brown-Cornell Eating Disorders Scale, purging; YBC-EDS-r, Yale-Brown-Cornell Eating Disorders Scale, restriction; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

eating disorders, distorted body perception, inhibition, and alexithymia.[24,25] For that matter, neuroimaging techniques such as ^{18}F-FDG-PET, single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) have been of great assistance, once functional and structural differences are found between the brains of anorexic patients and healthy individuals.[26]

Most of these differences can be observed in the limbic lobe, in the pre-frontal cortex, and in the cingulate cortex, areas responsible for the management of emotions and behavior.[11,27] For instance, the components of the reward system, especially NAc, which belong to the cortex–striatum–thalamus–cortical circuit, are dysfunctional in anorexic individuals. Such dysfunction explains why food, naturally a primary reinforcer, is likely to trigger an appetite-aversion response in anorexia nervosa patients.[14,25]

Also, anorexic patients are prone to consider themselves heavier and larger compared with other people.[1] This pathological feature may be explained by the reduced activity of the parietal cortex in anorexic patients, as shown by SPECT, positron emission tomography (PET), and fMRI.[28] The parietal cortex is responsible for the visuospatial abilities and the construction of body image; therefore, its hypoactivity contributes to the distorted self-perception in anorexia nervosa patients.[14]

Another distinctive finding in patients with anorexia nervosa is mood and affective disorders, partly derived from dysfunctional actions of the ventromedial prefrontal cortex and orbitofrontal cortex, which stimulate non-adaptive behaviors, such as self-starvation and self-harm, in these individuals.[29] In addition to this, fMRI studies have revealed hypoactivity in the ventral striatum, supplementary motor area, and frontal-striatal circuits in anorexic patients, which may justify the low levels of cognitive flexibility of these individuals. Moreover, the subcallosal and subgenual cingulate cortex are involved in major depressive disorder, OCD, and abnormal mood seen in anorexia nervosa patients.[28,30]

Positron emission tomography/SPECT studies have also demonstrated the presence of abnormalities in the dopamine

and serotonin systems in anorexic patients. It seems that anxiety manifestations, behavioral inhibition, and body image distortions are associated with alterations in 5-HT1A and 5-HT1B receptors, as well as in serotonin transporters in limbic and cortical structures. Dopamine is pathologically increased in the brain of anorexic patients, leading to anxiety symptoms, which are alleviated through starvation.[14]

Conclusion

Anorexia nervosa is a debilitating and, in some instances, lethal disorder. Deep brain stimulation has been used experimentally in multiple targets of the neurocircuitry of anorexia nervosa, such as NAc, SCC, striatum, subgenual cingulate, and BNST. The results have shown that DBS is a safe and effective method in the regression of the symptoms of this disease. However, it is important to emphasize that DBS is still an experimental approach for the treatment of anorexia nervosa. Therefore, a larger number of studies with a broader scope is needed in order for the clinical use of DBS can be recommended.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Deep Brain Stimulation for the Treatment of Resistant Depression: Systematic Review of the Literature

Estimulação cerebral profunda para o tratamento de depressão resistente: revisão sistemática da literatura

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Abstract

Depression is the leading cause of disability worldwide, and it is related to high suicide rates. Furthermore, a great number of patients do not respond to any of the available treatments. Deep brain stimulation (DBS), a versatile technology with expanding indications, is considered a potential treatment for resistant depression. However, in over 10 years of clinical research, its efficacy has not been completely proven. Although new trials using DBS for treatment-resistant depression keep emerging, two of the three Level I evidence-based studies recently conducted have not provided conclusive data. Methodological limitations and major biases have compromised the obtention of clearer results. In this systematic review of the literature, we intend to critically assess the clinical trials performed in this field.

Keywords

- deep brain stimulation
- treatment-resistant depression
- refractory depression

Resumo

A depressão é a maior causa de incapacitação em nível mundial, e ela está relacionada com altos índices de suicídio. Ademais, um grande número de pacientes não responde a nenhum dos tratamentos disponíveis. A estimulação cerebral profunda (ECP), uma técnica versátil com indicações em expansão, é considerada um tratamento potencial para depressão refratária. Contudo, em mais de 10 anos de pesquisas clínicas, sua eficácia ainda não foi completamente comprovada. Embora novos estudos utilizando ECP para tratamento da depressão refratária venham sendo realizados, dois dos três ensaios recentemente conduzidos baseados em evidência com Nível 1 não forneceram dados conclusivos. Limitações metodológicas e vieses importantes comprometeram a obtenção de resultados mais claros. Nesta revisão sistemática da literatura, pretendemos avaliar criticamente as pesquisas clínicas executadas nesta área.

Palavras-chave

- estimulação cerebral profunda
- depressão resistente ao tratamento
- depressão refratária

Introduction

Depression is a severe psychiatric disorder, presently recognized as the most frequent mental illness and the leading cause of disability worldwide.[1] It currently affects 260 million people (3.6% of the global population) and is 1.5 to 2 times more common in women.[2] However, multimodal treatments have often failed in up to 30% of the patients,[3] a group considered to have treatment-resistant depression (TRD),[4] which exhibits a 2-fold suicide risk.[5] Globally, depression is the 2nd cause of death among 15 to 29-year-olds,[6]

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with alarming completed suicide rates of approximately 800 thousand per year, that is, 2,191 daily deaths.

Electroconvulsive therapy (ECT) is the most effective somatic treatment for depression, since it promotes remission rates $>$ 40%.[7,8] In spite of being effective, $\sim$ 52% of the patients resistant to antidepressants (ADs) do not respond to ECT either.[9]

Deep brain stimulation (DBS) consists in modulating deep brain structures through electrodes implanted using the stereotactic technique,[10] and it has also been used for the treatment of depression. It is reversible, adjustable, and can be applied in combination with ADs. Moreover, the simultaneous use of DBS and ADs allows titration of both methods. Nonetheless, efficacy, optimal targets, and stimulation parameters (frequency, amplitude, pulse width, duration) for TRD remain unclear.[11,12] The success of DBS for the treatment of Parkinson disease (PD), dystonia, obsessive compulsive disorder (OCD), and, more recently, epilepsy, points to the versatility of this surgical procedure in clinical settings, instigating laser-focused research for TRD. Therefore, the present systematic review of the literature aimed to critically assess clinical evidence of DBS for TRD.

Historical Remarks

Depression has long been known,[13] and so has neuromodulation through electricity and invasive brain procedures, inasmuch as Hippocrates (469–399 BCE) described trepanation for the management of intracranial hypertension.[14,15] Ancient Greek doctors modulated pain with electric eels.[16] The Greek word for these fish is *narka*, meaning "relief from pain", the root of the word *narkoun*, meaning "to benumb", which, in turn, is the root of the term "narcotics".[17]

Scribonius Largus (1–50 CE) described the use of the shocks of *Torpedo nobiliana*, a species of electric ray, for headaches and gout derived chronic pain. This therapy drew the attention of Galen (130–210 CE), and this started a "torpedonism" trend described in several medical documents, including the Canon of Medicine, written by Avicenna, where this treatment was proposed for melancholy.[18–20] This mental state is related to the melancholic depressive subtype and anhedonia, a core symptom of major depressive disorder (MDD)[21] associated with the reward circuitry.[22] Accessing the brain had further indications in other parts of the world, such as in Peru, where witch doctors (ca. 1000–1250 CE) employed this procedure to release bad spirits and treat mental illnesses.[14]

More recently, ablative surgery preceded in 30 years the advent of the first psychiatric drugs, that is, antipsychotics.[23] The stereotaxy apparatus brought minimally invasive procedures, allowing the access to subcortical, deep brain structures.[24] The term psychiatric neurosurgery,[25] fitting the idea of recognized dysfunctional circuits in the brain, emerged in the 20th century.[23] A pioneer trial targeting the subgenual anterior cingulate cortex (sACC) inaugurated the modern era of neurosurgery for TRD,[26] labelled later by the main investigator in the field as "keeping an eye on a moving target".[27]

Putative Neurocircuitry and Pathophysiology of Depression

Although the taxonomy of psychiatric disorders is still incipient, knowledge of the underlying biology of depression has expanded from the concept of a disease purely correlated to limbic structures[28] to a mental disorder involving several neural networks.[29] Cortical structures thought to be implicated in depression involve several Brodmann areas (BAs), such as the dorsomedial prefrontal cortex (DMPFC), the medial prefrontal cortex (mPFC), the dorsolateral prefrontal cortex (DLPFC), the dorsal anterior cingulate cortex (dACC), the anterior cingulate cortex (ACC), the ventromedial prefrontal cortex (vmPFC), and the globus pallidus pars interna (GPI).[14,29,30] The DLPFC and the orbitofrontal cortex (OFC)[31] are connected to subcortical structures, such as the hippocampus, the amygdala nuclei, and the nucleus accumbens (NAcc).[32] The cingulate gyrus and the hippocampus connect the vmPFC to the DLPFC. Furthermore, the hippocampus is intimately linked, both anatomically and physiologically, to the hypothalamus through the fornix, an axonal bundle that inhibits the hypothalamic pituitary adrenal (HPA) axis.[32]

Neoneurogenesis in the hippocampus is stimulated by monoaminergic agonists (e.g. selective serotonin reuptake inhibitors) and brain neurotrophins (e.g. brain derived neurotrophic factor [BDNF]), and negatively modulated by stress, corticosteroids, and glutamatergic agents.[32] In patients presenting with depression, the prefrontal cortex (PFC) would fail to inhibit overactive limbic structures implying cognitive, behavioral, mood, neuroendocrinal, pain modulation, and neurotransmitter activities due to its connection to the hypothalamus and the midbrain, notably the periaqueductal gray area.[33] Rumination, suicidality, and complex symptoms suggest dysfunction of neural networks, rather than targets,[34] outreaching the domain of anatomical/structural (overactive OFC/vmPFC, ACC, hippocampus, and amygdala, and hypoactive DLPFC), molecular (increased cortisol, corticotropin-releasing hormone, proinflammatory cytokines, decreased BDNF, serotonin, and noradrenalin), or cellular alterations (neurons, neural ensemble,[35] and glia).[32,36] It is believed that a major factor, yet to be unveiled, would trigger a cyclic "short-circuiting" in susceptible individuals,[32] relying on a substrate of genetic predisposition,[32] personal history, and affective temperament.[29] That would ultimately disrupt adequate neurotransmission, neuroendocrine response, autonomic response, and cognitive function.

To date, putative DBS targets for the treatment of TRD include:

1. Subcallosal cingulate gyrus (SCg): also called subgenual cingulate gyrus, subcallosal cingulum, or SCg25 in the context of DBS TRD trials, it is the portion of the ACC lying ventrally to the corpus callosum, below its genu.[37] It corresponds primarily to BA 25, as well as to the caudal portions of BA 32 and of the inferior BA 24.[26,29,38] The converging region in the SCg implicated in the response to fluoxetine[39] was chosen as the first DBS experimental target.[35]

2. Ventral capsule/ventral striatum (VC/VS)/ventral anterior limb of the internal capsule (vALIC)/NAcc: The VC/VS comprehends a target region considered related to the pathophysiology of OCD and depression.[40] The vALIC contains the prefrontal corticopontine tract and the anterior thalamic radiation (ATR), interconnecting mPFC and cingulate gyrus with the anterior and dorsomedial thalamic nuclei,[41] both extensively connected with the cortical and subcortical limbic areas,[29,41] a functional link between the frontal lobe and the thalamus. The NAcc is a component of the VS linked to the ventral tegmental area (VTA), the amygdala, the hippocampus, the OFC, the mPFC, the motor territories of the caudate nucleus, and the GPI.[42] Moreover, the NAcc is indirectly connected to the SCg and to the mPFC, and acts as "hub", amplifying or decreasing the signals from emotion centers.[43]
3. Bed nucleus of the stria terminalis (BNST): located in the adjacencies of the VC/VS and NAcc regions, partially overlapping the VC/VS but distinct from it, it is an output pathway of the amygdala, and it regulates anxiety and threat vigilance,[44] with projections to the medial forebrain bundle (MFB) and to the NAcc.[45] The rationale for borrowing this target from OCD is that strong antidepressant effects appeared, particularly if the contacts were situated in or near the BNST.[45]
4. MFB: a white matter tract that mediates connectivity to the VTA and the NAcc, the hypothalamus (medial and lateral), the preoptic regions (lateral and medial), and the BNST. Its anatomical and functional connectivities have been described in diffusion tensor imaging studies.[46,47] The MFB hypothetically mediates positive emotions,[48] particularly through the superolateral branch of the medial forebrain bundle (slMFB), and opposes the negative emotion modulation of ATR. The VTA is a key node of the reward circuit, mostly through dopamine. Rat models for optogenetics evidenced dopamine cell firing from the VTA.[49]
5. Inferior thalamic peduncle (ITP): a fiber bundle connecting the nonspecific thalamic nuclei/dorsomedial thalamus (midline, intralaminar, and paralaminar) to the OFC. Subcaudate tractotomy includes the ITP and is classically described to treat TRD. Hypothetically, metabolic abnormalities in the frontal cortical regions are associated with depression, which could be modulated by employing DBS of the ITP.[50]
6. Lateral habenula (LHb): is a brain structure projecting to several monoaminergic brainstem nuclei, involved in the metabolism of dopamine (substantia nigra pars compacta and VTA), serotonin (dorsal and medial raphe),[51] and noradrenalin (locus coeruleus).[52–54] Augmented activation in the nucleus of the LHb has been reported in depressed patients,[55] and shown to downregulate neurotransmitters and stimulation of the HPA axis.[56]

Methods

A systematic review of the literature was carried out aiming to identify the efficacy of DBS for the treatment of TRD by two independent investigators, following the protocols of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). The databases searched for this review were: Australian New Zealand Clinical Trials Registry (ANZCTR), ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), Deutschen Register Klinischer Studien (DRKS), Instituto Brasileiro de Informação em Ciência e Tecnologia (IBICT), Latin American and Caribbean Health Sciences Literature (LILACS), Medical Literature, Analysis, and Retrieval System Online (MEDLINE), Netherlands Trial Registry (NTR), Portal de Periódicos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior do Ministério da Educação (CAPES/MEC), The Digital Library of Theses and Dissertations of the University of São Paulo (Digital Library USP), and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

The following descriptors were used alone and with Boolean operators: *depression*, *treatment-resistant depression*, *treatment-refractory depression*, *deep brain stimulation*,

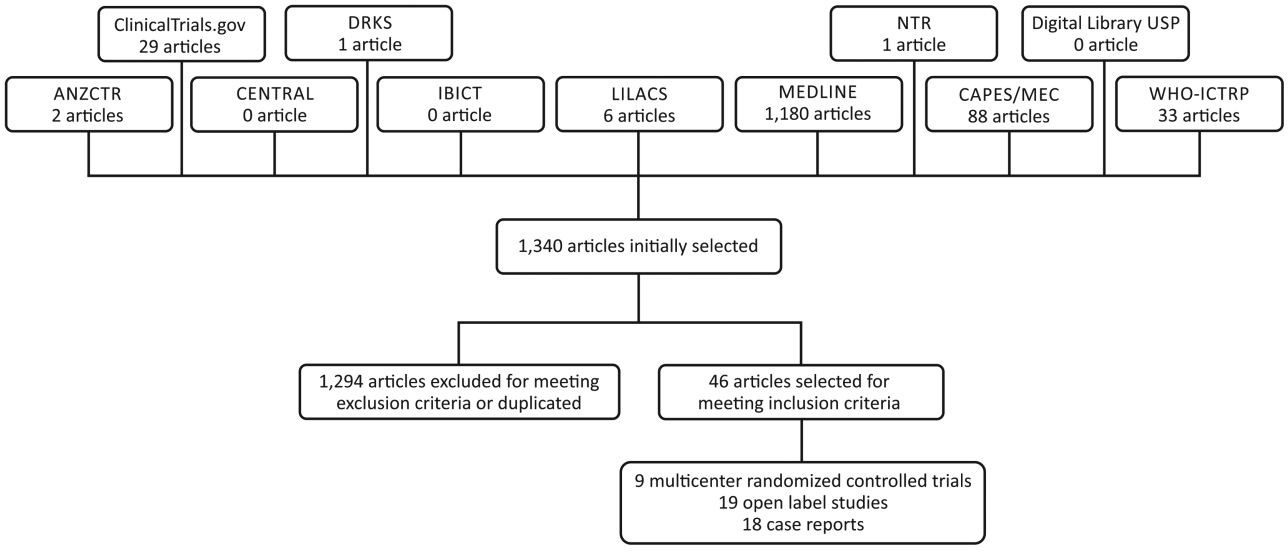

Fig. 1 Data collected during this systematic literature review.

Table 1 Articles selected in this systematic review

Target structure	Design	n	Follow-up	Stimulation parameters				Response/remission rates		Comment	Reference
				Electrode type	Amplitude	Frequency (Hz)	Pulse width (μs)	Response (%)	Remission (%)		
SCg	OLS	6	6 months	BL, MP	4.0 V	130	60	66	50	Reduction in local cerebral blood flow and changes in downstream limbic and cortical sites; 35% improvement in the Clinical Global Impressions Scale	Mayberg et al[26]
SCg	OLS	20	6 months	BL, MP	3.5–5.0 V	130	90	55	33	Mood improvements within 1 month lasting for at least 1 year in TRD patients	Lozano et al[57]
SCg	OLS	6	12 months	MP	3.0–4.0 V	130	60	66	NA	Improves cognitive functions with time without producing positive effects on mood behavior	McNeely et al[58]
SCg	CR	1	16 months	BL, BP	5.0 V	150	210	NA	NA	Reduced amygdalar-thalamic and amygdalar-SCg connections could be a contraindication to DBS for depression	McNab et al[59]
SCg	CR	1	12 months	BL, BP	3.6 V	135	90	100	0	Decrease in relapse rate and maintenance therapy of electroconvulsive therapy	Puigdemont et al[60]
SCg	CR	1	18 months	UL, MP	4.5 V	120	90	NA	NA	Suggests the preeminence of right hemisphere in regulation of depression	Guinjoan et al[61]
SCg	CR	1	6 months	BL, MP	6.0 mA	130	91	NA	NA	Report a marked and sustained antidepressant response	Holtzheimer et al[62]
SCg	OLS	20	36–72 months	BL, MP	3.5–5.0 V	130	90	64.3	42.9–50	Follow-up for long run DBS remains a safe and effective treatment for TRD patients	Kennedy et al[63]
SCg	OLS	17	24 months	BL, MP	4.0-8.0 mA	130	91	92	58	No patient achieving remission experienced a spontaneous depressive relapse and supported the long-term safety	Holtzheimer et al[64]
SCg	OLS	12	4–24 weeks	BL, MP	6.0–8.0 V	130	90	67.8	NA	FTC can serve as early biomarker for screening DBS effect on depression severity	Broadway et al[65]
SCg	OLS	8	12 months	BL, BP	3.6 V	135	90	62.5	50	Potential utility of this target to treat TRD patients	Puigdemont et al[66]
SCg	CR	1	6 months	BL, MP	2.5 V	130	90	NA	NA	Monoamine oxidase inhibitor potentiates the effects of DBS	Hamani et al[67]
SCg	OLS	21	12 months	BL, MP	3.5–5.0 V	110–140	65–182	29	NA	Reduction in depressive symptomatology and disease severity in patients	Lozano et al[68]
SCg	OLS	6	24–36 weeks	BL, MP	2.5–10.0 V	130	90	33.3	33.3	Exerts moderate acute and chronic antidepressant effects	Merkl et al[69]
SCg	OLS	4	36 weeks	BL, MP	0–10.5 V	2–185	60–450	50	50	Demonstrates association between longer pulse widths (270–450 μs) and reductions in HDRS scores	Ramasubbu et al[70]
SCg	OLS	7	1 months after 6 months of DBS	BL, MP	4.0–8.0 mA	130	91	92	NA	Reduction in negative words endorsed as self-descriptive associated with a reduction in depression severity	Hilimire et al[71]
SCg	OLS	7	9 months	BL, MP	3.5–5.0 V	135	120–210	NA	NA	Inactive stimulation decreases metabolism in Brodmann area 24/6 and putamen with respect to active stimulation	Martín-Blanco et a.[72]

Table 1 (*Continued*)

Target structure	Design	n	Follow-up	Stimulation parameters				Response/remission rates		Comment	Reference
				Electrode type	Amplitude	Frequency (Hz)	Pulse width (μs)	Response (%)	Remission (%)		
SCg	RCT	5	6 months	BL, MP	3.5–5.0 V	130–135	120–240	NA	NA	Continuous electrical stimulation is required to maintain therapeutic effects in TRD patients	Puigdemont et al[73]
SCg	OLS	8	12 months	BL, BP	3.6 V	135	90	NA	NA	Improvement in memory performance without worsening of cognitive function after chronic stimulation	Serra-Blasco et al[74]
SCg	OLS	4	12 months	BL, MP	2.0–5.0 V	130	90–450	50	NA	SCg-DBS for TRD may be associated with decreased levels of serum brain derived neutrophic factor	Ramasubbu et al[75]
SCg	OLS	5	24 months	BL, MP	5.0 V	130	90	79	20	DBS of the bilateral posterior gyrus rectus found effective in one patient as compared with SCg-DBS	Accolla et al[76]
SCg	CR	1	6 months	BL, MP	4.2 V	130	90	NA	NA	DBS targeting the limbic system may increase the risk of seizure in depressive patient	Richieri et al[77]
SCg	RCT	90	24 months	BL, MP	4.0–8.0 mA	130	91	20% (active) 17% (control)	5% (active) 7% (control)	No statistically significant antidepressant effects after 6 months of active versus sham stimulation in randomized, double-blind, sham-controlled trial	Holtzheimer et al[78]
SCg	OLS	11	12 months	BL, MP	6.0–8.0 mA	130	91	81.8	54	Tractography-based surgical targeting to reduce variability and increases number of responders	Riva-Posse et al[79]
SCg	RCT	9	13 months	BL, MP	4.0–8.0 mA	20 or 130	91	23.1	NA	High-frequency stimulation exhibits superior antidepressant effects in long-term study	Eitan et al[80]
SCg	RCT	8	28 months	BL, MP	2.5–10.0 V	130	90	33.3	33	Double-blind assessment fails to show significant antidepressant effect between sham and active	Merkl et al[81]
NAcc	CR	1	12 months	BL, MP	3.0–4.5 V	130	90	NA	NA	Extremely effective treatment of alcohol dependency using DBS of NAcc and improvement of depression	Kuhn et al[82]
NAcc/caudate nucleus VC/VS	OLS	15	12 months	BL, MP	6.7 V	127	113	53.3	40	Significant improvements in depressive symptoms	Malone et al[83]
NAcc/caudate nucleus VC/VS	OLS	17	14–67 months	BL, MP	2.5–8.0 V	100–130	NA	71	35	Sustain improvements across multiple scales of depression, anxiety and global function in TRD patients	Malone et al[84]
NAcc/caudate nucleus VC/VS	CR	1	48 months	MP	6.0 V	130	120	NA	NA	DBS might compensate for reward deficits and reduce smoking	Strong et al[85]
NAcc/caudate nucleus VC/VS	OLS	6	12 months	BL, MP	4.0–8.0 V	130	60	NA	NA	NAcc is a key structure within the cortico striatal loop in the pathophysiology of TRD	Millet et al[86]
NAcc/caudate nucleus VC/VS	RCT	30	16 weeks	BL, MP	8.0 V	NA	90–210	23.3 (active) 20 (control)	200	Double-blind RCT VC/VS-DBS is not an efficacious therapy for TRD patients	Dougherty et al[15]
NAcc/caudate nucleus	CR	1	30 months	BL, MP	4.0–6.0 V	130	90	NA	NA	Acute and reproducible improvements of mood, related to DBS of the NAcc	Giordana et al[87]
vALIC	RCT	25	52 weeks	BL	2.5–6.0 V	130–180	90	40.0	20.0	Double-blind RCT, a significant decrease of depressive symptoms in 10 of 25 patients	Bergfeld et al[88]

(*Continued*)

Table 1 (*Continued*)

Target structure	Design	n	Follow-up	Stimulation parameters				Response/remission rates		Comment	Reference
				Electrode type	Amplitude	Frequency (Hz)	Pulse width (μs)	Response (%)	Remission (%)		
vALIC	RCT	25	52 weeks	BL	2.5–6.0 V	130–180	90	40.0	20.0	No lasting positive or negative impact on cognition in TRD patients	Bergfeld et al[89]
vALIC/BNST and ITP	OLS	7	3–8 years	BL	NA	NA	NA	71.4	28.5	Stimulation of both targets decreases depressive symptoms, but six out of seven patients preferred vALIC/BNST stimulation versus ITP-DBS	Raymaekers et al[90]
MFB	OLS	7	12–33 weeks	BL, BP	2.0–3.0 V	130	60	86	57.1	Rapid onset of antidepressant efficacy and a higher proportion of the population responded	Schlaepfer et al[91]
MFB	OLS	8	12–48 months	BL, BP	2.0–3.0 V	130	60	75	50	Long-term results suggest acute and sustained antidepressant effect	Bewernick et al[92]
MFB/BNST	CR	1	24 months	BL, BP	2.8–3.0 V	130	60	NA	NA	Blurred vision problem occurred after 10 months of DBS; therefore, patient reoperated for other brain region after 2 years	Blomstedt et al[44]
LHb	CR	1	15 months	NA	10.5 V	NA	NA	NA	NA	Shows a sustained full remission of depressive symptoms in TRD patients	Sartorius et al[56]
ITP	CR	1	18 months	BP	3.0–5.0 V	130	450	NA	100	Produces antidepressant response as reflected by decrease in HDRS scores, without any potential side effects	Jiménez et al[93]
ITP	CR	1	3 years	BP	3.0–5.0 V	130	450	85.71	100	HDRS score changed from 42 to 6	Jiménez et al[50]
VCN	CR	1	15 months	BL	2.0–4.0 V	130	90–120	NA	NA	Deep brain stimulation of the ventral caudate nucleus markedly reduced this patient's symptoms of OCD and major depression and produced delayed onset of the alleviation of obsessional effects	Aouizerate et al[94]
GPI	CR	1	18 months	BL, MP	3.5–3.8 V	130	90	NA	NA	DBS at different targets located within this network, including GPI, could lead to a modulation of mood	Kosel et al[95]
BNST	OLS	5	Between 18 and 24 months	BL, MP	1.0–7.0 V	130	120–240	NA	NA	DBS applied to the BNST as therapeutic potential in patients with highly refractory depression	Fitzgerald et al[96]
slMFB	OLS	24	Between 12 and 33 weeks	BL	NA	NA	NA	85	57	The medial forebrain bundle is an important structure of reward and motivation. The slMFB emerges as a potential region for the treatment of major depression with DBS	Coenen et al[97]

Abbreviations: BL, bilateral; BNST, bed nucleus of the stria terminalis; BP, bipolar; CR, case report; DBS, deep brain stimulation; FTC, frontal theta cordance; GPI, globus pallidus pars interna; HDRS, Hamilton Depression Rating Scale; ITP, Inferior thalamic peduncle; LHb, lateral habenula; MP, monopolar; NA, not available; NAcc, nucleus accumbens; MFB, medial forebrain bundle; mo, month/s; OLS, open label study; RCT, multicenter randomized controlled trial; SCg, subcallosal cingulate gyrus; slMFB, superolateral branch of the medial forebrain bundle; TRD, treatment-resistant depression; UL, unilateral; vALIC, ventral anterior limb of the internal capsule; VCN, ventral caudate nucleus; VC/VS, ventral capsule/ventral striatum.

DBS, *neurofunctional surgery*, *electrode implantation*, *neurostimulation*, *neuromodulation*, and *psychiatric surgery*, and their equivalents in Portuguese, Spanish, German, French, Dutch, and Czech. The terms were searched in all fields of the databases.

For the selection of the studies, the following inclusion criteria were adopted: 1. studies correlating TRD and DBS as a treatment strategy; 2. studies published until September 2018; 3. publications in English, Portuguese, Spanish, German, French, Dutch, and Czech. 4. human experimental trials.

The exclusion criteria chosen for the present review were: 1. duplicate publications; 2. studies involving animals; 3. studies involving the ethical and existential implications of DBS; 4. editorials, comments of the authors, and debates; 5. studies addressing depression secondary to any other diseases; 6. studies reporting any neurosurgical interventions other than DBS.

Articles with short- and long-term outcomes of the same trial published separately were both included, because some featured new patients and/or novel stimulation strategies. Official documents released by relevant societies and references used in experimental articles were also examined. Subsequently, the results were manually reviewed and selected for analysis.

Results

A total of 46 papers were selected for the present systematic review, including 9 multicenter randomized controlled trials (RCTs), 19 open label studies, and 18 case reports (►**Fig. 1**, ►**Table 1**). The targets employed were the BNST, the GPI, the ITP, the LHb, the MFB, the NAcc, the SCg, the slMFB, the vALIC, the ventral caudate nucleus (VCN), and the VC/VS.

A double-blind multisite RCT (20 institutions), known as the Brodmann Area 25 Deep Brain Neuromodulation (BROADEN) trial, targeting the SCg and involving 90 participants, has been the largest psychiatric DBS study so far. Response to treatment was defined as a decrease $\geq$ 40% in the Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline and no worsening in the Global Assessment of Functioning (GAF) score. The DBS parameters were adjusted using an algorithm, and the concomitant use of ADs was allowed as long as the doses remained steady. Patients with chronic, unremitting depression were implanted and randomly assigned to 6 months of active or sham DBS, followed by 6 months of open-label SCg DBS. Both groups exhibited overall improvement on daily function (average of 132.2%), 92% of the patients reached a MADRS decrease from baseline of at least 50%, and 58% of them had complete remission.[78]

However, during the double-blind sham-controlled phase (12 patients with active versus 5 with sham DBS), the sham response rate was 17%, but no statistically significant difference was found in the responses of both groups. No psychiatric or neuropsychological adverse events (AEs) were reported at the 6- or 12-month follow-ups. Major AEs included suicidality (3/17), with 2 suicides in the control group during the 6-month open-label phase, anxiety (5/17), infection (5/17), system malfunction (3/17), and worsening of the depression (2/17).[78]

During the long-term open-label follow-up at 12, 18, and 24 months, the responses were 29%, 53%, and 49%, respectively. Of the 30 subjects in this phase, 26 decided to continue with DBS stimulation. A futility analysis was performed when approximately half of the patients received active DBS, completing the double-blind phase, indicating that the study had a 17% chance of success if continued. Although at the given timepoint this number did not meet the definition for futility ($\geq$ 10% chance of success), the study was halted.[78]

The rationale of targeting the SCg started in a pioneer study that included six patients aiming to access the feasibility and safety of DBS modulation of the SCg and of the adjacent white matter. A decrease $\geq$ 50% in the 17-item Hamilton Depression Rating Scale (HDRS-17) was considered a response to treatment. Response and remission rates at the 1- and 6-month follow-ups were 35%, 10%, 60%, and 35%, respectively.[26]

Neuropsychological analyses revealed that DBS was also effective to improve self-negative bias.[71] Neuroimaging evidenced metabolic changes, and a neurocognitive assessment in six patients proved the procedure to be safe.[58]

A 12-month follow-up incorporated an additional 14 patients to this cohort, and adjustable stimulation parameters were based on the presence of acute behavioral effects. The benefits were maintained and no permanent AEs occurred.[57] The extended follow-up showed average response rates of 62.5%, 46.2%, 75%, and 64.3% after 1, 2, 3, and 3 to 6 years, respectively. Overall, AEs were transient, and the most frequent was suicidality (3/20), with a confirmed suicide at 35 months and an attempted suicide at 75 months. Also, worsening of the depression (3/20), infection (3/20), and 1 case of perioperative seizure were registered.[63] Despite the initial good response, 1 patient from this series relapsed 4 years later; nonetheless, the use of tranylcypromine, a monoamine oxidase inhibitor (MAOI), along with DBS decreased the MADRS score by 60% after 4 months.[67]

Another case study from this series presented transient oscillation of response and important depressive episodes, one of them related to battery depletion. However, the patient was responsive to medication adjustments and obtained an overall sustained response.[62]

Investigators replicated the design of SCg DBS in a multicenter approach involving 21 patients during 12 months, but employing a different stimulation device. Setting the response criterium at $\geq$ 50% decrease in the HDRS-17, the results were 57%, 48%, and 29% at the 1-, 6-, and 12-month follow-ups, respectively. After 12 months of DBS, establishing the response criterium at $\geq$ 40%, total responders increased to 62%, which was attributed to amelioration in disease severity. Major AEs were nausea/vomiting and suicidality (2/21).[68]

The same system was also investigated in a cohort study with a sham-controlled design including 10 unipolar TRD individuals and 7 bipolar subtype II treatment-resistant

patients. At the 2-year endpoint, the response was 92%, whereas the remission was 58%. Two suicide attempts were reported, an MDD remitter at 2 years, and a bipolar patient at 54 months of follow-up.[64]

In a pilot study, baseline frontal theta cordance (FTC) appeared as a biomarker for predicting 6-month clinical response to SCg DBS for TRD. In addition to that, lower FTC at baseline and higher FTC after 4 weeks were predictors of lower depression severity scores at the 24-week follow-up.[65]

A multicenter double-blind randomized crossover of 13 months was carried out with 9 MDD patients resistant to treatment to evaluate the effects of high (130 Hz) vs low (20 Hz) frequency BA 25 DBS. Response ($\geq$ 40% MADRS) was achieved by 4/9 patients, with similar improvements in high and low frequency stimulation groups after 6 months. In the second period of the trial, the high frequency group showed higher improvement regarding the response criteria.[80]

An uncontrolled double-blind (delayed versus non-delayed stimulation onset) study included five patients with TRD and one with bipolar affective disorder type I who underwent SCg DBS. Two attained remission (HDRS-24 $\geq$ 10) at 24 and 36 months, with no AEs due to acute high intensity stimulation ($>$ 10 V). The main outcome was depression severity assessed using the HDRS-24, and the secondary outcome parameters were MADRS and Beck Depression Inventory (BDI) scores. Acute 24-hour stimulation caused moderate decreases in all the scales. Between 24 and 36 weeks, 2 patients were remitters and 4 were non-responders.[69]

Another report by the same group included participants in the aforementioned cohort, encompassing seven patients with TRD and one with bipolar affective disorder type I. The response rate was 51%, and 2 patients achieved remission (33.3%) at the 28-month and 4-year follow-ups. No statistical differences were found between different onset groups.[81]

A diffusion tensor imaging study on this same series found that the only responder had the contacts located bilaterally in the posterior gyrus rectus (BA 14). This displayed strong connectivity between the stimulated regions and the mPFC.[76]

A Spanish group initiated a study in 2008 performing SCg DBS in 8 TRD patients following an open-label design.[66] In a preliminary result, 1 patient from this series relapsed at 4 months and presented with psychotic symptoms. The DBS system was turned off and, after nine sessions of frontal ECT, when DBS was turned on again, the patient successfully reached remission.[60]

After 1 year of stimulation, they obtained a response of 62.5% in the HDRS-17 and remission in 50% of the cases, with improvement in social function and neurocognitive safety, as well as benefit for the memory.[74] Except for a suicide attempt in the group of nonresponder patients, no other serious AEs occurred.

Subsequently, stimulation was ceased in the 5 previous responders under a double-blind randomized design, resulting in sustained remission (2/5), relapse (2/5), and progressive worsening without relapse (1/5) in their 3-month sham protocol.[73] Simultaneously, remitters underwent double-blind sham stimulation.[72] Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) scans evidenced metabolism decreases in the dACC (BA 24), in the premotor region (BA 6), and in the putamen, not followed by changes in HDRS-17 scores.

In a pilot cohort, four patients with TRD underwent SCg DBS surgical procedure. After that, the frequency and pulse widths were randomly changed weekly. Evaluations of changes in mood and depression were performed using a visual analogue scale (VAS) and the HDRS-17. Longer pulse widths (270–450 µs) were related to short-term clinical improvement (HDRS-17) in 3 participants and to positive mood response (according to results indicated in the VAS) in all of the patients. No associations between DBS frequency and mood or clinical response were found. After 6 months of the open-label postoptimization phase, 2 patients (50%) showed clinical response, and 1 showed partial response.[70]

The same group of researchers carried out a double-blind trial including the same patients. They found that the stimulation was related to decreases in serum BDNF concentration compared to pre-DBS baseline.[75]

In an open-label cohort of 11 patients, the fibers activated were proven to be more related to the response than the site of the implanting (mainly projections to BA 10), using whole brain activation volume tractography. At 6 months, 8 patients had an increase in current from 6 to 8 mA. Response, considered as $\geq$ 50% decrease in the HDRS-17, was reached by 72.7% of the sample at 6 months, and by 81.8% at 12 months. Remission criterium (HDRS-17 $\geq$ 7) was attained by 6 patients, and 2 never met it. One of them had minimal variation in the HDRS-17, whereas the other achieved 40% decrease in this score at 12 months. A whole brain activation volume tractography and the common probabilistic tract map generated for all subjects (responders and nonresponders) at 6 months featured the inclusion of the forceps minor, the uncinate fasciculus, the frontostriatal fibers, and of the cingulum bundle.[79]

In an Argentinian case report, patient-blind unilateral stimulation produced rapid mood worsening on the left hemisphere. Most electrodes placed in the SCg and in the adjacent white matter produced stimulation related to acute onset of orthostatic hypotension, both at the postoperative testing and at a the 6-month assessment (the contacts were permanently kept turned off). No alterations were observed in the opposite hemisphere.[61]

In a French case report, a patient with long-term MDD and TRD, who had undergone extensive unilateral ECT that led to cognitive deficits, presented with late postoperative seizures as a possible side effect, displayed at standard stimulation parameters (90 µs, 130 Hz, 4.2 V). Most likely, DBS has revealed a previously existing temporal lobe epilepsy, although the participant had no individual or family history of convulsions. The patient was responsive to treatment.[77]

A study from England reported a patient with bipolar disorder and treatment resistance, with an infarct in the right thalamus (dorsomedial nucleus) that produced severe depressive symptoms within hours and TRD at 9 months

(BDI-II: 41; Beck Anxiety Inventory: 26). DBS of sACC at high frequency (> 150 Hz) did not produce any clinical effects, probably due to the reduction in structural connectivity from the sACC back to the amygdala on the right side. Projection to frontal areas was not clearly differentially disrupted. The patient was followed-up 1 year after the procedure, when the battery of the DBS was running low, but cessation of stimulation had no effect. This patient died in his sleep 16 months after the DBS surgery.[59]

In a randomized clinical trial, 25 patients in the Netherlands underwent DBS of the vALIC for TRD. An open-label optimization trial was conducted for 52 weeks followed by a sham-controlled double-blind multisite crossover RCT. The response criterium was $\geq$ 50% decrease in the MADRS from baseline to the 16th week of the blind phase, while the remission criterium was HDRS-17 $\geq$ 7 at the 2nd assessment. At the end of the optimization phase, 10 patients were responders and 15, non-responders. In the crossover phase, 16 of these patients – 9 responders and 7 non-responders – participated. During active DBS, the HDRS-17 scores were significantly lower (13.6). Adverse events included: suicide attempts (5), increased suicidal ideation (2), suicide (1), euthanasia (1), and surgery-related extreme nausea (1) that interrupted the operation, which was performed 2 weeks later with success. Battery depletion was suspected in two patients. Active DBS had significant antidepressant effect in 10 out of 25 TRD patients compared with sham DBS, classified as responders ($\geq$ 50% decrease) and partial responders ($\geq$ 25 but < 50% decrease).[88] No permanent impact (either positive or negative) on cognition was observed in a posterior study with the same sample.[89]

A double-blind crossover trial with seven TRD patients investigated the stimulation in either the anterior limb of the internal capsule/BNST or in the ITP. All of the patients participated in the follow-ups for at least 3 years, but some were followed-up up to 8 years after the procedure. A significant average decrease in the HDRS-17 score (61%) was attained by 5 responders and 2 remitters. Only one participant preferred ITP stimulation. Most patients reported fluctuant worsening of depressive symptoms and suicide ideation, and the patient that preferred ITP stimulation presented with transient extrapyramidal-like AEs (hypomimia, micrographia, hesitant walking, and less fluent movement). Two patients had a suicide attempt history prior to implanting and committed suicide at 39 and 80 months after the procedure, respectively.[90]

A 16-week randomized blind sham-controlled trial of DBS, known as RECLAIMTM, targeted the VC/VS in 30 patients with TRD, with a subsequent open-label phase. The response, set as a decrease $\geq$ 50% in the MADRS score, was 20%, 26.7%, and 23.3% at the 12-, 18-, and 24-month follow-ups, respectively. However, no significant differences in response rates were found between the active and sham treatments, or changes in the MADRS scores at the end of the 16-week controlled phase. A total of 71 serious AEs were recorded for 22 patients, and the most frequent were worsening of the depression (8), suicidal ideation (5 in the active and 3 in the sham group), suicide attempts (4), and a completed suicide of a nonresponder who ceased stimulation while preparing for explanting. During the blind phase, the most frequent psychiatric AEs in the active group were worsening depression and insomnia.[10]

In a multisite open-label investigation, 14 MDD patients and 1 bipolar (subtype not specified), 13 of which had failed both AD and ECT, and 2 who were also resistant to vagus nerve stimulation, were treated with DBS of the VC/VS. The response rates were 40% and 53.3% in the HDRS, and 46.7% and 53.3% in the MADRS, and the remission rates were 20% and 40% in the HDRS, and 26.6% and 33.3% in the MADRS at the 6-month and last follow-ups, respectively.[83]

A following study enrolled two additional patients, both AD- and ECT-resistant, who also underwent DBS of the VC/VS. Response was attained by 53 and 71% of the sample ($n = 17$) at the 3-month and last follow-ups, respectively. Interestingly, 35% of the patients continued in remission (MADRS score $\leq$ 10) at the last follow-up, and a remarkable reduction in suicidality occurred at 1 month and persisted in the next 12 months ($p \geq 0.001$). Serious AEs related to DBS included: anxiety, autonomic effects, mood changes, and paresthesia. However, they were transient and, after adjusting the stimulation parameters, all of them disappeared.[84]

One of the patients of the aforementioned multisite open-label investigation,[83] who had been a remitter for 4 years, experienced increase in smoking (50–200%) and concurrent worsening depressive symptoms in 3 different occasions, all related to interruption of DBS caused by battery depletion. Nevertheless, once DBS stimulation was restarted, the smoking pattern reverted to baseline and the depressive symptoms decreased.[85]

A patient with TRD, comorbid bulimia, and borderline personality disorder showed improvement in depression (as per results in the HDRS score) after initial placement of electrodes in the ITP without electrical stimulation, probably because of a microlesion effect. After a phase of stimulation (130 Hz, 0.45 µs, 2.5 V), it was discontinued in a double-blind fashion, and the HDRS score did not return to preoperative levels, remaining between 2 and 8. This patient was later explanted and remained in remission up to 7 years.[93]

A patient with a history of treatment-resistant OCD, recurrent MDD, and unsuccessful cognitive-behavioral therapy was referred to DBS of the VCN. Nonetheless, several AD strategies improved the depressive symptoms prior to the procedure. In the first 3 months of stimulation, depressive symptoms progressively worsened, but at the 6-month follow-up, the patient achieved MDD remission (HDRS = 7; Hamilton Anxiety Rating Scale = 10), which was sustained until the end point, 15 months after the surgery. The patient also attained OCD remission, but more slowly, markedly between the 12- and 15-month follow-up, with progressive increase in Global Assessment of Functioning (GAF) scores. No negative neuropsychological effects were noted.[94]

A group of 10 patients presenting with very severe forms of TRD, refractory to ADs, psychotherapy, and ECT, underwent DBS of the NAcc. Response (50% decrease in the HDRS-28) was reached by 50% of the patients at the 12-month

follow-up, and 3 participants achieved remission (HDRS-28 $\leq$ 10) for a period of 1 month.[98]

The long-term effects of DBS of the NAcc were assessed in the same group of participants described above[98,99] and in an additional patient enrolled posteriorly. Follow-ups were carried out 12 months, 24 months, and 4 years after the procedure with 11, 10, and 5 patients, respectively. Adverse events related to DBS were transient. By the 12-month follow-up, 1 patient had committed suicide and 1 had attempted suicide, both nonresponders to the surgery. After 12 months, 45% of the participants were considered responders, and did not show worsening symptoms at the 4-year follow-up.[100]

In a double-blind placebo-controlled trial, three patients with extreme forms of TRD (resistant to psychotherapy, ADs, and ECT) received DBS implantation in the NAcc. The voltage ranged from 0 to 4 V in 1-V steps, in a double-blind manner. At each step, HDRS-24 and MADRS were reapplied, and a negative correlation was observed for both scores in all of the patients. No relevant AEs occurred. Single items of both scales, often used to assess aspects of anhedonia, were verified, but no significant changes were found, in spite of clear clinical changes in anhedonia. Metabolic imaging displayed activations in bilateral VS (including NAcc), bilateral DLPFC and DMPFC, bilateral cingulate cortex, and bilateral amygdala, simultaneously with deactivations in the vmPFC, the ventrolateral PFC, the dorsal caudate nucleus, and in the thalamus.[43]

In a case report of a patient with a 20-year history of MDD, agoraphobia, and alcohol dependence for the previous 10 years, DBS of the NAcc produced acute pleasure. In 12 months, the patient became an occasional drinker. However, decreases in depression or anxiety were minimal.[82]

A depressed woman, with a 46-year history of severe MDD and 9 years of TRD, failed to respond to ADs and ECT. Her depressive episode at the intervention included delusions of guilt, mutism, and pronounced anxiety, with HDRS-21 rates around 45. Deep brain stimulation of the LHb produced full remission of depressive symptoms within a period of 4 months. The patient relapsed, and the voltage was increased, leading to stable remission. One accidental switch off caused an additional relapse, but it was transient.[56]

The superolateral branch of the medial forebrain bundle (slMFB) was targeted based on a neuroanatomical and functional hypothesis using new fiber tracking techniques: two opposing systems, the ATR and the slMFB, were anatomically described and assumed to mediate negative (ATR) and positive (slMFB) emotions.[48]

A decrease $\geq$ 50% in the HDRS was achieved by 6 patients, and 4 reached remission 12 months after DBS of the slMFB. Moreover, long-stable effects were reported up to 4 years after the procedure. The main AEs were oculomotor effects (blurred and double vision), responsive to reduction of amplitude of stimulation. Discontinuation of a nonresponder at 18 months decreased the score, but not exceeding baseline, and explantation kept remission until 12 months.[92]

The same design used above was replicated by the Houston group using deterministic tractography. After 52 weeks, 4 out of the 5 remaining patients that ended the trial had a decrease $>$ 70% in the MADRS scores compared to baseline. The modulated fiber tracts revealed significant common orbitofrontal connectivity in all of the responders. Neuropsychological testing verified safety, and ^{18}F-FDG-PET cerebral metabolism evaluations at baseline and at 52 weeks showed minimal changes. Increased depression was associated with battery depletion in four patients, and accidental deactivation in three.[101]

Evaluation of the tractographies showed that responders typically have their active contacts exclusively situated in the center of the triangle, with no contact with the nuclear environment. Thus, every treatment should be based on individual slMFB (tractography) geometry.[97]

A case report presented a patient with TRD and nervous anorexia who was treated with DBS and showed great response. However, after 10 months, she presented blurred vision and was reoperated with electrodes placed on the BNST. At 12 months, the results were: MADRS = 13; HDRS = 6; HAM-A = 5.[44]

A pilot open-label series included five female patients resistant to AD and ECT, who underwent DBS of BNST. Clinical response was observed by means of various assessments rather than by a stated definition. Stimulation induced: 1 remission at 6 months; 1 response and 1 remission at 12 months; 3 remissions at the last follow-up, 2 of them stable (MDRS of 1 and 3) up to 6 years; and an eventual reoccurrence and restoring of remission after battery replacement. One patient had explantation of DBS, which was reimplanted in the sACC, but, by the end of the second treatment, she committed suicide. A significant increase in quality of life and depression scores, as well as neurocognitive stability, were attained. Two suicide attempts, apparently not related to stimulation, occurred during the trial, and one of these patients reached remission later. Transient insomnia was the most common AE related to increase in stimulation.[96]

An anecdotal case report targeted the GPI for TRD and severe tardive dyskinesia (TD) in a patient with a history of failing to over 60 psychotropic drugs, who had been treated with typical and atypical neuroleptics, and developed severe neuroleptic-induced TD. The patient attained a $\geq$ 50% decrease in the HDRS 18 months after DBS implantation. The HDRS score dropped from 26 at baseline preoperatively to 13 at the 18-month follow-up, whereas the Burke-Fahn-Marsden Dystonia Rating Scale score decreased from 27 to 17.5 (35%).[95]

A preliminary study of four patients targeted the NAcc and, in the event of failure, the caudate nucleus, in a limbic vs cognitive fashion. The primary and secondary outcomes were $\geq$ 50% HDRS and remission, defined as HDRS = 7 after 4 months, respectively. Stimulation of the NAcc was performed from the 1st to the 5th month. At month 5, nonresponders underwent stimulation of the caudate target until month 9, followed by a 6-month extension phase (up to month 15), with adaptable parameters and concomitant treatments. A significant improvement in mood was achieved by 3 patients, with lower HDRS scores at the end

of the 15 months. Following the start of stimulation, benefit was obtained at the extension phase, with open parameters. One patient did not meet response criteria at month 5, but NAcc stimulation was kept due to clinical perception of improvement. Furthermore, aripiprazole was added at month 11, leading the patient to a stable improvement until reaching response.[86]

A case report featured amplitude and dynamics of the mood changes, systematically quantified using the HDRS-17, in a nonresponder after DBS of the Nacc. The patient rapidly achieved and sustained remission 11 months after increasing the voltage of the most distal contact of each electrode located in the NAcc to 5V. Some worsening due to battery depletion was also reported.[87]

Discussion

Deep brain stimulation research for the treatment of patients with TRD has been marked by amelioration[102] contrasting with inconsistent results of the three largest multicenter RCTs.[10,78,88] Therefore, it could be inferred that DBS is not effective for TRD, at least in the way it has been currently performed and assessed. Aiming to understand these controversial outcomes, we tried and dissected factors that may be impacting trials and leading to fails.

On the one hand, little can be said about the efficacy of SCg as a DBS target based exclusively on the interrupted BROADEN trial.[78] On the other hand, open-label studies focused on optimizing targets, as well as on mapping response patterns, patient subtypes, and connectomics, obtaining exceptional results.[79]

The largest study followed the standard paradigm focusing on the Food and Drug Administration (FDA) validation at 6 months, with restricted parameters, that is, the surgical intervention was adequately isolated by not allowing post-surgical support, psychological or pharmacological treatment before the trial, and potentially reduced the chance of patient recovery at the short endpoint of the futility analysis.[78]

A significant increase in response after SCg DBS was observed in the open-label original series from the 1st to the 3rd year, since the average response rose from 62.5 to 75%.[62,63] In sum, BROADEN could have been more thorough in terms of duration, adjustment of parameters, and optimization phase.

Considering open-label studies and case reports, the SCg remains promising, although BA 24 is probably the key area underlying the effects.[61] In addition to this, unilateral vs bilateral hemisphere stimulation matters persist.[49]

The blind-treatment phase of the RECLAIM™ trial was probably too short and avoided high stimulation parameters to preserve blinding and prevent AEs. No significant differences were found during the sham phase, contrasting with the findings of a previous phase of the trial, in which 36% of the patients achieved response in 1 year and 92% in 2 years.[64]

The solely good performance of the vALIC large RCT highlights some particular characteristics, such as: a smaller sample; a 52-week open-label parameter optimization phase; stratification of response (partial response if 25–50% decrease in symptoms); and the intent-to-treat analyses to discriminate response from non-response.[88]

The case reports corroborated the severity of TRD in highly resistant patients and related complications such as TD[95] and cognitive deficit after years of ECT.[77] They also described strategies biased by the small casuistic, which were nevertheless life-changing in the context they were proposed, that is, contraindication to ECT,[60] MAOI restoring DBS response,[67] and substance dependance.[82] After all, these are common exclusion criteria in studies, but in the case reports selected, the patients presenting with them were treated using DBS.

Heterogeneity inherent to psychiatric neurosurgery occurs within trials in multiple domains: selected patients, pretrial treatments, trial designs (open label, crossover, and parallel), optimization of parameters (if allowed and duration), surgical technique, individual variability due to structural and functional connectivity,[102] scales to define and monitor response and remission.

Major depressive disorder is a bureaucratic diagnosis, based on clinically-derived, however, arbitrary criteria. A mathematical analysis showed that 227 different combinations of depressive symptoms[103] can fulfill the DSM-5 diagnostic criteria for MDD.[21] Given that some items are multiple or alternative symptoms (i.e., insomnia or hypersomnia), if each component symptom is considered separately, 14,528 combinations are possible.[103]

Lack of a global definition of TRD potentially adds a second level of phenotype heterogeneity labelled together with the population of interest; therefore, the inclusion criteria consistently diverge between studies. It is possible that by targeting DBS for TRD, distinct phenotypes/subtypes of this mental condition fall under the same label. This way, they have probably been addressed using the same circuits and the effects vary according to the deficits. Stage 5 treatment-resistant depression (irresponsiveness to three ADs and ECT)[104] seems the most adequate definition of TRD for trial purposes.

The definition of response varies, but it is frequently set as a decrease by 50% in depressive symptoms assessed using HDRS and MADRS.[105] Even though the former has different versions and numbers of items (i.e. HDRS-17, -21, -24, and -28), the exact scale is not always mentioned in the studies.[44]

The fallacy of thresholds, a methodological bias explored for AD trials with TRD patients, showed that scales lose statistical power when used to compare treatment against placebo.[106] By doing so, researchers assume that sensibility and specificity are the same in both groups, responders in the placebo group might fit "intuitive definitions" of response less well than patients under treatment, and patients in the adjacencies of cutoff scores of scales are often clinically indistinguishable.[107]

For Parkinson disease (PD), the Unified Parkinson's Disease Rating Scale[108] was necessary to validate the evident impact DBS had on symptom control. Given that modeling mood disorders is even more complex, research on TRD should possibly follow the same path by developing a specific scale.[35]

The MFB study showed exceptionally good immediate and sustained efficacy (~ 80%). This makes this target the most promising of the open-label trials selected.[97]

The MFB is the most rapid to produce response, most probably because it lies at the center of the reward pathway,[14,91,109] with acute effects also more pronounced on the NAcc.[87] Nonetheless, whenever acute responses are present, the insertional effect (possibly related to acute inflammatory mediators[11] or glial released neurotransmitters[12,32] in early time-points must be considered. Sustained and low progressive improvement in the blind stimulation cohorts and acute mood changes related to alterations in parameters months after surgery[87] tend to indicate efficacy of the surgical procedure.[110]

Although sham designs mitigate placebo effect, especially if longer shams are employed, this effect is still relevant (five times stronger than medications in DBS for PD). It possibly happens due to expectation per se following the instructions of the doctor, follow-up visits, and high-frequency stimulation potentially rising subtle AEs and affecting patient blinding. Yet, placebo effect and spontaneous remissions are not usual in patients with very severe TRD.[7,26] Worsening symptoms because of unintended "shams" such as battery depletion were frequently highlighted in the present systematic review, corroborating the efficacy of DBS. Strategies to overcome placebo effect include longer shams and optimization phases. Nevertheless, the latter may imply selection bias in the randomization phase. The counterpart effects, nocebo and lessebo,[66,110] cannot be rejected whenever patients are aware of the possibility of being in the sham arm, which the inform consent provides.

The suicides reported appear to be dissociated from system malfunction or from changes in parameters, and were comparable to mortality rates in naturalistic studies.[111,112] Whether suicide after DBS occurs due to lack of efficacy and disease progression or because stimulation lowers the suicide threshold remains unanswered.

Overall, other stimulation AEs are transient and responsive to parameter adjustment. Visual disturbances are particularly common in patients undergoing high stimulation parameters at some targets, especially the slMFB. Therefore, this AE is a relative limitation to slMFB DBS.[44] Emphasis should be given to investigational studies, as this target reportedly exhibits the most rapid and a sustained response. Additionally, high oculomotor-stimulating frequencies are likely associated with DBS efficacy.[64]

Optimal DBS parameter settings are still under debate.[31,34,53,75] Evidence points that short pulse width–low intensity, short pulse width–high intensity, as well as long pulse width–low intensity stimulation are the possible combinations. The high- versus low-frequency debate arises,[31] with some strong evidences[34,53] indicating that high-frequency stimulation promotes better AD response.[73,80]

The fact that the commercial value of being first to market is undoubtedly appealing[25] might have contributed to the prematureness of the three pivotal researches.[10,78,88] Whereas the trials herein presented have used open-loop systems, alternatively closed-loop or adaptive DBS systems, in dynamic stimulation settings based on a patient-control variable, in a feedback-like manner, tend to play a significant role in a near future.[113] This dynamic model seems coherent with the most common symptoms of the disease and with the idea that different phenotypes fall under the umbrella of TRD.

Since in standard magnetic resonance imaging sequences the slMFB is not visualized, tractography generates the hypothesis of a target, culminating in response above 80%. Therefore, tractographies are mandatory for this target.[97]

Outcome predictors of efficacy of DBS for TRD appear to be related to symptoms rather than to the syndromic diagnosis, as underpinned by evidence of symptom-target relationship such as the connection of negative mood[26] to the SCg25, the MFB, and the NAcc.[91] This brings psychiatrists to the operating room, where the presence of this professional enhances patient trust,[28] and the functional neurosurgeon to a clinical interdisciplinary health care team.[114]

Evidently, treatment options for MDD have never been so diverse, and, yet, suicide and depression rates have been increasing.[115] Deep brain stimulation is promising; however, it is restricted to specialized centers and highly selected patients, the market is dominated by a few companies,[116] and the procedure is costly.[117] This illustrates the long way ahead before DBS for TRD achieves efficacy and effectiveness.

Based on our exploratory exercise prior to the present systematic review of the literature, we conveniently conveyed inclusion criteria to allow psychiatric comorbidities, obtaining highly heterogeneous populations, closer to the reality of resistant populations. However, the theoretical modeling of DBS for TRD was compromised, posing a limitation to the present study. Furthermore, statistical analyses were not performed, since the trials selected are substantially different and, thus, not statistically comparable. Consequently, the successful and failing outcomes presented must be interpreted with caution, as these limiting factors potentially impair generalizations.

Conclusion

The current DBS research for TRD shed some light on the understanding of the most prevalent mental disorder. The studies here examined are among the most sophisticated to date. Nonetheless, they were not sufficient to reject or confirm the clinical pertinence of DBS. Despite the expansion of the therapeutic range of somatic therapies for depression, contemporary concerns on the repercussions of TRD and its lethality make DBS key to engross the list of treatment modalities. Thus, DBS remains one of the most promising and versatile strategies of this potential toolkit.

Conflicts of Interests

The authors have no conflicts of interests to declare.

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Orbital Schwannoma: Case Report and Review

Schwannoma de Órbita: Relato de caso e revisão

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Abstract

Orbital schwannomas are rare, presenting a rate of incidence between 1 and 5% of all orbital lesions. Their most common clinical symptoms are promoted by mass effect, such as orbital pain and proptosis. The best complementary exam is the magnetic resonance imaging (MRI), which shows low signal in T1, high signal in T2, and heterogeneous contrast enhancement. The treatment of choice is surgical, with adjuvant radiotherapy if complete resection is not possible. We report the case of a 24-year-old male patient with orbital pain and proptosis, without previous history of disease. The MRI showed a superior orbital lesion compatible with schwannoma, which was confirmed by biopsy after complete resection using a fronto-orbital approach.

Keywords
- orbit
- schwannoma
- extraconal tumor

Resumo

Schwannomas de órbita são raros, apresentando incidência entre 1 e 5% de todas as lesões de órbita. Seus sinais clínicos mais comuns são causados pelo efeito de massa da lesão, estando entre eles a dor orbitária e proptose. O melhor exame complementar é a ressonância magnética (MRI) que mostra uma lesão hipointensa em T1, hiperintensa em T2 e de captação heterogênea de contraste. O tratamento de escolha é cirúrgico, com uso de radioterapia adjuvante quando a ressecção completa não for possível. Neste estudo, relatamos, um paciente masculino de 24 anos com dor orbitária e proptose, sem historia de doenças prévias. A ressonância mostrou uma lesão na região superior da órbita comparável com um schwannoma, que foi confirmada por biópsia após a completa ressecção usando um acesso fronto orbitário.

Palavras-chave
- órbita
- schwannoma
- tumor extraconal

Introduction

Schwannomas are slow-growth benign tumors, which normally originate from a sensitive nerve sheath. Among the cranial nerves, the vestibule-cochlear is most commonly affected one, with an incidence of 8 to 10% of all intracranial tumors.[1–3]

Orbital schwannomas are rarely described in the literature, presenting between 1 and 5% of all orbital neoplasms. The orbital nerves more commonly involved are trigeminal branches, like the supratrochlear and supraorbital nerves.[1,4]

The most important orbital schwannoma clinical symptoms are orbital pain and proptosis, which are promoted by progressive mass effect. For this reason, small tumors are

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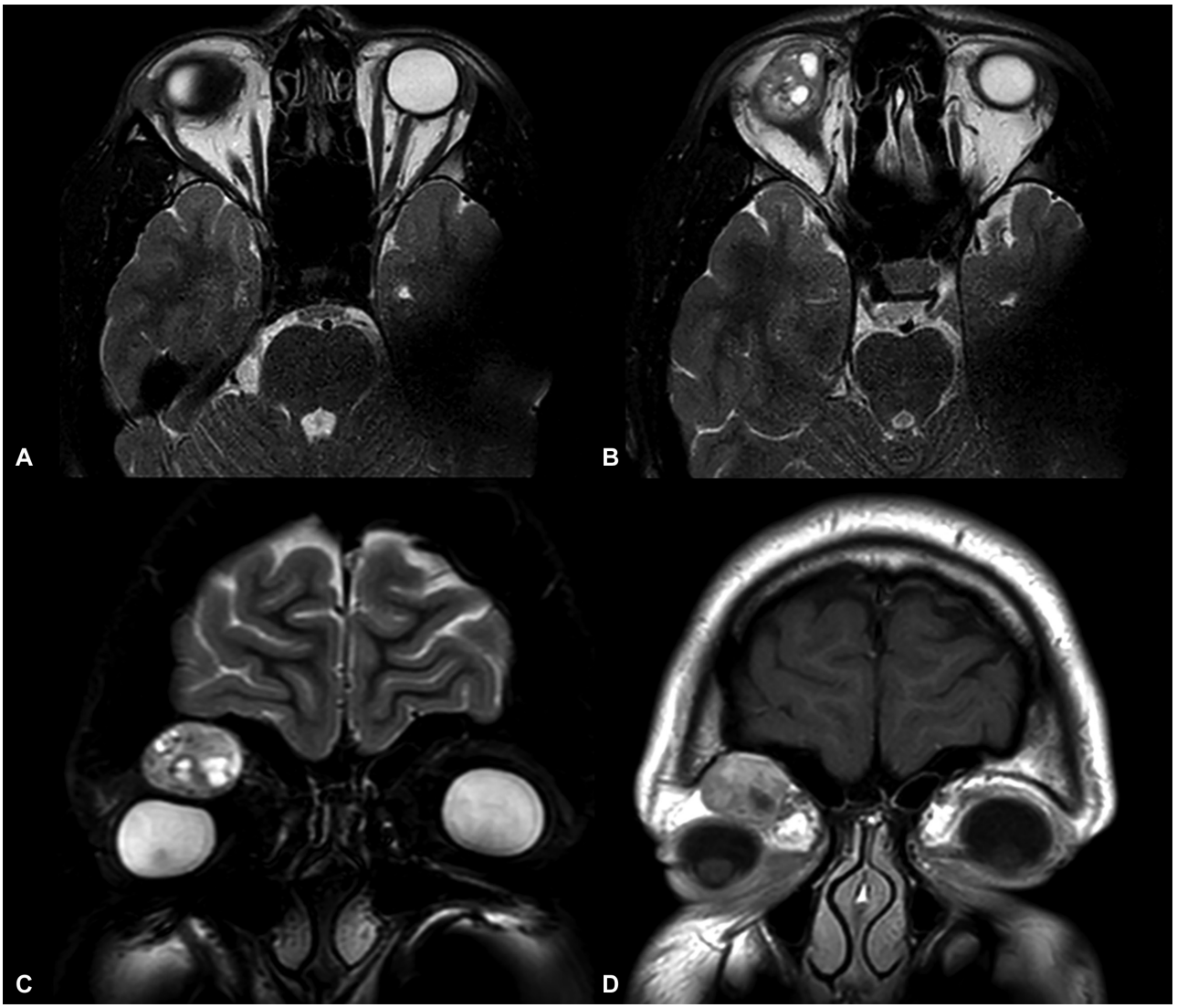

Fig. 1 A and B – Magnetic resonance imaging: axial T1 gadolinium sequence showing a right orbit lesion, superior to eye with heterogeneous enhancement. C – Coronal T2 sequence showing the relationship between the tumor and the right eye. D – Coronal T1 sequence that evidences the tumor and its disposition, lateral and superior to the optic nerve.

frequently asymptomatic for a long time until they become large enough for symptoms to appear.[5]

Surgical approaches can vary with tumor location, and they can be transcranial, facial, or endoscopic.

In the present study, we describe the case of a young male with orbital schwannoma and discuss this pathology.

Case Report

We report the case of a 24-year-old male patient who presented with a 2-year history of progressive pressure frontal headache and enlarging mass on the right upper eyelid. Two months before hospital admission, he noticed worsening of the vision . There was no report about family cancer or medications in use. Physical examination showed right eye proptosis and lateral inferior dislocation. There were diplopy and right visual field impairment; however, the extrinsic ocular movements and pupillary reactions were preserved.

The orbital MRI evidenced a mass with major dimensions of 3.1 × 2.5 × 1.5 cm located above the right eye. It had a high intensity signal on T2-weighted images, a low intensity on T1-weighted images, and heterogeneous contrast enhancement. (►**Fig. 1**)

Due to the large size of the lesions and its localization, the transcranial approach was chosen. The incision was arcuate, starting from the superior rim of the zygomatic arch to the midline of the skull in the frontal region and ending back at the hairline because patient expressed the desire to avoid a scar on his face.

A fronto-orbital craniotomy provided a good superior and lateral orbital exposition. The mass was encapsulated and attached to the supraorbital nerve. In the next step, a delicate dissection from orbital fat, nerves, and muscles was made, allowing the “en bloc” resection.

After a complete tumor resection and rigorous hemostasis, the orbit and bone flap were closed with the help of titanium plates and bone cement.

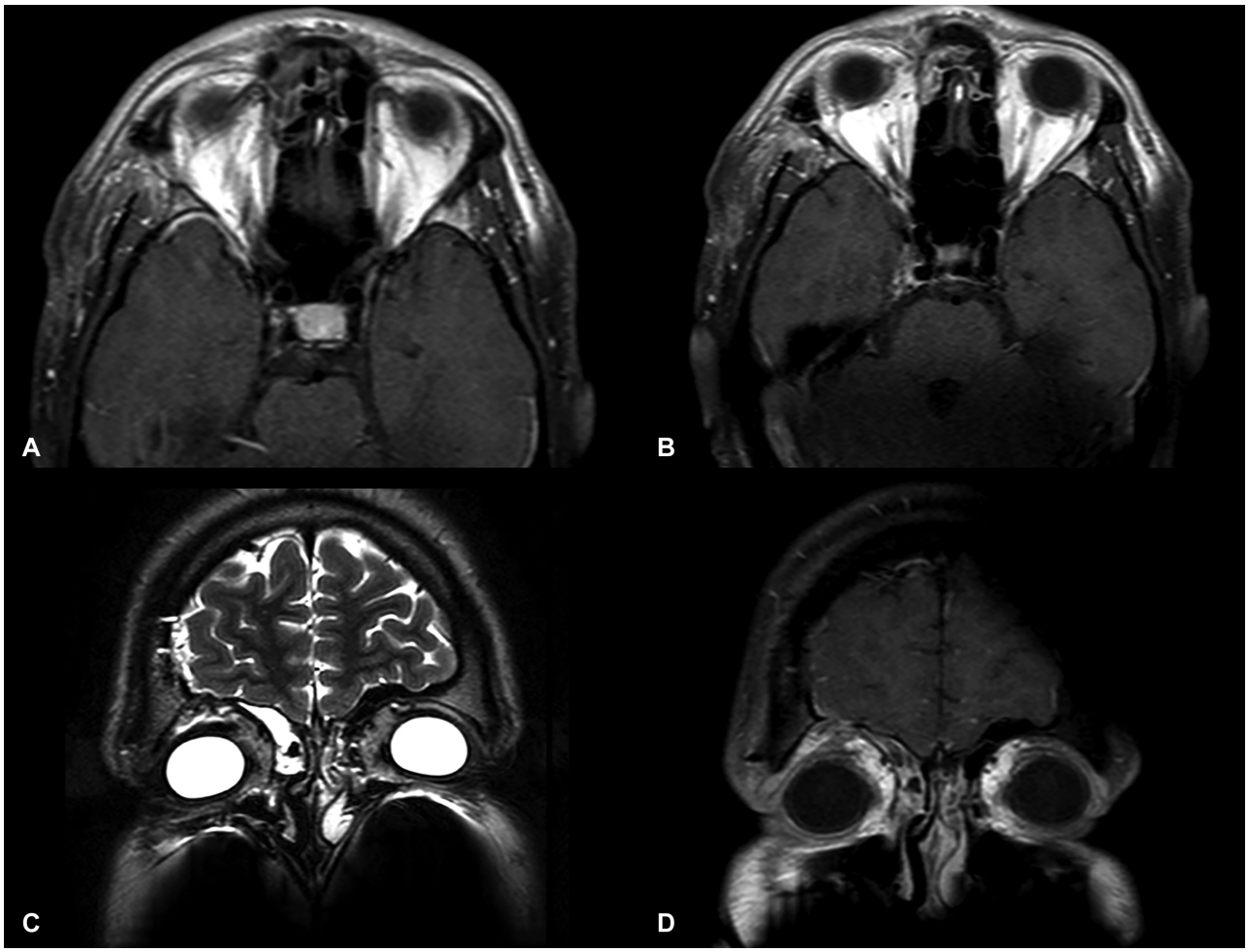

Fig. 2 Postoperative axial and coronal magnetic resonance imaging showing a complete tumor resection with eye symmetry return and preservation of orbital structures.

The postoperative period occurred without complications. Fifteen days after the surgery, the patient showed campimetry with progressive improvement of the visual field. Physical examination presented symmetric ocular globes, without diplopia, facial sensibility, palpebral elevation, or extrinsic ocular muscles alterations. An orbital MRI confirmed complete resection of the lesion, and the pathological definitive study revealed a grade I schwannoma with a ki-67 of 2%. (►**Fig. 2**).

Discussion

Orbital schwannomas are rare, presenting frequency between 1 and 5% of all orbit neoplasms, with age variation from 20 to 70 years old and without gender prevalence.[1–3,6]

In general, schwannomas originate from sensory nerves. In the case of orbital schwannomas, it is not different, with the supratrochlear and supraorbital nerves being the ones most frequently affected. This explains the delay in affecting the vision and extraocular movements, which occurs late in the clinical presentation. Although less common, nerves like the oculomotor, trochlear, and abducens can be affected and must be suspected if there are eye movement deficits without previous symptoms.[7]

The most common symptoms are caused by orbital structures compression, which include orbital pain and proptosis, as reported by our patient during the clinical examination. Other symptoms, in decreasing order of frequency, are diplopia, visual acuity decrease, facial hypoesthesia, and headache.[5–9]

It is difficult to identify the origin of the tumor during surgery, because there is a large volume of fat and many nerve fibers crossing the orbit. We believe that the clinical examination is a good way to identify the nerve of origin of the tumor.[7–9]

The complementary examination involves computer tomography (CT) of the brain, which can show an isodense image in relation to the orbital muscles, orbital bone enlargement and bone deformities. Magnetic resonance imaging is the preferred imaging exam due to its elevated sensibility. The orbital schwannoma has low intensity in T1 and high intensity in T2 sequences and has regular contours. It commonly have a heterogeneous appearance, enhanced by gadolinium which allows your distinction from the homogeneous pattern exhibited by cavernous hemangiomas. Orbital lymphomas may be similar to schwannomas regarding shape and location, but they present intermediate signal in T2-sequence and adapt to the surrounding structures, unlike the schwannoma, which may distort the anatomy of adjacent structures.[8,10–12]

Anatomically, the orbit should be imagined as an irregular pyramid with four sides.

Lesions located in the superior half of the orbit can be accessed by orbital roof with a frontotemporal approach. If a lateral to medial vision is needed, the orbitotomy should be added to the approach. In cases of lateral inferior tumors, a lateral orbitotomy called Burke-Kronlein, with or without zygomatic osteotomy, can be used.[13,14]

To access the medial inferior quadrant of the orbit, one option is endoscopic access, which has the advantage of being less invasive than the transcranial route.[13–15]

For small lesions located in the anterior half of the orbit, approaches without osteotomies, like eyelid superiorly or subciliary and orbital rim inferiorly can be tried. The disadvantage of anterior approaches is a restricted vision field which promotes difficulties in locating and preserve the anatomical structures.[13–15]

In our case, we choose a transcranial fronto-orbital approach to get more space to work due to a big size presented by tumor in relation to patient orbit.

When complete resection is not possible, adjuvant radiotherapy can be considered.[16]

Conclusion

Orbit schwannoma is a rare tumor, which generates mainly mass effect as clinical presentation. The standard treatment is surgery-based, with complete excision whenever possible. The approach can vary according with the location of the tumor, depending from orbital anatomical side and need to be individualized.

Conflitos de Interesse
The authors declare that there are no conflicts of interest.

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Bilateral Transverse Sinus Angioplasty for the Treatment of Idiopathic Intracranial Hypertension – Case Report and Literature Review

Angioplastia de Seio Transverso Bilateral para Tratamento de Hipertensão Intracraniana Idiopatica - Relato de caso e Revisão da literatura

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Abstract

Idiopathic intracranial hypertension (IIH) is a disease characterized by an increase in intracranial pressure, without presence of parenchymal lesions or hydrocephalus that justify it. Over 90% of cases there is association with stenosis of the dural venous sinuses. It is characterized by headache, tinidus, nausea, vomiting and visual disturbances. Initial treatment is clinical and when it fails there is indication of invasive procedures, among them shunts and fenestration of the optic nerve sheath. Angioplasty of dural venous sinuses, when indicated, has shown an alternative with better results and less complications. We report a case of a female patient, with 27 years old, diagnosed with IIH and bilateral transverse sinus stenosis, which was treated by bilateral stenting and total resolution of symptoms. Besides describing the case we review the literature about the subject.

Keywords
- intracranial hypertension
- angioplasty
- venous sinus stenosis

Resumo

Hipertensão intracraniana idiopática (HII) é uma doença caracterizada pelo aumento da pressão intracraniana, sem a presença de lesões parenquimatosas ou hidrocefalia que a justifiquem. Em $>$ 90% dos casos, há relação com estenose de seios venosos durais. O quadro clinico é caracterizado por cefaleia, tinnitus, náuseas, vômitos e distúrbios visuais. O tratamento inicial consiste em uma modalidade clinica, e quando esta é ineficaz, há indicação de procedimentos invasivos, dentre os quais estão as

Palavras-chave
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derivações liquóricas e a fenestração da bainha do nervo óptico. A angioplastia dos seios venosos, quando indicada, mostra-se uma alternativa com melhores resultados e com menos complicações. Relatamos o caso de uma paciente de 27 anos com diagnóstico de HII e estenose de seio transverso bilateral na qual o tratamento realizado foi o implante de stents, com melhora completa dos sintomas. Além do relato de caso, revisamos a literatura a respeito do assunto.

Introduction

Idiopathic intracranial hypertension (IIH) is characterized by increased intracranial pressure (ICP) without the presence of cerebral parenchymal lesions or hydrocephalus to explain it. More than 90% of the cases are associated with stenosis of the dural venous sinuses.[1] Its pathophysiology is poorly defined, and its etiology is believed to be multifactorial, leading to changes that modify cerebrospinal fluid (CSF) dynamics, thus causing increased CSF production or reduced CSF absorption.[2] Although IIH is considered a benign disease, it can cause irreversible visual impairment in between 10 and 20% of the patients.[3] The estimated incidence is of 1.2 cases per 100,000 individuals per year in the general population, and the prevalence is highest in overweight young women.[4]

The clinical picture is characterized by headache of variable intensity (present in up to 94% of patients); tinnitus, which can be unilateral or bilateral; nausea and vomiting; and, most importantly, visual disturbances. These include diplopia (due to involvement of the abducens nerve), papilledema (reflecting increased ICP), and, in some cases, reduction of visual acuity due to chronification.[5] The diagnosis is made through a multidisciplinary neuro-ophthalmological evaluation, with demonstration of papilledema through fundoscopy and of increased ICP by lumbar puncture with measurement of CSF pressure.[6] Concomitantly, other causes of intracranial hypertension should be ruled out through neuroimaging. Magnetic resonance imaging (MRI) of the brain may demonstrate secondary signs of IIH, such as empty sella, posterior flattening of the globe, and increased subarachnoid space around the optic nerve.[7]

Angioplasty of the venous sinuses, when indicated, is an alternative that provides better outcomes with fewer complications than conventional surgical treatments. We report a case of IIH treated successfully by stent placement for bilateral transverse sinus stenosis, and briefly review the relevant literature.

Case Report

A 27-year-old woman with no past medical history, no comorbidities, and not overweight was referred to the neurosurgery department by her ophthalmologist. She reported a 1-month history of progressively worsening, nonradiating, nontension-type bifrontal headache without triggering factors. She reported having sought urgent care several times due to recurrent headache. She noticed a gradual deterioration of visual acuity and then saw an ophthalmologist, who detected bilateral papilledema and promptly referred her to our service for evaluation.

A magnetic resonance imaging (MRI) of the brain showed no space-occupying lesions and no signs of hydrocephalus or of demyelination. Magnetic resonance angiography of the cerebral circulation ruled out cerebral venous thrombosis, but demonstrated possible bilateral transverse sinus stenosis.

A diagnosis of IIH was suggested due to the refractory symptoms of the patient, to the neuroimaging findings, to the evidence of increased ICP, and to the persistent visual deficit. To confirm this hypothesis, lumbar puncture was performed, which showed an opening CSF pressure of 37 cmH_2O. Approximately 40 mL of CSF were drained; after the procedure, the patient reported substantial improvement of the headache.

We decided on a trial of clinical treatment and prescribed acetazolamide 250 mg every 6 hours. There was slight improvement of the headache, but no improvement of the visual deficit; in addition, the patient experienced several adverse effects, including abdominal discomfort, nausea, vomiting, and postural hypotension.

After discussing additional therapeutic options with the patient, we decided to perform angiography to determine the trans-stenotic pressure gradient. If there was a change of $>$ 8 mmHg, stent placement would be indicated. The angiogram revealed bilateral transverse sinus stenosis (►**Fig. 1**) with a prestenosis venous pressure of 37 mmHg and a poststenosis pressure of 9 mmHg on the right, and a prestenosis pressure of 35 mmHg and a poststenosis pressure of 8 mmHg on the left (pressure differential, 28 mmHg on the right and 27 mmHg on the left). Intravenous ultrasound confirmed bilateral venous narrowing (►**Fig. 2**). With confirmation of the large bilateral pre- and poststenosis pressure gradient, stents were placed in both transverse sinuses. After the procedure, a new pressure gradient measurement was performed and revealed a significant reduction, with a prestenosis pressure of 11 mmHg and a poststenosis pressure of 9 mmHg in the right transverse sinus. On the left, the prestenosis and poststenosis measurement was 11 mmHg and 10 mmHg, respectively. In the immediate postoperative period, the patient reported slight worsening of her headache, possibly due to the manipulation of the venous system, which improved gradually with corticosteroids. She had an uneventful course and was discharged early free of pain.

At the outpatient follow-up 2 weeks after the procedure, the patient reported no pain. Recovery of visual acuity

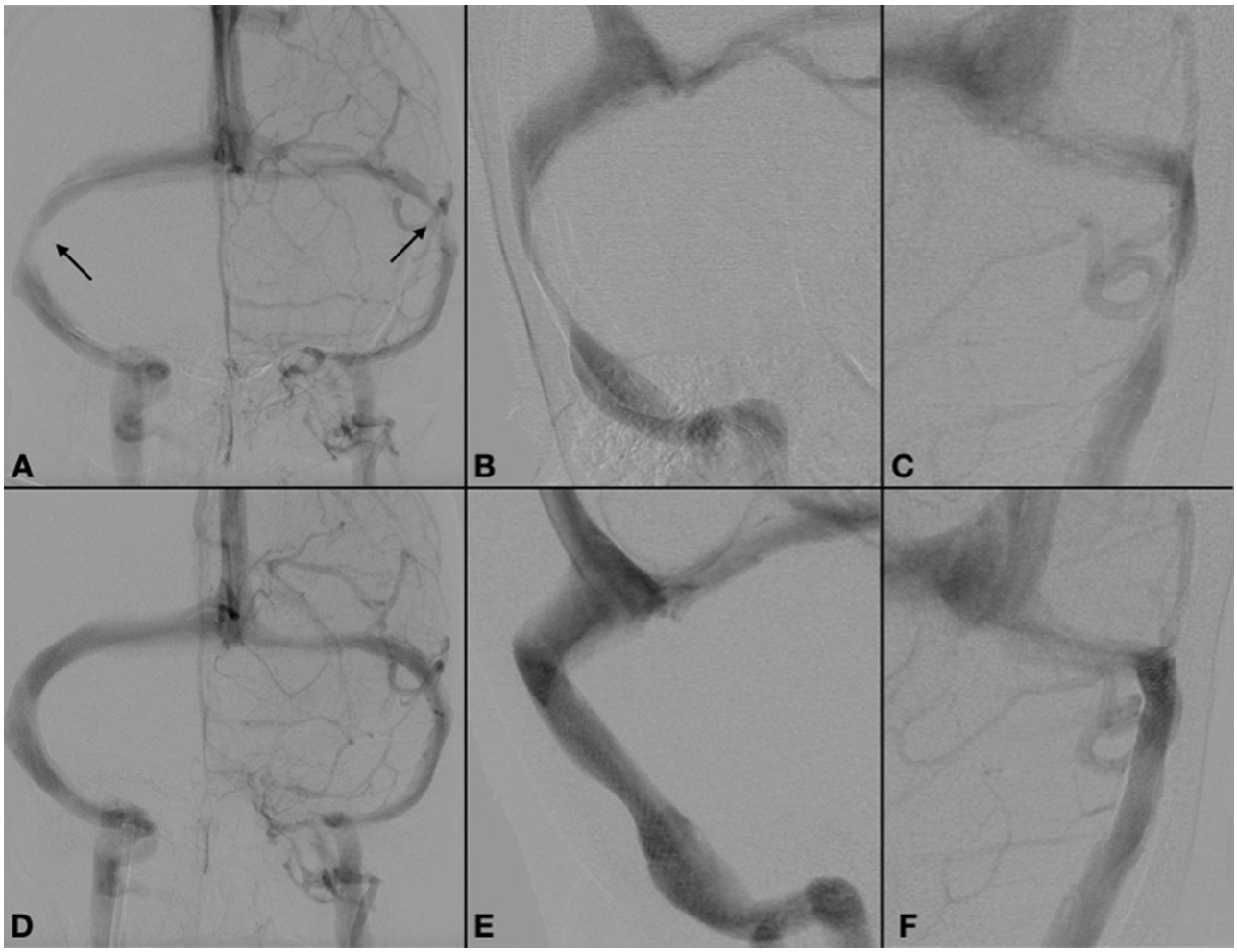

Fig. 1 Venography before stent implantation demonstrating bilateral transverse sinus stenosis - arrows (A). Right transverse sinus stenosis (B). Left transverse sinus stenosis (C). Images after stent implantation (D). Postoperative right transverse sinus (E). Postoperative left transverse sinus (F).

followed at $\sim$ 1 month. Repeat ophthalmologic evaluation demonstrated complete resolution of the papilledema. At the time of writing, 6 months after the procedure, the patient is symptom-free. Clinical follow-up with the neurosurgery and ophthalmology teams is ongoing; we have not performed control angiogram or lumbar puncture, which would be unjustifiable in an asymptomatic patient.

Procedure

The patient began dual antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) 5 days before the procedure. First, conscious sedation was administered for the measurement of pressure gradients. Access was achieved through the right femoral artery with a 5F sheath for angiographic control and road mapping, and through the left femoral vein with a 6F sheath for stent placement. A bolus injection of 5000 IU of unfractionated heparin was administered, and a 6F guide catheter was advanced to the right jugular bulb. A 0.027-inch Rebar microcatheter (Medtronic, Minneapolis, MN, USA) was passed coaxially, over a 0.014-inch Hybrid microguidewire (Balt Extrusion, Montmorency, France), to the sites designated for pre- and poststenosis pressure measurement, with the results described above.

With the confirmation of gradients $>$ 8 mmHg, general anesthesia was induced for stent placement. The 6F venous introducer was replaced with a 60-cm 10F sheath, and a 90-cm 8F guide catheter was passed coaxially over a 0.35-inch hydrophilic guidewire and was advanced to the right jugular bulb. Then, a 0.014-inch BMW Extra Support microguide (Abbott, Chicago, IL, USA) was passed up to the poststenotic segment of the left transverse sinus. A 9 $\times$ 30 mm Wallstent (Boston Scientific, Marlborough, MA, USA) was navigated and deployed to cover the stenosis on the left side. A 9 $\times$ 40 mm Wallstent (Boston Scientific, Marlborough, MA, USA) was then navigated through the same system and deployed to cover the contralateral stenosis (►**Fig. 3**). No balloon dilation was performed. Finally, a 0.027-inch Rebar catheter (Medtronic, Minneapolis, MN, USA) was again navigated for repeat measurement of the venous pressures, which showed normalization of the gradients. The patient completed a 30-day course of dual antiplatelet therapy, after which clopidogrel was discontinued. She continues to take aspirin (100 mg/day).

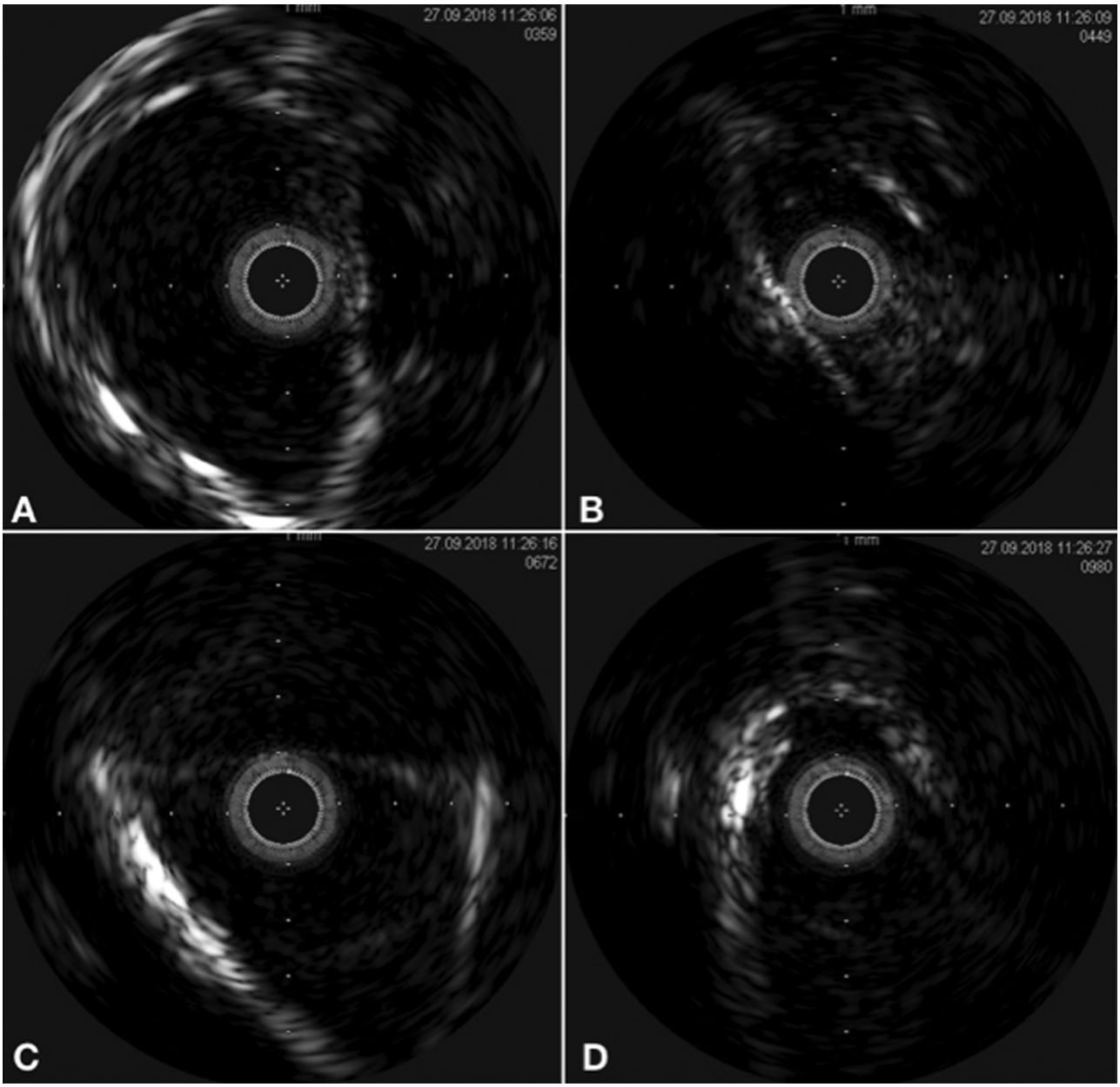

Fig. 2 Images of intravenous ultrasound. Poststenosis left transverse sinus (A). Interior of left transverse sinus stenosis (B). Prestenosis right transverse sinus (C). Interior of right transverse sinus stenosis (D).

Discussion

The first line of IIH treatment is clinical, and consists of weight reduction, adequate diet, analgesics to relieve headache, and carbonic anhydrase inhibitors such as acetazolamide (1.5 to 3 g/day divided into 3 or 4 doses) or methazolamide (50 to 300 mg/day); furosemide or topiramate may be used as a second option in some cases.[8,9] Obesity plays an important role both in the development of IIH and in its refractoriness to treatment. Excess weight is believed to result in increased intrathoracic pressure, which impairs venous drainage of the head and of the neck, consequently leading to an increase in ICP.[10]

Surgical treatment is reserved for cases with symptoms refractory to conservative management or rapid, significant deterioration of visual acuity. The recommended modalities are optic nerve sheath fenestration (ONSF) or shunting (ventriculoperitoneal, lumboperitoneal).[11] In recent years, venous angioplasty has gained an increasing role in the treatment of this disease, with promising results and low morbidity and mortality,[12] providing a minimally invasive and highly effective alternative to the usual surgical procedures. Whether dural venous stenosis is a cause or a consequence of IIH remains unknown. The most accepted theory is that intracranial hypertension causes extrinsic compression of the dural venous sinuses.[13] Venous stenting both relieves this compression and reduces ICP.[14] Conversely, medical management and CSF drainage have no impact on venous stenosis, even when ICP improves.[15]

In our case, we chose to perform the pressure measurements with conscious sedation because some studies have

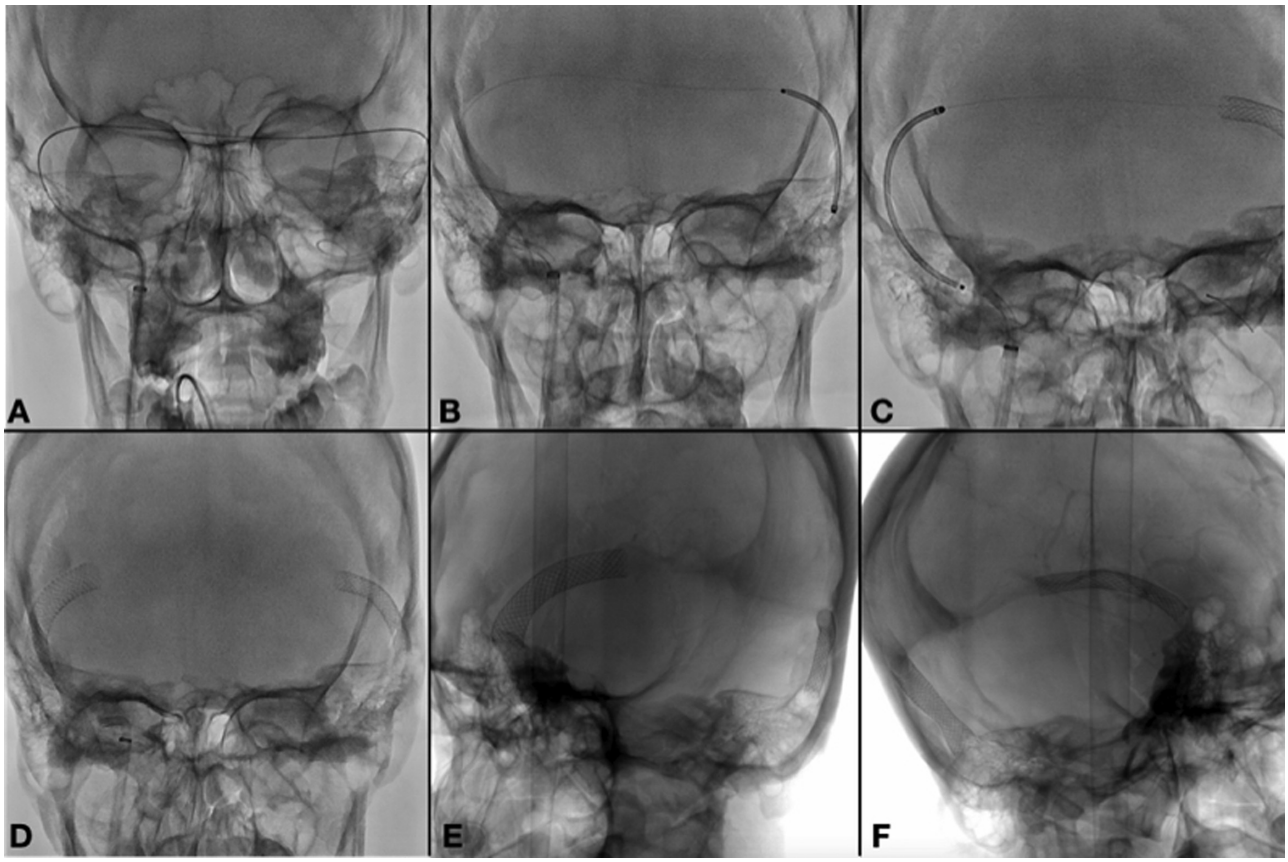

Fig. 3 Step-by-step procedure. 10F sheath and 8F guide catheter in the right jugular bulb (A). Stent implantation on the left (B). Stent implantation on the right (C). Images of postoperative control (D, E, F).

shown that general anesthesia causes a substantial decrease in the pressure gradient of the venous system, which may bias the results of the procedure.[16] Once the gradient had been confirmed, we switched to general anesthesia for patient comfort, as manipulation of material within the venous system can cause considerable pain.

In most cases, dural venous stenosis occurs in the transverse sinus, and in between 70 and 80% of the cases, it is bilateral. This raises another question: should angioplasty be performed bilaterally or only in the dominant sinus? Koovor et al[17] described a series of 16 treated patients, of whom 75% had bilateral transverse sinus stenosis; nevertheless, in all of the cases, only the dominant sinus was treated. Headache improved in 10 patients, and the papilledema improved in all of them. No complications were reported. In our case, although the right transverse sinus was dominant, there was abundant flow to the left, and the pressure gradient on this side was also quite considerable, which is why we chose to place stents bilaterally. From a technical standpoint, it was easy to pass the stent from right to left and to deploy it in the craniocaudal direction, and easier still to then pass the other stent and to treat the stenosis ipsilateral to endovascular access.

Several studies have compared treatment alternatives for dural venous stenosis. A meta-analysis published in 2015[18] compared outcomes in 136 patients who were treated with angioplasty, 712 with ONSF, and 435 with CSF shunt placement. In the ONSF group, there was improvement of vision in 59%, of headache in 44%, and of papilledema in 80%. In the CSF shunt group, there was improvement of vision, headache, and papilledema in 54%, 80%, and 70%, respectively, while in the angioplasty group, there was improvement of vision, headache, and papilledema in 78%, 83%, and 97%, respectively. The complication rates were 18% in the ONSF group, 40% in the CSF shunt group, and 7.5% in the angioplasty group. These findings confirm the greater success and lower complication rates of angioplasty.[19]

►**Table 1** describes major case series of patients treated with dural venous angioplasty, demonstrating low rates of complications and high rates of symptomatic improvement.[21–27] Most of the complications reported were related to vascular access, such as local hemorrhage and pseudoaneurysm, rather than to stent implantation. Ducruet et al,[20] in their series of 30 cases, reported intrastent stenosis in 4 patients, and proximal stent stenosis in 5. None of these required new stent implantation, and five patients did undergo CSF shunt placement. A recent meta-analysis[28] of 473 patients reported restenosis in 14% of the cases, most of them proximal or distal to the stent. The mechanisms judged most likely by the authors were intimal hyperplasia or simply because extrinsic intracranial hypertension continued to compress the sinuses. Thus, it seems plausible that using longer stents could reduce the rate of restenosis.

Table 1 Results of case series in the literature

Study	Number of patients	Headache (%)	Visual symptoms (%)	Papilledema (%)	Opening presssure (mm Hg)	Pain alleviation (%)	Complications (*n*)
Higgins et al., 2003	12	100	100	67	33.7	42	0
Donnet et al., 2008	10	100	80	100	40.2	80	0
Bussiere et al., 2010	13	100	77	92	NR	100	1
Ahmed et al., 2011[3]	52	83		88	32.9	85	7
Fields, et al., 2013	15	100	100	100	NR	67	1
Ducruet et al., 2014[20]	30	100	NR	100	NR	70	1
Aguilar et al., 2017	51	74	78	50	35.5	84	9
Satti et al., 2017	43	100	88	65	#5.8	69	0
Shields et al., 2018	42	100	100	100	38	43	1

Over the years, the endovascular approach has emerged as the leading treatment modality for IIH, instead of as an alternative to surgery. Cappuzzo et al[29] proposed an algorithm whereby, in case of confirmed diagnosis and failure of medical management, or if there is rapid visual deterioration, digital subtraction angiography with pressure gradient measurement should be performed. If a gradient > 8 mmHg is present, stenting is indicated; if symptoms recur or if there is no improvement, only then is surgical shunting to be considered. Most of the current literature suggests that failure pos stenting should be treated exactly thus. However, if many patients have bilateral transverse sinus stenosis and the standard treatment is to perform angioplasty only on the dominant side, should this subgroup of patients not benefit from stenting of the other sinus before thinking of surgical shunting? There have been reports[27] of patients requiring retreatment because of restenosis of the previously treated side, but stenting of the contralateral transverse sinus was not attempted. We believe there is a subgroup of patients that might benefit from bilateral sinus stenting, but comparative studies are needed to support this theory.

Conclusion

Transverse sinus angioplasty seems to be a safe and relatively simple procedure for the treatment of IIH, with very good short-term outcomes and low complication rates. Additional research is needed to confirm these findings.

Conflicts of Interests

The authors have no conflicts of interests to declare.

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Physiopathological Aspects of Sellar Epidermoid Cyst Determining Endocrine Disturbances: A Case Report

Aspectos fisiopatológicos de cisto epidermoide selar determinando alterações endócrinas: Relato de caso

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Abstract

Epidermoid cysts (ECs) of the central nervous system (CNS) constitute benign circumscribed lesions that are more common in lateral than in midline sites. Epidermoid cysts of the CNS arise more frequently in the cerebellopontine angle, around the pons, near the sella, within the temporal lobe, in the diploe, and in the spinal canal. Most common tumoral lesion of sellar region is pituitary adenoma, and sellar cystic epithelial masses may be difficult to differentiate based only on clinical and imaging findings. Epidermoid cysts are covered by keratinized squamous epithelium and are usually filled with keratin lamellae. The process is, for the most part, maldevelopmental in origin, presumably arising from trapped surface ectodermal elements in association with the developing CNS during the closure of the neural groove or formation of the secondary cerebral vesicles. In the present study, the authors describe a case of sellar epidermoid cyst producing endocrine alterations and visual disturbance in a 35 years woman, and review the physiopathological and diagnostic criteria of this lesion.

Keywords
- epidermoid cyst
- sellar region
- pathology
- central nervous system cysts
- brain neoplasms

Resumo

Os Cistos Epidermoides (CE) do sistema nervoso central (SNC) constituem lesões benignas circunscritas, que são mais comuns na linha media do que em regiões laterais. Os CE do SNC ocorrem com maior frequência no ângulo pontocerebelar, ao redor da ponte, próximo à sela, no lobo temporal, na diploe e no canal espinhal. A lesão tumoral mais comum da região selar é o adenoma hipofisário, e as massas epiteliais císticas selares podem ser difíceis de diferenciar baseando-se apenas nos achados clínicos e de imagem. Os CE são cobertos por epitélio escamoso queratinizado e geralmente são preenchidos por lamelas de queratina. O processo é, em sua maior parte, de origem

Palavras-chave
- cisto epidermoide
- região sellar
- patologia
- cistos do sistema nervoso central
- neoplasias cerebrais

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malformativa, presumivelmente em decorrência de elementos ectodérmicos de superfície aprisionados no desenvolvimento do SNC durante o fechamento do sulco neural ou na formação das vesículas cerebrais secundárias. Neste trabalho, os autores descrevem um caso de cisto epidermoide selar, que determinou alterações endócrinas e distúrbios visuais em uma mulher de 35 anos, e revisam os critérios fisiopatológicos e diagnósticos dessa lesão.

Introduction

Epidermoid cyst (EC) is a benign cystic lesion covered by mature keratinized squamous epithelium and occupied by keratin lamellae, without adnexal structures in its wall. The process corresponds to ~ 0.2 to 1.8% of all primary intracranial tumors and are 4 to 9 times as common as dermoid cysts.[1–4] Most ECs compromising the central nervous system (CNS) are extraaxial, leptomeningeal lesions, with the cerebellopontine angle (40–50% of patients) being the most common location. Epidermoid cysts can also be found in the 4th ventricle (17%), in the sellar/parasellar region (10–15%), in the cerebral hemispheres, in the brainstem, in the skull, and in the spine.[1–6]

Most tumoral and non-tumoral sellar lesions are solid process, and pituitary adenoma is the most common tumor in this topography. Cystic sellar lesions are not as frequent as pituitary adenoma, and Rathke cysts and craniopharyngioma are usually the final diagnosis. Epidermoid cysts of the CNS present slowly progressive symptoms, such as headache and cranial nerve dysfunction.[2,3,6–11] Epidermoid cysts arise from ectodermal inclusion during the neural tube closure in the third to the fifth week of embryogenesis. They have an excellent long-term survival, and gross total resection is usually curative.[1,2,8–11]

The authors describe a case of sellar EC presenting endocrine alterations and progressive visual disturbance in a 35 years female patient, and discuss the most common physiopathological findings of this lesion, and its differential diagnosis.

Case History

A female patient, 35 years old, presenting clinical complaint of amenorrhea in the previous 20 months was referred to the neurosurgical service due to a sellar cystic mass. The patient had been accompanied by an endocrinologist during this period, with regular use of prednisone (5 mg/day) and levothyroxine (100 ucp/day). In the last 4 months, the patient complained of visual disturbances. Magnetic resonance imaging showed an increase in the dimensions of the process, which also exhibited hemorrhagic areas, and measured 2.7 × 2.0 × 1.7 cm (►**Fig. 1**). The campimetry showed peripheral visual loss. On physical examination, no signs of neurological deficits were found. Chest and abdominal computed tomography (CT) did not identify significant alterations. A clinical hypothesis of pituitary adenoma with degenerative changes was established, and resection of the lesion was proposed. The transsphenoidal approach identified an expansive lesion compromising the sellar region

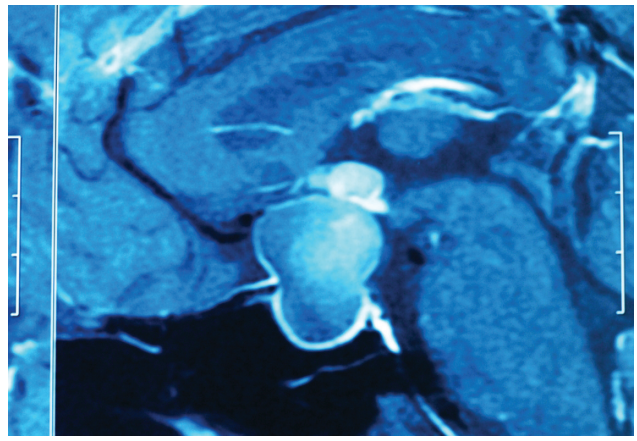

Fig. 1 Epidermoid cyst: preoperative magnetic resonance imaging showing an expansive sellar process.

(►**Fig. 2**), with significant compression of the optic chiasm. A gross total resection was performed. The pathological specimen was composed of some elastic, pale gray, irregular fragments of tissue, the largest one measuring 1.1 × 1.0 × 0.8 cm. At microscopy, a benign cystic lesion covered by keratinized stratified squamous epithelium and a fibrous wall was found (►**Fig. 3**). The process was filled with keratin lamellae and dystrophic tissue, and was contiguous to normal hypophyseal tissue. The diagnosis of sellar EC was then

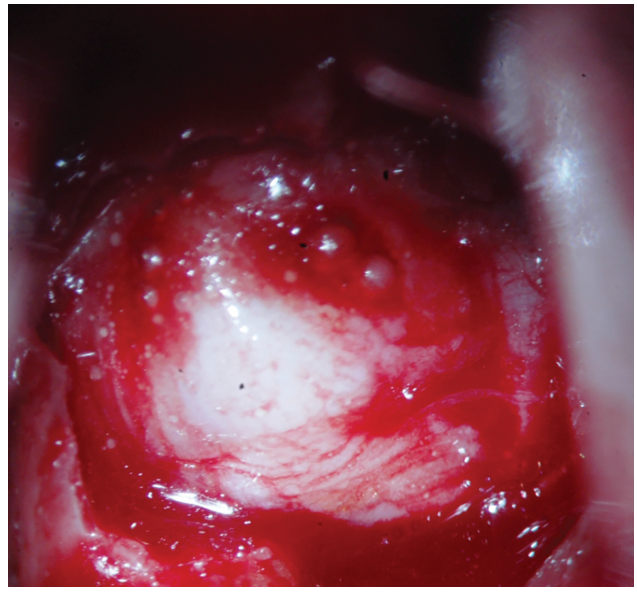

Fig. 2 Sellar epidermoid cyst: a pale gray expansive lesion.

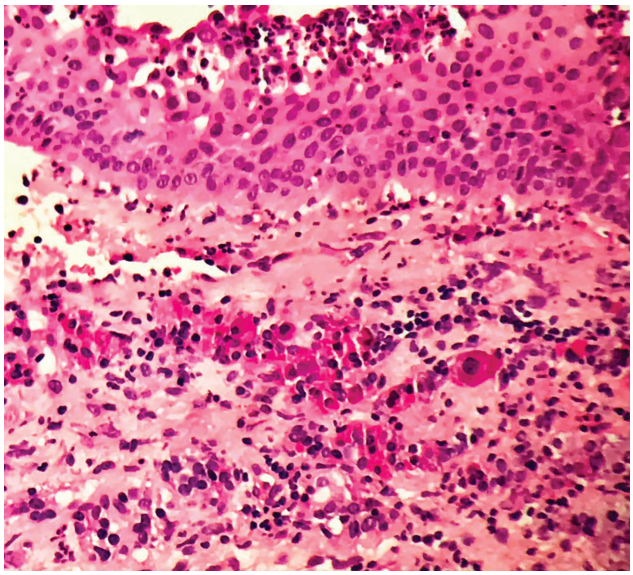

Fig. 3 Sellar epidermoid cyst: A benign cystic lesion covered by keratinized stratified squamous epithelium, hematoxylin-eosin, 200x.

established. In the immediate postoperative period, the patient developed diabetes insipidus, which was controlled with the use of desmopressin. After a follow-up of 8 months, no signs of recurrence were identified on radiological evaluation, and the patient was asymptomatic. During this period of clinical follow-up, the patient presented normal serum levels for pituitary hormones and estrogen. The use of prednisone, levothyroxine, and desmopressin was then discontinued.

Discussion

Epidermoid cysts are rare processes that probably represent developmental lesions resulting from embryologic displacement of ectoderm into the CNS tissue.[6] The pattern of embryological formation of the hypothalamic-pituitary-axis plays a major role in its propensity in the development of sellar ECs.[3,4,12–16] Neurulation can be divided broadly into primary and secondary phases. In primary neurulation, which occurs throughout the future brain, the neural tube is formed by neural folding. The formation and closure of the neural tube occur between 18 and 26 days postconception. Closure of the neuropores occurs at the end of this developmental process around day 26.[12–14] The current hypothesis is that there are multiple local (possibly five) neural tube closure sites. Primary neurulation begins with neural induction, leading to the appearance of the neural plate, a thickened dorsal midline ectodermal structure. The neural folds converge toward the midline and fuse, forming the neural tube on day 22 in the future cervical/occipital boundary. Initially, the wall of the neural tube is composed by a columnar pseudostratified neuroepithelium. The skull base and facial skeleton are derived from the neural crest.[12–14] The pituitary diverticulum of the stomodeum roof (oral ectoderm) will give rise to the adenohypophysis. The neurohypophyseal diverticulum of the diencephalon floor (neuroectoderm) will give rise to the neurohypophysis. Adenohypophyseal tissue can be trapped anywhere along the path followed by Rathke's pouch during fetal development.[12–14] Two general patterns of neural tube malformation are encountered. In the first, there is a failure of the developing neural tube to close properly, with secondary disruption of the axial mesoderm, which determines abnormal neuroectodermal tissue protruding through a secondary defect in mesenchymal structures.[12–14] In the second pattern, the primary embryonic defect is related to the development of the axial mesoderm, and the neural tube is closed. During these development cellular events, including migration, proliferation and differentiation, abnormal ectoderm tissue can be associated with the future development of midline ECs. Neural tube defects include meroencephaly, craniorachischisis, occult spina bifida, meningomyelocele, encephalocele, and myeloschisis.[12–14] Unfrequently, CNS ECs arise from implants of epithelium carried into the meninges during percutaneous aspiration of the subdural or subarachnoid space. A proportion of spinal ECs, especially those in the lumbosacral region, occur in conjunction with spina bifida or diastematomyelia. Unlike dermoid cysts, ECs often occur laterally, without a preference for midline sites.[3,4,12–18]

Intracranial ECs account for only 1% of all intracranial tumors, if suprasellar examples are excluded. The cerebellopontine angle and parapontine regions are the most common intracranial site for ECs.[2,3,8,11,15–17] Epithelial rests may be transplanted to regions such cerebellopontine angle by the lateral migrating otic capsule or developing neurovasculature. Intraspinal lesions are less common. Rarely, ECs are located in the cranial diploe of the middle ear region or frontal bone, where they present as a lytic defect.[2,3,7,8,11,15–18]

The authors reported a female patient with clinical complaint of amenorrhea due to a sellar EC. Symptoms associated to sellar EC can be related to a slow growing mass effect, and include focal neurologic deficits or nonlocalizing signs such as headache, visual alterations, and pituitary dysfunction.[15,18–22] Epidermoid cysts tend to surround adjacent structures, and its rupture can produces chronic inflammation of the leptomeninges or ependyma.[15,18–21] Sellar/suprasellar ECs can determine disturbances in the release and/or production of hormones, because the compressive effect of the process may affect the physiology of the pituitary gland or even determine hypothalamic disorders. Since any hypothalamic hormone can be synthesized in more than one hypothalamic nucleus, and a single nucleus may express several hormones, different clinical signs can be identified.[19] Alterations in the suprachiasmatic nucleus of the hypothalamus can be associated with decrease in gonadotropin release.[19] Lesions of the supraoptic nuclei can decrease the synthesis of oxytocin and vasopressin. Damage of the ventromedial nucleus results in obesity; conversely, destruction of the ventrolateral nucleus causes anorexia and cachexia. The arcuate (infundibular) nucleus plays a major role in the modulation of anterior pituitary function. The paired medial and lateral nuclei are associated with autonomic function, in special temperature control and olfaction.[19] The posterior nucleus

has been implicated in temperature regulation, and its large neurons are thought to be the source of hypothalamic efferents, which descend to the reticular formation of the brainstem. Increase of prolactin serum levels can be attributed to injury of the arcuate nucleus, which controls the secretion of dopamine (an inhibitor of prolactin secretion).[19] Hyperprolactinemia exerts an inhibitory activity on the positive feedback effect of estradiol on gonadotropin-releasing hormone (GnRH) secretion. Increase of prolactin seems to depend on decrease of factors that inhibit prolactin secretion, such as dopamine produced by the arcuate nucleus of the hypothalamus (probably compressed by EC). In females, hyperprolactinemia can determine galactorrhea, oligomenorrhea/amenorrhea and infertility.[19]

Sellar ECs determining hypothalamic hyperfunction syndromes can be related to early puberty, ectopic production of hypothalamic hormones, and inappropriate secretion of antidiuretic hormone. Hypofunction syndromes can be associated to different endocrine disorders like hypothalamic dwarfism, diencephalic syndrome, obesity, hypothalamic hypogonadism, amenorrhea, diabetes insipidus, and hypopituitarism.[19] Other alterations include changes in appetite and thirst, hypothermia, hyperthermia, disorders in the pattern of sleep and wakefulness, behavioral disorders, visual disturbances, spasticity, hyperreflexia, ataxia, and uncoordinated movements.[19]

On CT, most sellar ECs are circumscribed, nonenhancing, extraaxial lesions, which can exhibit calcification areas around 10% of cases. Magnetic resonance imaging findings include variable intensity on T1-weighted images, and hyperintensity on fluid-attenuated inversion recovery (FLAIR) and T2-weighted images.[1,4,6,10,15,17,19,20] On gross, sellar ECs are a pale-gray, uniloculated, translucent lesion, which can measure from a few millimeters to over 4 cm in diameter.[1,4,6,9,15,16,21,22] At microscopy, ECs are covered by a mature keratinizing squamous epithelium, and the lumen is occupied by lamellae of keratin. No evidence of atypias can be found and the wall is constituted by connective tissue. Mitotic figures are very rare and foreign body giant cell reaction is present in cases of a ruptured cyst. Sellar EC shows positive immunoexpression for keratins and negative pattern for glial fibrillary acidic protein (GFAP) and synaptophysin.[1,4,6,9,15,20,22]

In the sellar/suprasellar region, the differential diagnosis of EC includes dermoid cysts, craniopharyngioma, enterogenous cyst, neuroglial cyst, arachnoid cysts, endodermal cyst, Rathke cleft cyst with extensive squamous metaplasia, eventually metastatic well differentiated squamous cell carcinoma, and mature teratoma.[4–6,9,11,15,20,23,24] Dermoid cysts (DCs) arise more commonly in the midline of infants, being related to fontanel, the fourth ventricle, or the spinal canal. Dermoid Cyst (DM) exhibit a thick wall and contain adnexal structures, such as hair follicles and sebaceous glands.[4–6,10,13,20–22] Adamantinomatous craniopharyngioma exhibits a thick, complex, palisaded epithelium, while papillary craniopharyngioma shows a thick epithelium disposed in irregular papillae with fibrovascular core. Papillary craniopharyngioma lacks keratohyalin granules and anucleate squames. Mature teratoma are more frequently solid masses constituted by cartilaginous tissue, sebaceous gland, and mature dermis and epidermis.[4–6,10,15,21,24,25]

The curative treatment for sellar ECs is gross total surgical removal by transsphenoidal approach, but the presence of dense adherence of the lesion to the adjacent structures can limit the complete resection of the cyst.[2–4,8,16,25] The most common postoperative complications are diabetes insipidus, endocrine disturbances, and chemical meningitis, due to leakage of keratin into the cerebral spinal fluid (CSF) pathways.[2–4,6,8,16] After a follow-up of 9 months, no signs of recurrence or endocrine disturbances were noted.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Intracranial Subdural Hematoma after Spinal Anesthesia: Report of Two Cases with different Outcomes

Hematoma subdural intracraniano após raquianestesia: relato de dois casos com diferentes desfechos

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Abstract

Spinal anesthesia is a technique commonly used for local anesthesia and in obstetric surgeries. Rarely, the formation of an intracranial subdural hematoma (SDH) may result from spinal anesthesia, constituting a serious condition that often leads to severe neurological deficits. The presentation and course of this pathology may occur in a completely different way, which makes its diagnosis and management difficult. In the present article, the authors report two cases of patients with intracranial SDH after spinal anesthesia with completely different presentations and outcomes, demonstrating the variability of the manifestations of this condition. A quick review of key points of its pathophysiology, symptomatology, diagnosis, and treatment was also performed.

Keywords
- subdural hematoma
- spinal anesthesia
- intracranial bleeding
- anesthesia complication.

Resumo

Raquianestesia é uma técnica comumente utilizada para procedimentos locais e cirurgias obstétricas. Raramente, a formação de um hematoma subdural intracraniano pode ser resultado de uma raquianestesia, constituindo uma condição grave que frequentemente leva a déficits neurológicos severos. A apresentação e o curso desta patologia podem ocorrer de formas completamente distintas, fato que dificulta seu diagnóstico e manejo. No presente artigo, os autores relatam dois casos de pacientes que desenvolveram um hematoma subdural intracraniano após raquianestesia com apresentações e desfechos completamente diferentes, demonstrando a variabilidade das manifestações desta condição. Uma rápida revisão dos pontos-chave da fisiopatologia, da sintomatologia, do diagnóstico e do tratamento também foi realizada.

Palavras-chave
- hematoma subdural
- raquianestesia
- hemorragia intracraniana
- complicação anestésica

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Introduction

Spinal anesthesia is a technique commonly used for local anesthesia and in obstetric surgeries. It is considered a safe procedure and has a complication rate of ~ 0.05%.[1,2] The most commonly reported complication is postdural puncture headache (PDPH), characterized by its short duration and its relation to postural changes.[3,4] This complication usually has its resolution spontaneously, without further repercussion for the patient. However, more rarely, the formation of an intracranial subdural hematoma (SDH) may result from spinal anesthesia, constituting a serious condition and often leading to severe neurological deficits.[4,5]

The authors report two cases of intracranial SDH after spinal anesthesia that had completely different outcomes, suggesting the variability of the course of this rare complication. A review of the literature, presenting the key points of its clinical course, diagnosis, and treatment are discussed in the present article.

Case Report

Case 1

A 29-year-old female, with no previous comorbidities and no history of use of antiplatelet or anticoagulant medication, was submitted to spinal anesthesia for a cesarean delivery. The procedure had no complications and the patient was discharged in good general condition.

About 48 hours after hospital discharge, the patient sought emergency care due to a sudden onset of a left hemicranial headache of moderate intensity that was associated with nausea and vomiting, which improved in dorsal decubitus. Due to the clinical suggestion of intracranial hypotension, postspinal headache was suspected and she was recommended to rest, receiving simple analgesics and being released to go home.

However, after 72 hours, she presented back to the emergency department due to the persistence of the symptoms. Due to the unusual course of the case, a computed tomography (CT) was requested, which showed no abnormalities, and the patient was released again.

About 2 weeks later, she sought our service with worsening of the headache, this time without the postural features, associated with weakness of the right side of the body and speech disorders. The neurological physical examination demonstrated expressive dysphasia, muscle strength grade 4 in the right upper limb, and grade 4+ in the lower right limb, according to the modified scale of the Medical Research Council (mMRC), and mild right hyperreflexia. A magnetic resonance imaging (MRI) exam of the skull was performed, demonstrating a left parietal subdural collection, with a slight mass effect characterized by deletion of the sulci and of the adjacent cortical rotations, without shifting of the midline structures (►**Fig. 1**). Conservative treatment with analgesics, dexamethasone, and phenytoin was indicated.

The patient progressed well, without sequelae, and was discharged 3 days later on dexamethasone and phenytoin. At the last follow-up, 18 months after discharge, the patient presented no symptoms. The MRI performed at the follow-up demonstrated a complete resolution of the subdural collection (►**Fig. 2**).

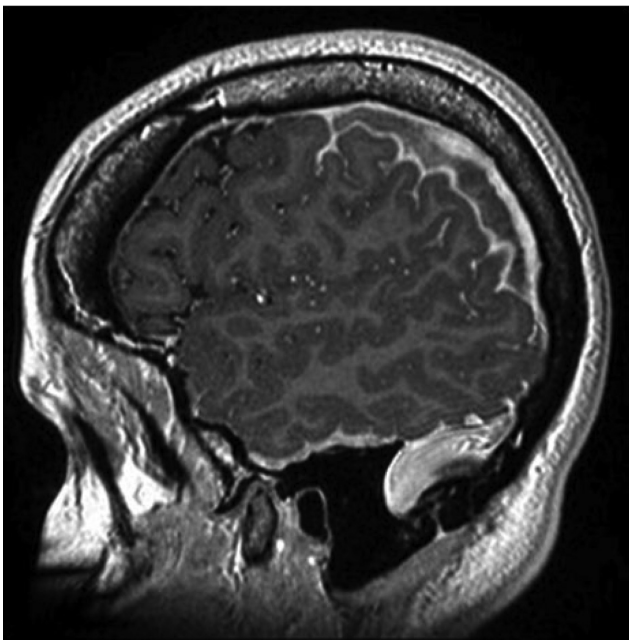

Fig. 1 Magnetic resonance imaging of the skull, T1-weighted, sagittal plane, 14 days after spinal anesthesia, demonstrating left subacute subdural hematoma.

Case 2

A 37-year-old female, with no previous comorbidities and no history of use of antiplatelet or anticoagulant medication, was submitted to spinal anesthesia for a cesarean delivery. The procedure was performed without intercurrences;

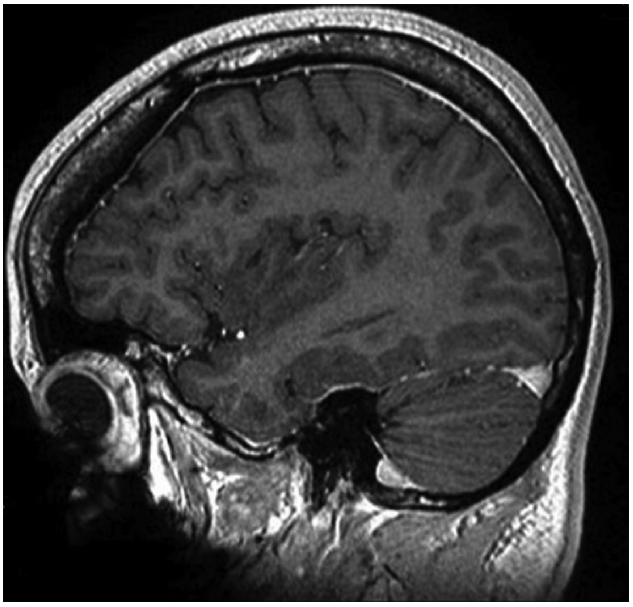

Fig. 2 Magnetic resonance imaging of the skull, T1-weighted, sagittal plane. Section evidencing complete reabsorption of the hematoma 18 months after the diagnosis.

however, 12 hours after hospital discharge, the patient presented with a right hemicranial headache of strong intensity and vomiting associated with altered level of consciousness: mental confusion and drowsiness. The patient was submitted to a CT of the head, which demonstrated a hematoma in the subdural space in the right frontotemporal region. The collection exerted mass effect and distorted the ventricular and brainstem anatomy.

Faced with the diagnosis of an acute SDH that generated an important neurological deficit, the patient underwent surgical drainage of the clot by burr holes. The procedure was performed without intercurrences; but, in 24 hours, the patient presented worsening of the level of consciousness and anisocoria. A new CT revealed the presence of a large hemispheric edema ipsilateral to the lesion that increased the shifting of the midline structures (►**Fig. 3**).

Due to the acute scenario of neurological deterioration, the patient was submitted to emergency decompression craniectomy and was transferred to the intensive care unit (ICU) (►**Fig 4**). The postoperative period was marked by slow recovery of motor and cognitive functions. After 18 days, cranioplasty was performed, which occurred without complications.

The patient was released after 1 week and remained with mild changes in cognitive functions in the follow-up.

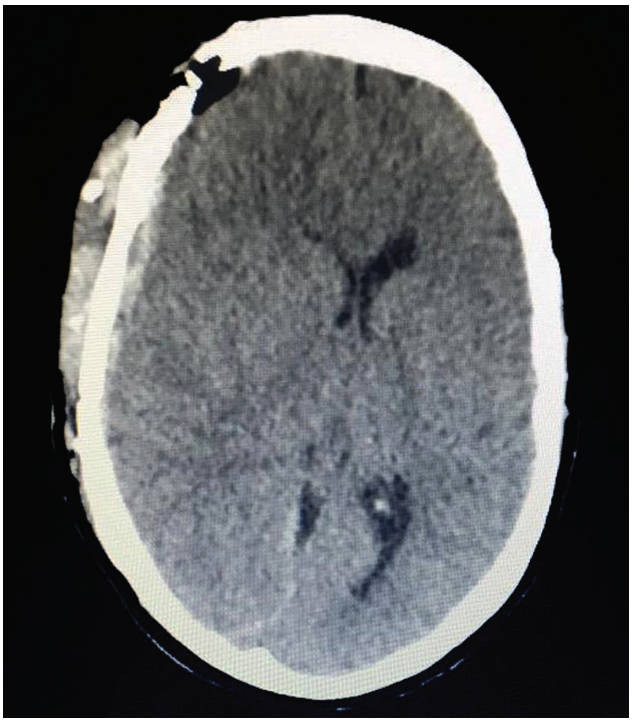

Fig. 3 Computed tomography of the skull, axial plane. Computed tomography before craniectomy. Presence of a large right hemispheric edema that increased the shifting of the midline structures and distorted the ventricular anatomy.

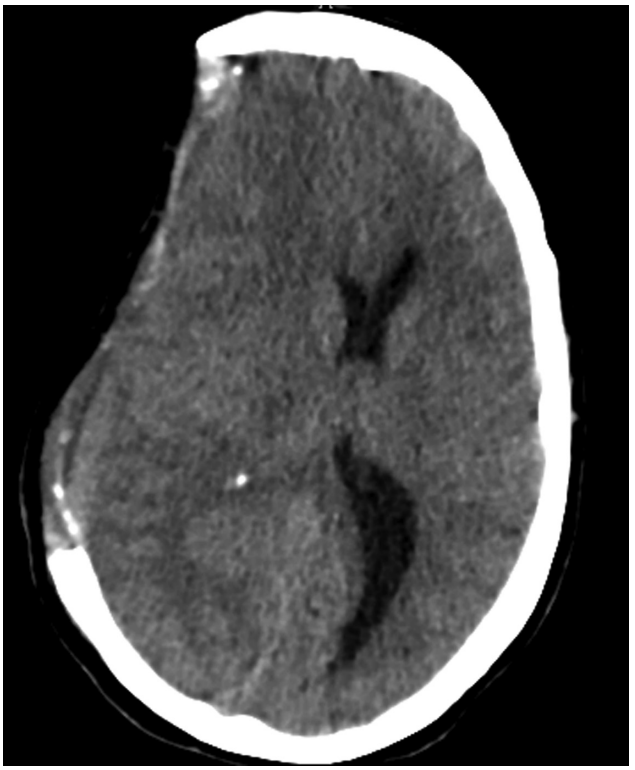

Fig. 4 Computed tomography of the skull, axial plane. Aspect of the immediate postoperative period after decompressive craniectomy, demonstrating persistent signs of shifting of the midline structures.

Discussion

The most common complication of spinal anesthesia is PDPH, and its pathophysiology involves a process of cerebrospinal fluid (CSF) hypotension in the cranial subarachnoid space. This hypotension generates displacement and dural traction that depolarizes the sensitive neurons of the meninges and, hence, the algic process.[6,7] Headache usually lasts for a few days and resolves spontaneously as the CSF is renewed.[7]

The venous drainage of the brain is made through short venous trunks called bridge veins, which pass directly from the brain to the dural sinuses, adherent to the internal plank of the skull.[8] More rarely, CSF hypotension may persist and produce traction and rupture of these veins of the subdural space, leading to the formation of hematomas between the dura mater and the arachnoid space.[6,7] Hypertension induced by surgical stress may be another factor that contributes to the rupture of the bridge vessels.[4]

Intracranial SDH may have different presentations, and often the symptoms are similar to those of PDPH, which makes the initial diagnosis difficult. According to a review of literature of 21 intracranial SDH cases after puncture of the dura mater, the earliest diagnosis occurred 2 days after the procedure, and the latest occurred after 20 weeks.[6] This variability in the timing of the diagnosis can be explained by the nonspecific symptoms that the SDH may present.

The symptoms depend on age, on the level of brain atrophy, on the size of the clot, on the topography, and on the adjacent structures involved. Thus, velocity of the clot formation and previous comorbidities of the patient may have a role in the clinical manifestations.[4,9]

In addition, factors related with the puncture technique (multiple attempts or inadvertent dural puncture during the

procedure), with the size of the needle, and with the thickness of the dura seem to change the complication rates in this scenario.[10,11] Finally, the use of anticoagulants in the pre- or postoperative period can lead to higher rates of complications in spinal anesthesia.[7]

Often, SDH can present with contralateral paresis and paresthesias, seizures, change of level of consciousness, and severe headache that are not related to orthostatism.[7] Secondly, there may be intensification of headache due to intracranial hypertension syndrome, which may be associated with nausea, vomiting, papilledema, and signs of radicular irritation.[4]

In suspicion of an intracranial SDH (by the presence of any of the symptoms cited above), a neuroimaging technique should be performed to identify the nature of the neurological dysfunction. Computed tomography of the head is the most widely used imaging study owing to its speed, relative simplicity, widespread availability, and good capacity to identify intracranial hematomas. Magnetic resonance imaging is also a good imaging technique for the detection of small, tentorial, and interhemispheric SDHs.[12]

Our first case presented with an insidious hematoma that generated important symptoms in the patient. The diagnosis was made 3 weeks after the anesthetic procedure, and conservative management was chosen. The outcome was favorable: the patient did not present neurological symptoms in the follow-up period, and control imaging evidenced complete reabsorption of the hematoma.

However, our second case had an unfavorable evolution, presenting important neurological symptoms, such as change of level of consciousness and shifting of the midline structures. Two surgical interventions were performed, including an emergency craniectomy due to quick neurological deterioration.

Our cases illustrate the difficulty of the diagnosis of intracranial SDH after spinal anesthesia due to its variability of presentations and course. The same etiologic agent may be treated nonsurgically without major complications, but may require neurointensive care due to severe structural damage to the brain.

The choice of treatment is based on the size of the hematoma and on the patient's clinic. Small clots, which cause few symptoms that do not course with shifting of the midline structures in neuroimaging, can be monitored conservatively and do not require surgery. In a review of 35 cases of intracranial SDH following spinal anesthesia, 27 patients (77%) required surgical intervention, 4 (11%) developed neurologic deficits, and 4 (11%) died.[4] The present review showed that this type of complication may have a broad spectrum of possible outcomes, which are difficult to predict in its early stages.

Conclusion

Due to the potential lethality of this condition, intracranial SDH after spinal anesthesia should be identified and treated as early as possible. Situations that can alert the physician to suspect this condition include: postural headache for >1 week or changes in this pain to nonpostural headache, or the development of other neurologic signs or symptoms besides the headache. In this scenario, a CT or an MRI are mandatory for a proper evaluation of this disease.

Conflicts of Interests

The authors have no conflicts of interests to declare.

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Four-rod Technique Stabilization after Pedicle Subtraction Osteotomy (PSO) for the Treatment of Thoracolumbar Hyperkyphosis Secondary to Pott Disease: A Two-Year Follow-Up Case Report

Técnica das quatro hastes após osteotomia de subtração pedicular para o tratamento de hipercifose toracolombar secundária à doença de Pott: Relato de caso de dois anos de seguimento

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Abstract

Pedicle subtraction osteotomy (PSO) is a powerful tool for the management of sagittal misalignment. However, this procedure has a high rate of implant failure, particularly rod breakages. The four-rod technique diminishes this complication in the lumbar spine. The aim of the present study is to provide a case report regarding PSO and four-rod technique stabilization in the treatment of short-angle hyperkyphosis in the thoracolumbar (TL) junction. The authors describe the case of a patient with TL hyperkyphosis secondary to spinal tuberculosis treated with L1 PSO and fixation with a four-rod technique. There were no major surgical complications. The self-reported quality of life questionnaires (the Short-Form Health Survey 36 [SF-36] and the Oswestry disability index) and radiological parameters were assessed preoperatively, as well as 6, 12 and 24 months after surgery, and they showed considerable and sustained improvements in pain control and quality of life. No hardware failure was observed at the two-year follow-up.

Keywords
- pedicle subtraction osteotomy
- kyphosis
- spinal tuberculosis
- four-rod technique
- postoperative complications
- thoracolumbar spine

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Resumo

A osteotomia de subtração pedicular (OSP) é uma ferramenta importante no manejo de doenças com desalinhamento sagital. Entretanto, este procedimento apresenta altas taxas de falência do instrumental, em especial a quebra de hastes. A técnica de fixação com quatro hastes reduz essa complicação na região lombar. O objetivo deste estudo é relatar um caso de hipercifose na transição toracolombar (TL) tratado com OSP e estabilização com a técnica das quatro hastes. Os autores descrevem o caso de uma paciente com hipercifose TL secundária a tuberculose espinhal, tradada com PSO e fixação com a técnica das quatro hastes. Não houve complicações cirúrgicas maiores. Os questionários autorrelatados de qualidade de vida (Short-Form Health Survey 36 [SF-36] e índice de incapacidade de Oswestry) e os parâmetros radiográficos foram avaliados no pré-operatório e 6, 12 e 24 meses após a cirurgia, e demonstram considerável e estável melhora na qualidade de vida e no controle da dor da paciente. Não houve falência da instrumentação após 2 anos de seguimento.

Palavras-chave

- osteotomia de subtração pedicular
- cifose
- tuberculose da coluna vertebral
- técnica das quatro hastes
- complicações pós-operatórias
- coluna toracolombar

Introduction

Pedicle subtraction osteotomy (PSO) is a powerful tool for the management of sagittal misalignment, and it can restore angular sagittal alignment up to 30° to 40°.[1] However, rod breakage after PSO is common, occurring in 15.8 to 25% of patients who undergo this procedure.[2–7] Most of these instrumental failures (89%) occur at the index level vertebra or in adjacent vertebras. Furthermore, 71% of rod breakages happen in the first 12 months after the corrective surgery.[5] Gupta et al (2017)[3] reported the use of a 4-rod technique in lumbar PSO for the treatment of adult spinal deformities that had considerably reduced the rate of rod breakage.

The aim of the present study is to present the case of a patient with late thoracolumbar (TL) junction hyperkyphosis secondary to spinal tuberculosis that was successfully managed with PSO followed by four-rod technique stabilization.

Case Report

A 64-year-old woman was referred with severe mechanical low back pain that progressively increased mainly over the previous 6 months, and that was associated to pain in the buttocks and posterior thighs, without radicular trajectory. She was unable to stand or walk for more than 20 minutes. Ten years before she had been treated for spinal tuberculosis (also known as Pott disease) in the TL junction according to the Brazilian guidelines, with successful remission.[8]

Neurological Examination

The patient presented a forward trunk shift while standing or walking, and a TL junction kyphosis on inspection. On palpation, there was severe and painful paravertebral muscle contracture in the thoracic and lumbar regions. She reported severe back pain during assisted lumbar extension or rotation that was more intense in the lumbar region rather than in the apex of the deformity. The neurological examination was normal, except for bilateral hypoactive Achilles tendon reflexes. The Oswestry disability index (ODI) was of 32%, a finding compatible with moderate disability. The Short-Form Health Survey 36 (SF-36) physical and mental scores were 0 and 40 respectively.

Diagnostic Imaging

The computed tomography (CT) of the lumbar spine revealed TL kyphosis, with a wedge-shaped L1 vertebral body and sclerotic bone from T10 to L3 (►**Fig. 1b**). Narrowing of the spinal canal was observed at L1 and L2 by CT and magnetic resonance imaging (MRI), which also showed conus medullaris and cauda equina encroachment (►**Fig. 1b-e**). Scoliosis radiographs displayed a short-angle kyphosis with apex at L1 (T12L2 Cobb angle = 34°), thoracic hypokyphosis (T4T12 Cobb angle = 22°) and lumbar hyperlordosis (L1S1 Cobb angle = 69°). The spinopelvic parameter values were: pelvic incidence, 48°; pelvic tilt (PT), 13°; sacral slope, 35°; and sagittal vertical axis (SVA), +1 cm (►**Table 1**; ►**Fig. 2a** and **c**). Surgical treatment was indicated due to refractory mechanical back pain secondary to TL hyperkyphosis and associated with lumbar hyperlordosis. Informed consent for the procedure was obtained from the patient.

Surgical Technique

The patient underwent an L1 PSO and spinal stabilization with the four-rod technique.

Positioning. After induction of general anesthesia, the patient was placed in prone position. Intraoperative neurophysiological monitoring (IONM) was not used.

Exposure. Through a midline incision, the paraspinal muscles were dissected subperiosteally from the spinous processes to the tip of the transverse processes from T9 to L4.

Instrumentation. The pedicle screws were inserted four levels above and three levels below the wedge vertebra (L1) under the guidance of fluoroscopy. In T9, T10, T11, L3 and L4, the entry points were in the superior facets. In T12 and L2, the entry points were in the mammillary processes, and their trajectories were of 22° to 30° medial to the sagittal plane, rather than the usual 0° to 10° at these levels. Thus, the screw heads of the levels adjacent to L1 were more lateral and slightly deeper than the cranial and caudal ones (►**Fig. 3d**).

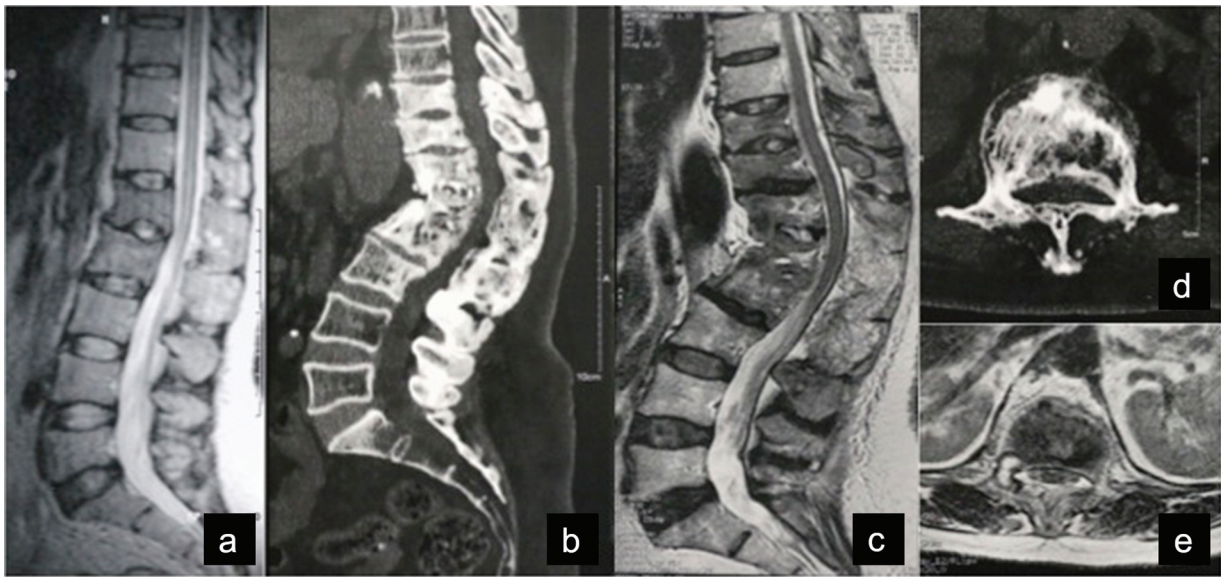

Fig. 1 A 64-year-old female was diagnosed with Pott disease and treated conservatively. The lumbar spine magnetic resonance imaging (MRI) exam – T2 sequence – shows a hypointense signal at L1 and L2 (a). Ten years later, the computed tomography (CT) and the MRI (b, c, d and e) show thoracolumbar (TL) junction kyphosis, bone sclerosis from T10 to L3, and spinal canal narrowing.

Table 1 Preoperative, Postoperative and Follow-Up Values of the Sagittal Balance Parameters

Sagittal balance parameter	Preop	6 months po	12 months po	24 months po
T4-T12 thoracic kyphosis (°)	+22°	+41°	+43°	+40°
T12-L2 angle (°)	+34°	+3°	+6°	11°
L2-S1 lumbar lordosis (°)	−69°	−57°	−55°	−58°
Sagittal vertical axis (cm)	+1	+1	+1	+1
Pelvic tilt (°)	13°	–	10°	8°

Abbreviations: po, postoperative; preop, preoperative.

Pedicle subtraction osteotomy. The osteotomy was performed at L1 as previously described.[9,10] The posterior elements of L1, including the pedicles and transverse processes, were removed, as well as the spinous process and the caudal half of the T12 lamina. The nerve roots of T12 and L1 were exposed bilaterally. Finally, a partial wedge resection of the posterior vertebral body of L1 was performed mainly with osteotomes, and completed with rongeurs and a drill. In this step, the fluoroscopy was paramount to delineate the directions of the osteotomes, as well as the angle of the bone fragment to be removed (►**Fig. 3a** and **b**; ►**Fig. 4a**). Incidental durotomy occurred, but it was promptly sutured. The disks above and below remained intact. Before the closing procedure, a temporary rod was used to avoid translation in one side when the other side of the osteotomy was done.[11]

Kyphosis correction. Closure of the osteotomy was performed by bilateral alternating compression maneuvers over the screw heads of T12 and L2, fixed with short rods (►**Fig. 3c**; ►**Fig. 4b** and **c**). During the PSO, hemostasis with bone wax was avoided on the bone defect surfaces to prevent pseudarthrosis. Subtle compression of the left L1 nerve root was noticed soon after the osteotomy closure, and decompression was readily performed.

Stabilization, grafting and closure. Final stabilization was obtained with long titanium rods (6.0 mm) and caps inserted and tightened from T9 to L4, with satisfactory correction of the TL junction kyphosis. After decortication, local bone grafts were placed posterolaterally. To stiffen the construct, cross-links were used to connect the long rods to one another and to connect the short rods to the long ones ipsilaterally. Intraoperative fluoroscopy showed adequate placement of implants and correction of TL kyphosis (►**Fig. 3c**, **d** and **e**; ►**Fig. 4c** and **d**). Intrawound vancomycin powder (2 g) was used.[12–14] The wound was closed in layers, and a closed suction drain was left in place for 48 hours. The operating time was 515 minutes, and the patient received a packed red blood cell transfusion (950 mL).

Follow-up

The length of stay of the patient in the hospital was of 5 days. The patient presented bilateral meralgia paresthetica despite the protection of the iliac crests with cotton paddles. A TL vest was not recommended. Sixteen days postoperatively, she complained of moderate back pain and severe meralgia paresthetica, without motor function compromise. An examination revealed a superficial wound infection with no fluid leakage, which was solved with oral antibiotics for 3 weeks. The pain was treated with pregabalin (150 mg per day) for 6 months, and codeine (30 mg every 4 hours as needed).

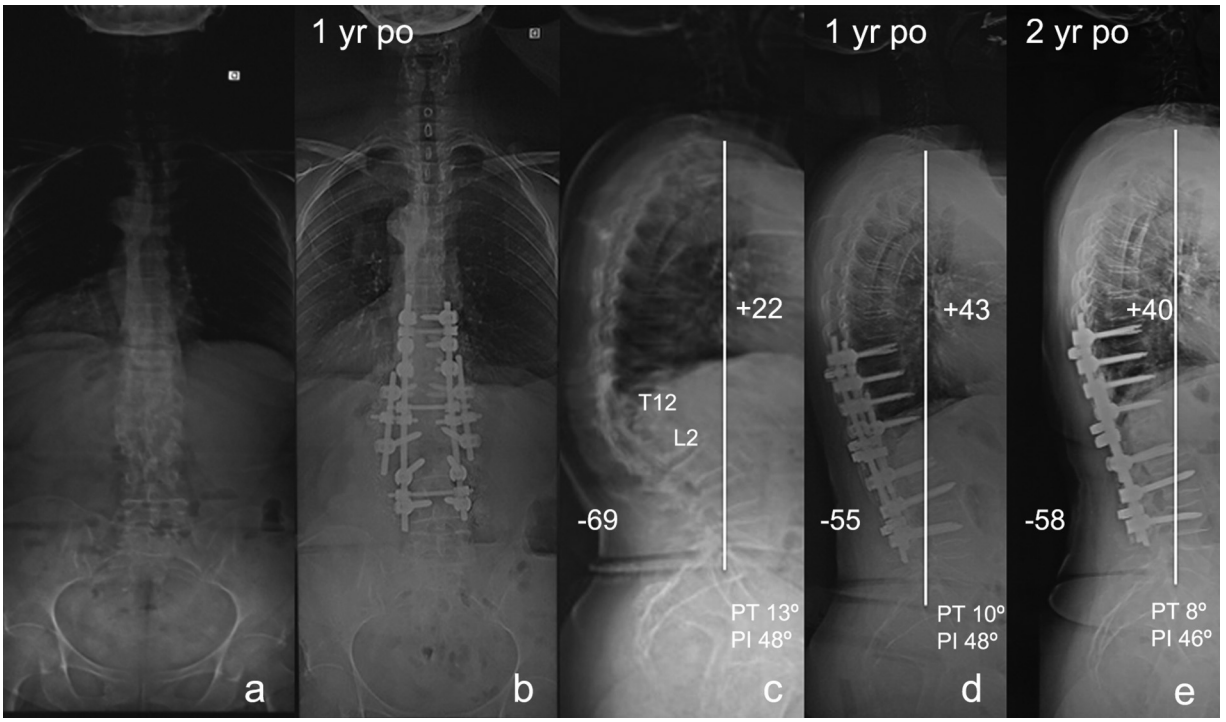

Fig. 2 Preoperative standing radiographs (a and c) show short angular kyphosis with apex at L1 (Cobb angle: 34°) and normal sagittal vertical axis (SVA). After pedicle subtraction osteotomy (PSO) at L1 using 4-rod fixation, the thoracolumbar (TL) transition angle was restored (Cobb angle: 11° at the 2-year follow-up), and the compensatory thoracic hypokyphosis and lumbar hyperlordosis were solved.

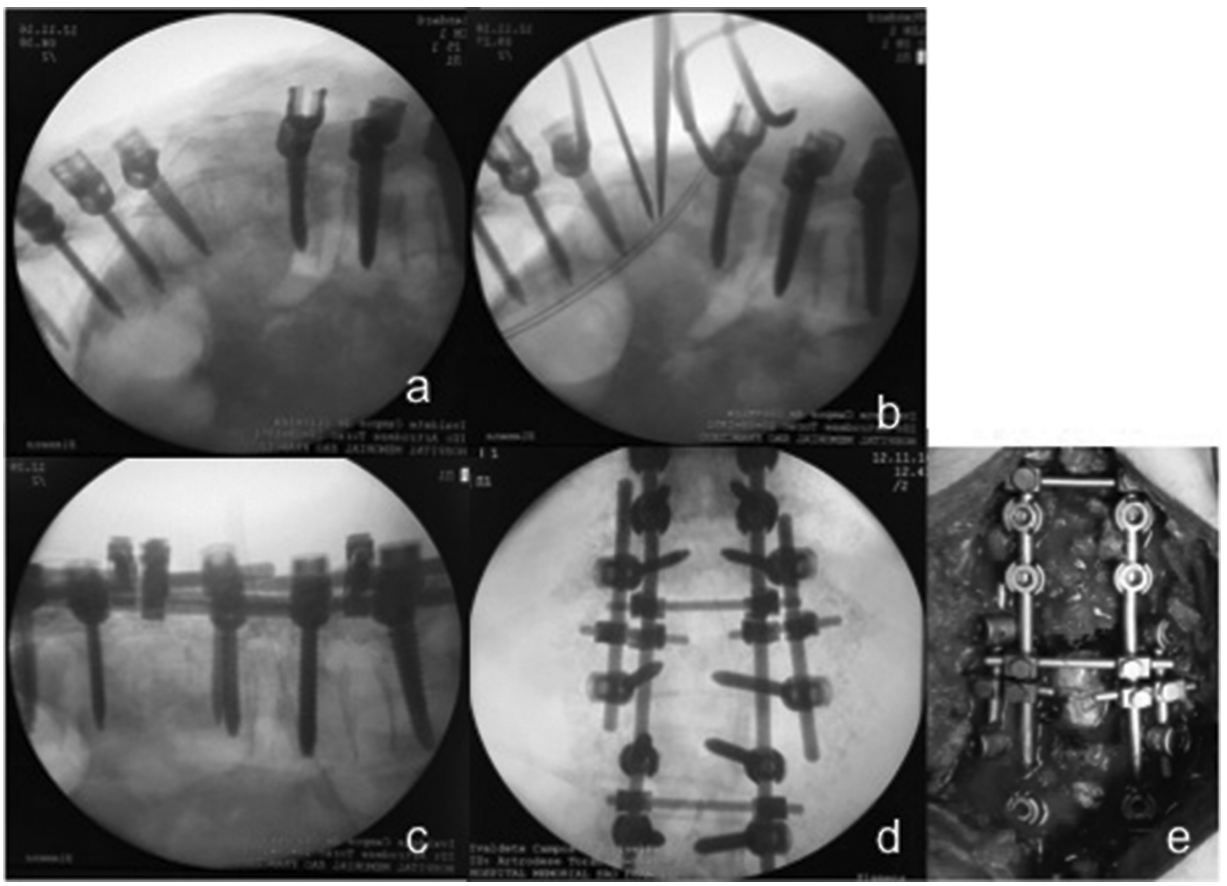

Fig. 3 Pedicle screws were inserted 4 levels above and 3 levels below the wedge vertebra (L1). In T12 and L2, the entry points were lateral at the junction of the superior facet and transverse processes (a). Pedicle subtraction osteotomy (PSO) was performed at the apex (L1) of the kyphosis and closed with bilaterally alternating compression maneuvers over the screw heads of T12 and L2, fixed with short rods. Final stabilization was obtained with long rods (c, d and e).

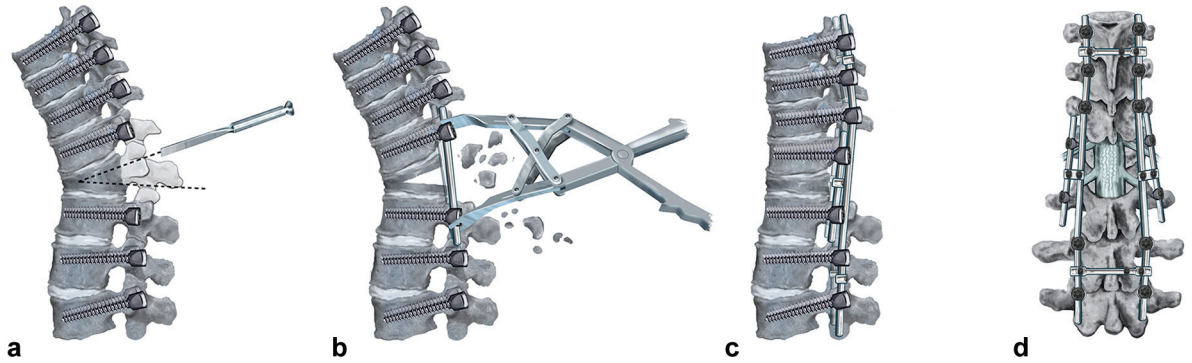

Fig. 4 Schematic illustrations of pedicle subtraction osteotomy (PSO) and four-rod technique stabilization to treat thoracolumbar hyperkyphosis. First, the pedicle screws are placed, then the posterior arches of T12 and L1, as well as the L1 pedicles, are removed; finally, the PSO is performed (a). Compression maneuver over the T12 and L2 screws heads to close the bone defect and correct the hyperkyphosis, followed by short rods locking, and then long-rod fixations (b and c). Posterior 3D image showing the final aspect of the instrumentation (d).

Radiological Outcomes

Standing scoliosis radiograph images 6, 12 and 24 months after the procedure showed normal sagittal alignment parameters, without compensatory mechanisms and no signs of pseudarthrosis or implant failure (►**Table 1** and ►**Fig. 2**). Considerable improvements were observed in the thoracic kyphosis (+22° versus +40°) and lumbar lordosis (−69° versus −58°) when the images obtained 24 months after the surgery were compared with the preoperative images (►**Table 1**, ►**Fig. 2**).

Clinical Outcomes

Six months postoperatively, the patient reported considerable improvement in both back pain and meralgia paresthetica, with sporadic use of analgesic drugs. Self-reported outcome questionnaires showed significant improvement at 6 months, which was maintained 12 and 24 months postoperatively. At the final follow-up, she reported considerable spine pain relief and increase in quality of life, despite feeling unilateral hip joint pain, which was managed conservatively (►**Table 2**).

Discussion

Thoracolumbar hyperkyphosis may cause sagittal misalignment, which is characterized by a forward dislocation of the body's gravitational center that elicits compensatory mechanisms, mainly thoracic hypokyphosis and lumbar hyperlordosis due to paravertebral muscle contractures, resulting in increased energy expenditure and chronic back pain.[15–19] Secondary trunk extension also overloads the facet joints, resulting in a painful condition as well.[17,19,20] Thus, restoration of the sagittal alignment counteracts this process and relieves discomfort.[21]

Table 2 Clinical Assessment by Self-Reported Outcome Questionnaires: Preoperative, 6 Months and 12 Months Postoperatively

Parameter	Evaluation period			
	Preop	6 months po	12 months po	24 months po
SF-36 (physical)	0	100	100	75
SF-36 (mental)	40	84	84	84
ODI	32%	0%	18%	6%

Abbreviations: ODI, Oswestry disability index; po, postoperative; preop, preoperative; SF-36, Short-Form Health Survey 36.

The reported case showed hyperkyphosis at the TL junction, the most common site affected by spinal tuberculosis.[22–24] According to the global alignment concept, the patient had *hidden sagittal imbalance*, as shown by the thoracic hypokyphosis (+22°), and lumbar hyperlordosis (−69°), which was associated with a preoperatively *balanced* pelvis (sagittal vertical axis (SVA): 1 cm; PT: 13°).[25]

Surgery is best indicated when there is significant pain associated with a kyphotic segmental deformity exceeding 20°.[26] Surgical treatment is also recommended if there is progressive neurological deficit secondary to canal encroachment and/or spinal cord tethering at the apex of the kyphosis, usually in the thoracic spine.

Different types of osteotomy might be necessary to treat hyperkyphosis.[1,9] The decision about which osteotomy to use depends on the anatomy of the lesion, the amount of angular correction needed to restore global spine alignment, and the type of curve (long or short). Ponte osteotomies (Schwab 2) at multiple levels allow corrections of 5° to 10° per level, and are recommended mainly for long kyphotic curves. A PSO, with or without superior diskectomy (Schwab 4 and 3 respectively), enables corrections of 30° to 45°, and is indicated to address short-angle hyperkyphosis.[1,9,27–31] However, in cases of severe kyphosis, mainly higher than 60°, vertebral column resection might be needed.[32–37] Thus, through a single posterior approach, a three-column osteotomy (PSO or vertebral column resection [VCR]) may enable the correction of sagittal misalignment in pathologies such as posttraumatic kyphosis, postinfection kyphosis, congenital deformities, adult spinal deformities, ankylosing spondylitis, and iatrogenic flat back.[17]

Gupta et al (2017)[3] have described a new 4-rod technique in which all rods are connected to pedicle screws in cases of lumbar PSO (L2, L3 and L4) for the treatment of adult spinal deformities. The two short rods are used to stabilize the

superior and inferior vertebras that are adjacent to the osteotomy level. The two other rods connect the remaining levels involved in the instrumentation (holding rods). None of the 29 patients treated with the Gupta technique experienced rod breakage during a 5-year follow-up. In comparison, the 4-rod technique decreased the rate of implant failure after PSO from 25% to 0 during a 5-year follow-up ($p = 0.008$; Gupta et al, 2017).[3]

In the TL junction, PSO has been successfully used to correct posttraumatic kyphosis as well as Pott-disease deformities. Significant improvement in clinical outcomes has been achieved after PSO for the treatment of TL hyperkyphosis secondary to tuberculosis, a result that has been related to hyperkyphosis correction and restoration of normal sagittal alignment.[29,33] In the present case we used the 4-rod pedicle-based technique to stabilize a short-angle TL kyphosis after L1 PSO.

Pseudarthrosis and implant failures (mainly rod breakage) are frequent complications after a PSO, since the correction of deformity places the implants under huge mechanical stress.[3,11,29,31,34,38–40] There are other strategies to improve the construct biomechanical stability and bone fusion to prevent rod breakage.

A large gap remains between the upper and lower transverse vertebral processes after PSO. Thus, autologous bone grafting should completely fill the posterolateral sites bilaterally. Furthermore, interbody implants with autografts in the cranial and caudal intervertebral disc spaces can be added to improve arthrodesis.[41] However, they do not seem to reduce motion or strain; instead they act mainly to maintain disk height.[42,43] They should preferably be placed prior to the osteotomy, before possible major bleedings. Although the use of cross-links might stiffen the construct, it can diminish the surface for bone fusion. One should set the bone graft before placing the cross-links to diminish this effect.

Placing additional accessory rods, connected to the holding rods with domino/cross-links, has proved to enhance the stability and stiffness of the construct in cases of 3-column osteotomy in both biomechanical and clinical studies (17% versus 3% when compared with standard 2-rod constructs).[11,44]

A biomechanical study[45] has shown that regarding the range of motion, two or four rods, made either of titatinum (Ti) or cobalt chrome (CoCr), have significantly and similarly (94.9% versus 99.4%) reduced flexion-extension and lateral bending when compared with the intact cadaveric lumbar spine model. However, total rod strain, which represents the stress delivered to the rods during the biomechanical cycles, both in flexion and extension, significantly decreased with accessory rods when compared with the Ti 2-rod (46% versus 65% for the Ti 4-rod and CoCr 4-rod respectively). Even though the CoCr rod significantly reduces rod strain, the use of accessory rods with either material provided the most immediate fixation. Besides, these rods receive greater strain than the primary rods.[45]

Deformity corrections with PSO are demanding procedures with high rates of complications (37% and 67% when performed in the lumbar and thoracic regions respectively), including 12 to 30% of sensitive or motor neurological deficits, most of them transient.[46–48] Intraoperative neurophysiological monitoring has presumably positive effects in identifying neurological deficits, but it still might neglect some neurological injuries.[49] Therefore, although IONM should be used in deformity corrective surgery involving PSO whenever available, its role in the decrease of new neurological deficits is still unclear.[50] An experimental study in swine[51] has demonstrated that spinal cord injury (SCI) occurred when the shortening was equivalent to the height of one vertebra at the thoracolumbar level. Thus, a PSO performed to correct sagittal TL hyperkyphosis should not result in neurological damage if judicious care is taken with dural sac retraction (more protection than retraction) and wide emerging root decompressions followed by inspection of neural elements during and after osteotomy closure.

The mean blood loss during a PSO is of 55% of the patient's volemia, and in 24% of cases there can be losses of $\sim$ 4 L of blood.[48] Thus, a cell saver should be preferably used to avoid massive transfusion. Dural tear is the most common complication after PSO for the treatment of short-angle kyphosis (15.8%).[34]

Conclusions

The present report highlights the rationale, surgical steps and outcome of spinal stabilization with the four-rod technique after a PSO in the TL junction. During a two-year follow-up, there was no pseudarthrosis or implant failure, and the patient experienced sustained improvement in pain control and quality of life, as depicted by the self-reported questionnaires. This technique has been proven to increase construct stiffness and prevent rod breakages in the lumbar spine. Also, the placement of short rods (and screws) is feasible, and should not considerably increase the complications and the operating time. Despite this, the technique must still be compared in larger series to other procedures used in the correction of short-angle kyphosis in the TL junction, such as circumferential stabilization, as well as PSO and two-rod fixation.

Ethical approval and consent to participate

The medical ethics committee of the Medical Sciences Center at Universidade Federal da Paraíba approved this study under the following registration number: CAAE 89898718.3.0000.8069. Before and during the present study, informed consent was obtained from the participant after a brief discussion and explanation.

Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and its accompanying images.

Availability of data and materials

The data and materials used during the present study are available from the corresponding author on reasonable request.

Competing interests

The authors report no competing interests concerning the materials or methods used in the present study or the findings specified in this paper.

Author contribution

AB was in charge of patient management. He also wrote the case summary, and was responsible for supervising, correcting and proof-reading the writings of other authors. SP was involved in writing the manuscript alongside AB, as well as in maintaining patient follow-up. TT was involved in patient management; she supervised and proof-read the writings of other authors as well. RN participated in the writings of the discussion session. All authors read and approved the final manuscript.

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Conflict of Interests

The authors have none to declare.

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Mesencephalotomy, How I Do It: Analysis of 34 Cases

Mesencefalotomia, como eu faço: análise de 34 casos

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Abstract

The present paper aims to demystify the use of rostral mesencephalic reticulotomy (mesencephalotomy) in the treatment of chronic pain in cancer patients. A retrospective review of the medical records from the Central Pain and Stereotaxy Department of the A. C. Camargo Cancer Center, São Paulo, state of São Paulo, Brazil, between 2005 and 2012, was performed. Surgical indication was restricted to patients with cancer pain refractory to etiological and symptomatic treatments, $>$ 2 months of expected survival, preserved cognition, and absence of coagulation disorders, of systemic infection, and of intracranial hypertension. We have selected 34 patients, with an average follow-up of 9.4 months, an average age of 54.3 years-old, and an average follow-up time until death of 6.4 months. Lung cancer was the most frequent diagnosis. Satisfactory and immediate pain relief was achieved in 91% of the cases, and 83% of these patients had no relapses. Among the complications, ocular movement disorder was the most frequent, but often transient. Permanent disturbances occurred in 8.8% of the cases (diplopia, rubral tremor, and paresthesia). Compared to the pharmacological treatment, mesencephalotomy was economically feasible, more effective, and improved quality of life. According to the data presented, it can be concluded that mesencephalotomy is a viable procedure for cancer pain control in selected cases.

Keywords
- pain
- functional neurosurgery
- facial pain
- cancer pain
- ablative procedure

Resumo

O presente artigo objetiva desmistificar o uso da reticulotomia rostral mesencefálica (mesencefalotomia) no tratamento da dor crônica em pacientes oncológicos. Foi realizada uma revisão retrospectiva dos prontuários dos pacientes submetidos a mesencefalotomia, entre 2005 e 2012, no Departamento da Central da Dor e Estereotaxia do A. C. Camargo Cancer Center, São Paulo, SP, Brasil. A indicação cirúrgica foi restrita aos portadores de dor oncológica refratária aos tratamentos etiológicos e sintomáticos, com expectativa de sobrevida $>$ 2 meses, cognição preservada, ausência de distúrbios de coagulação, de infecção sistêmica, e de hipertensão intracraniana. Foram selecionados 34 pacientes, com seguimento médio de 9,4 meses, idade média de 54,3 anos, tempo médio de seguimento

Palavras-chave
- dor
- neurocirurgia funcional
- dor facial
- dor oncológica
- cirurgia ablativa

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até o óbito de 6,4 meses. O câncer de pulmão foi o diagnóstico mais frequente. Houve alívio satisfatório e imediato da dor em 91% dos casos, e 83% não tiveram recidivas. Dentre as complicações, o distúrbio da movimentação ocular foi o mais frequente, sendo em sua maioria de caráter transitório. Distúrbios permanentes ocorreram em 8,8% dos casos (diplopia, tremor rubral, e parestesia). No que se refere à comparação com o tratamento farmacológico, o procedimento mostrou-se economicamente viável, mais efetivo, além de fornecer qualidade de vida. Com os dados apresentados, foi permitido concluir que a mesencefalotomia é um procedimento viável para o controle da dor oncológica.

Introduction

The 20th century and the beginning of the 21st century witnessed a progressive increase in the longevity of the world population. People afflicted by several diseases, whose diagnoses represented true condemnations and prophecies of suffering and death, came to survive. It was not long before the increased survival had an additional call for quality of life. It was not enough to stay alive, but to live well. There is no successful strategy to offer quality of life without adequate relief from a possible painful discomfort. There have been developments in etiological and symptomatic treatment throughout medicine, but despite this auspicious advancement, many people still suffer from pain refractory to analgesic pharmacotherapy and to therapeutic methods for underlying diseases, especially in oncology. Approximately 5% of people who complain of pain require a symptomatic interventional treatment.[1]

Several procedures have been used over the years, and new surgical techniques have been developed based on the increased anatomical and physiological knowledge of pain pathways.[2]

Despite its long history and efficacy, the use of destructive (or ablative) techniques has diminished in modern practice, being replaced by new conservative and nondestructive interventional approaches, such as the implantation of neurostimulation systems and the release of analgesic drugs into the central nervous system (CNS).[3]

History

In 1878, a patient with a gunshot wound injury reported loss of pain sensation and preserved touch awareness in one side of the body. Around the same time, a 2nd patient reported a similar loss of painful sensitivity. Necropsies revealed the anatomical involvement of the spinal cord anterolateral columns contralateral to the sensory alteration, which was traumatic in the 1st case and associated with a tuberculoma in the 2nd.

Spiller, in 1905, based on both reports, considered that the pain pathway preferably included lateral spinothalamic tracts. Seven years later, an open cordotomy was successfully performed by Martin; moreover, in 1963, it was successfully performed through a percutaneous approach by Mullan. It was not long before neurosurgeons identified the limits and risks of cordotomy in obtaining analgesia of more cranial pains from thoracic, brachial, and cephalic territories.[4–9]

Created and first performed by Dogliotti in 1938, the lateral spinothalamic tract injury to control refractory oncologic pain affecting areas above the nipple gained strength and recognition with Walkerin, in 1942. His studies showed that the posterior portion of the mesencephalon would be the safest and most effective region for approaching this tract, contrary to his predecessor, who advocated a pontine access to the target.[3]

The rostral mesencephalic reticulotomy (RMM) by stereotaxy, also known as mesencephalotomy, was first used in the treatment of cancer-induced pain in 1953, by the pioneers Spiegel et al.[1]

The procedure is based on the interruption of the spinothalamic tract, of the 5th thalamic tract, and of a portion of the reticular formation in the rostral region of the mesencephalic tegmentum, modifying the sensation of pain.[1]

Objectives

To demystify the unfounded aversion to an ablative surgical technique, known as mesencephalotomy, based on relatively high rates of permanent complications reported in early publications.

This objective will be achieved by comparing the results obtained in an extensive literature review about this procedure with those observed in a series of patients from the Department of Pain Management, Functional Surgery and Palliative Care of the Celestino Bourroul Cancer School of the Fundação Antônio Prudente (FAP, in the Portuguese acronym), São Paulo, state of São Paulo, Brazil, between 2005 and 2012.

Indication

Surgical indication was restricted to patients with cancer pain that was refractory to etiological and symptomatic treatments (multidisciplinary and multiprofessional), predominantly lateral, affecting the head, the neck, the upper chest, and the upper limbs. The patients should have $>$ 2 months of expected survival and preserved cognition; moreover, they should not present coagulation disorders, active systemic infection, nor signs or symptoms of intracranial hypertension.[2,10]

Surgical Technique

The RMM target is 5.0 to 5.5 mm posterior to the posterior commissure, or 18 to 18.5 mm posterior to the intercommissural midpoint (at the intercommissural line); 4.5 to 5.0 mm below the intermural plane, perpendicularly; and 5.0 to 10.0 mm lateral to the midline, passing through the middle of the 3rd ventricle and the Sylvius aqueduct, contralateral to the refractory pain complaint.[1,2,5,6,11] A simplification used in practice is the adoption of the calculation of the 1st coordinates – 5 mm posterior, 5 mm inferior, and 5 mm lateral to the midpoint of the posterior commissure – and then the performance of possible corrections from macrostimulation (►**Fig. 1**).

The experience of the team with target identification in the treatment of movement disorders and of refractory pain has allowed us to note that, depending on the angle between the floor line of the 4th ventricle and the intercommissural line, the mesencephalotomy target may travel anteriorly and vary from 14 to 19 mm from the intercommissural point.

Stimulation and Somatotopic Arrangement

Knowledge on the functional anatomy of the midbrain – especially from structures adjacent to the lateral spinothalamic tract (the periaqueductal gray matter, the ascending reticular activating substance, the medial lemniscus, the upper and lower colliculus, the nucleus rubrus, and the medial longitudinal fasciculus) – is essential to perform this procedure. Spiegel et al[1] reported a considerable incidence of painful anesthesia following RMM. They attributed this complication to the accidental injury of the medial lemniscus, which runs a little ventral and medial to the spinothalamic tract.[1] The medial lemniscus is an important discriminative pathway and plays a prominent role in the balance and function of the endogenous and pain suppressive system. Its transoperative stimulation causes discomfort in shocks, formication, and numbness in the contralateral hemibody, while stimulation of the lateral spinothalamic tract evokes thermal sensations, and, rarely, pain.[1,12]

►**Fig. 2** shows the interrelationships between the various nuclei, the ascending reticular activating substance, and the

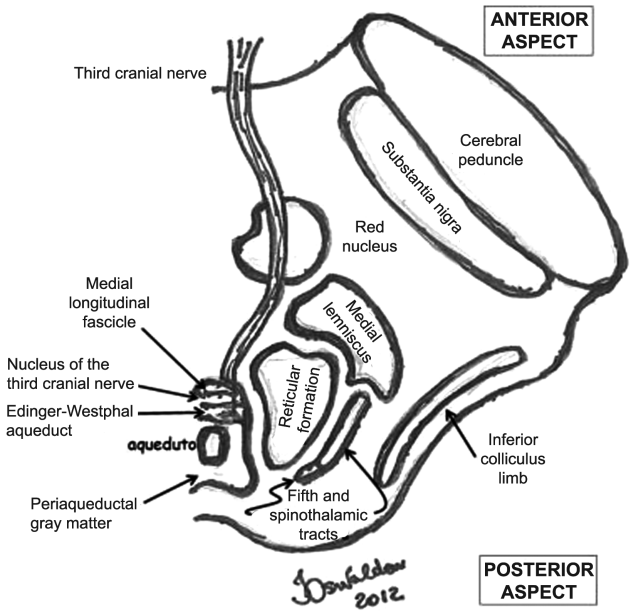

Fig. 2 Drawing of the midbrain at the inferior colliculus level, schematically illustrating the relationship between the nuclei.

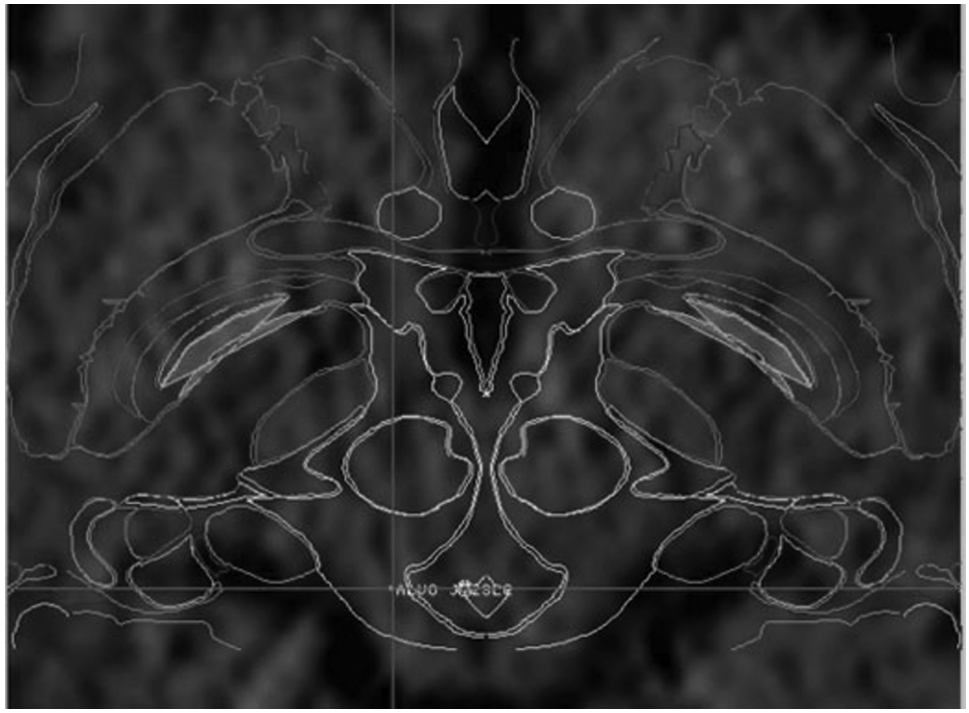

Fig. 1 Surgical planning showing a tomography image virtually fused with the Schaltenbrand atlas, in a thin section of the mesencephalic region, at the superior colliculus level.

Table 1 Relationship between stimuli and coordinates with the expected effects

Level	Distance (midline)	Subjective sensation	Referred site	Motor	Autonomic	Affective	Other
Posterior commissure (cranial)	0–5 mm	Vibration	Center of the face, head and chest	Eyelid closure, grimacing face, eye and cranial movement	None	Intense response, fear and panic	Hyperventilation, deep or fast breathing
Posterior commissure (cranial)	5–10 mm	Heat, pain and burning sensation	Contralateral face, upper limb and chest	Partial eyelid closure	Contralateral piloerection and sweating	Fright	Nausea
Superior colliculus (medial)	0–5 mm	Burning, cold, numbness	Head, nose, eyes, mouth, chest and upper limb	Eye movement, increased palpebral opening	Pulse frequency increase, breathing inhibition	Fright (strong response)	Vocalization, speech impairment
Superior colliculus (medial)	5–10 mm	Pain, burning, cold, shivering sensation	Face, chest, upper limb, trunk	Eyelid closure		Intense pain	Post-discharge pattern at EEG
Inferior colliculus (caudal)	0–5 mm	Pain, heat, funny feeling	Head, face, oral cavity and lower limb	Increased palpebral opening, eye oscillating convergence, ipsilateral facial contraction	Face and neck redness, piloerection in upper limb and trunk	Fright, strong response	Central pain, activation, sighed breath
Inferior colliculus (caudal)	5–10 mm	Pain, burning	Upper limb, face and shoulder	Eye movement		Crying	Postdischarge pattern at EEG

Abbreviation: EEG, electroencephalogram.

multiple tracts found in this specific part of the mesencephalic region.

►**Table 1** summarizes the different sensations obtained with stimulation $>$ 60 Hz in 3 midbrain depths (heights) (identifying the most representative structure from each level).[4]

►**Figs. 3** and **4** represent the ideal site for lesion performance, as well as the involved structures and body segment.

Data Analysis

After approval by the ethics committee, 34 medical records from patients submitted to RMM in the Department of Pain Management, Functional Surgery and Palliative Care of the Celestino Bourroul Cancer School of FAP between 2005 and 2012 were analyzed, as shown in ►**Table 2**.

All of the patients had cancer, except for two cases of aggressive neurofibromatosis that were refractory to clinical and surgical treatment.

The statistical analysis was performed at the SOFA Statistics software for Mac, Version. 1.3.

The mean age of the patients was 54.3 years old (standard deviation [SD]: 13.3 years old). The mean follow-up time was 9.4 months (SD: 17.15 months), but, excluding the 1st case of the series, which was a patient with neurofibromatosis surviving to this date, this average falls to 6 months.

The rate of loss to follow-up was relatively high, of 32.4%. However, because these are cancer patients and A. C. Camargo Hospital is a national reference hospital, having many patients from all over the country, this loss is understandable, since the mean time until the death of the patients submitted to the procedure was of 6.4 months.

Lung cancer was the most frequent diagnosis (►**Fig. 5**). Squamous cell carcinoma (SCC) was also very prevalent, affecting predominantly the face, the neck, and the trunk.

The improvement index was based on the report of the patients, mainly using a numerical verbal scale; however, reports of family members, medication reduction, and psychosocial aspects were also considered. ►**Fig. 6** illustrates the percentage of improvement in the intensity of the postoperative pain.

Patients who were lost to follow-up were excluded from the analysis of pain recurrence (►**Fig. 7**).

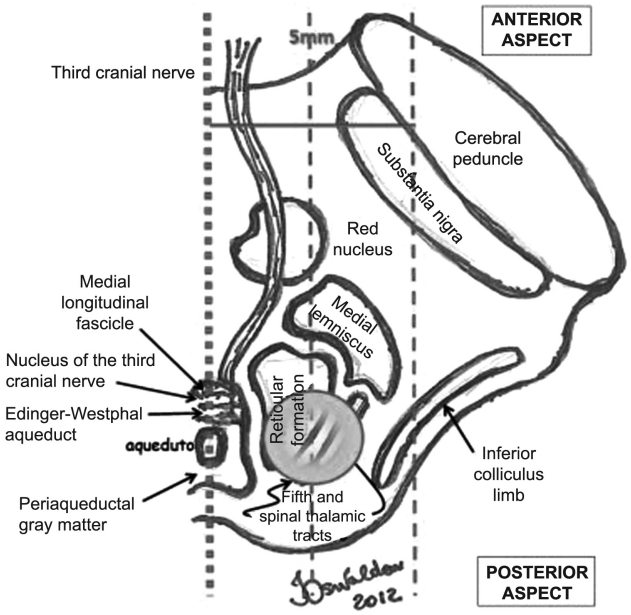

Fig. 3 Representative drawing of the ideal lesion site in mesencephalotomy

Among the postoperative complications (►**Fig. 8**), ocular movement disorder was the most present; however, it is important to note that most cases were transient. Permanent disturbances occurred in only 3 patients (8.8%), who evolved, respectively, with diplopia, rubral tremor, and paresthesia.

Discussion

Stereotactic RMM, also known as mesencephalotomy, was first used in the treatment of cancer-induced pain in 1953 by Spiegel et al, but was abandoned for a long time due to the large number of associated complications.[1]

The procedure is based on the interruption of the spinothalamic and of the 5th thalamic tracts at the rostral portion of the mesencephalic tegmentum, interfering in the main pain conduction pathway.[1]

The procedure provides hypoalgesia, not analgesia, in the upper portion of the contralateral hemibody (hemiface and upper limbs), with a frequent effect on the lower limbs.[1]

The path traveled by the pain stimulus begins in the peripheral nociceptors. These nociceptors generate impulses that are transmitted along A-delta and C-fibers to the cell bodies of the spinal ganglion, where they synapse mainly with the cells of the I, II and V layers from the dorsal horns. The two main ascending pathways that carry pain sensation in the dorsal horn are the lateral or neospinothalamic pathway and the medial or paleospinothalamic pathway.[12–15]

Primarily from finely myelinated fibroids, the oligosynaptic neospinothalamic tract is responsible for pain localization and intensity through the discriminative somatosensory pathway.[16]

The paleospinothalamic pathway is polysynaptic and originated mainly by fiber C stimuli; it is involved in the affective dimension of pain, and it is not related to cortical engrams. The data set undergoes upward dichotomy transmitted by the lateral, anterior and reticular spinothalamic tracts.[16]

Most painful fibers that constitute the spinothalamic tract are formed by axons from second order sensory neurons that cross the spinal cord soon after receiving synapses from peripheral pseudounipolar neurons.

The cephalic (cranial or rostral) continuation of the medullary gray matter (dorsal horn) is represented by the

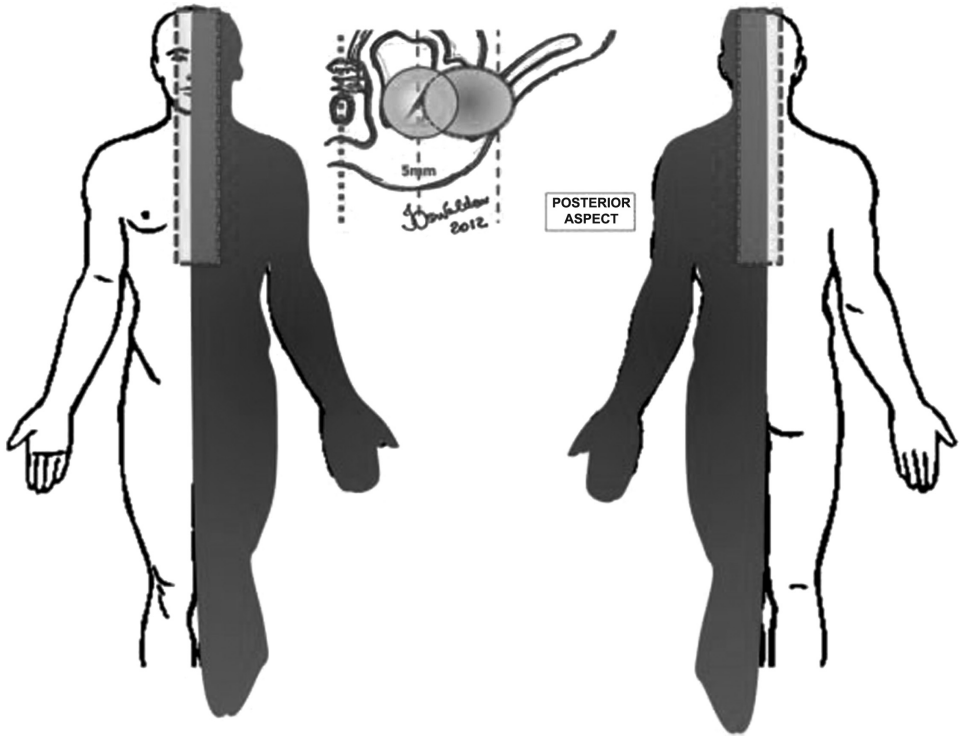

Fig. 4 Representation of the lesion and anatomical correlation.

Table 2 Analysis of the outcomes from the 34 patients who underwent mesencephalotomy

Patient	Age	Diagnosis	Follow-up	Outcome	Complication
P.H.M.	28	Neurofibromatosis	7 years	60% pain improvement	None
I. T. C.	56	Breast cancer	Lost to follow-up	100% pain improvement at IPP	Somnolence and confusion
A. A. M.	28	Leiomyosarcoma	Lost to follow-up	> 80% pain improvement at IPP	Intense somnolence and reversible diplopia
M. A. G.	59	Lung cancer	Death in 6 months	100% pain improvement until death	None
A. G. M.	64	Lymphoma	Death in 10 months	Pain improvement until last month of life	None
M. A. B.	65	SCC	Death in 3 months	100% improvement	Reversible somnolence and diplopia
J. M. G.	48	SCC	Lost to follow-up	100% pain improvement at IPP	Transient diplopia and somnolence
K. Y.	63	Colon cancer	Lost at follow-up	100% improvement	Transient diplopia and somnolence
A. T. M.	41	SCC		80% pain improvement	Transient diplopia
W. A. H.	52	Parotid cancer	Death in 4 months	100% improvement	None
L. C. H.	59	Parotid cancer	Lost to follow-up	100% pain improvement	Transient diplopia somnolence, and persistent hand paresthesia
L. A. F.	59	Lung cancer	Death in 2 years	> 80% pain improvement	None
N. B. C. F. P.	62	Lung cancer	Death in 3 months	> 80% improvement	None
F. S. S. B.	49	Lung cancer	Lost at follow-up	100% pain improvement at IPP	Vomiting and diplopia
M. L. P. A.	49	Breast cancer	Death in 1 year	100% improvement at IPP, 30% improvement after 4 months	Persistent diplopia and dysesthesia
A. J. R.	55	Kidney cancer	6 months	100% pain improvement	Rubral tremor
M. F. G. C.	51	Lung cancer	Death in 3 months	100% improvement at IPP, > 80% improvement at death	None
J. C. F. O.	38	Trapezoid liposarcoma	Death in 1 year and 2 months	100% pain improvement	Reversible diplopia and hypersomnia
W. V. F.	61	Lung cancer	Lost to follow-up	50% pain improvement	Diplopia
E. J. F.	66	SCC	Lost to follow-up	> 80% pain improvement	Left arm numbness resolved in 4 weeks
L. F. F. Z.	49	Lung cancer	Death in 6 months	100% improvement at IPP	Reversible diplopia and hypersomnia
V. A. A. M.	46	Breast cancer	Death in 2 months	100% pain improvement	Hypersomnia
A. A. O.	48	Lung cancer	Death in 1 year	100% improvement at IPP	Multidirectional nystagmus
				80% improvement until death	
R. B. A.	47	Lung cancer	Death in 3 months	100% pain improvement	Hypersomnia
M. S. L.	42	SCC	Death in 1 months	80% improvement until death	None
A. J. R.	71	Lung cancer	Death in 2 months	100% improvement	Palpebral ptosis
S. A. S.	54	SCC	Death in 7 months	100% improvement	None

Table 2 (*Continued*)

Patient	Age	Diagnosis	Follow-up	Outcome	Complication
L. G. A. P.	63	Nasopharyngeal SCC	Death in 2 months	Procedure not concluded due to intraoperative respiratory disorder	Procedure not concluded due to intraoperative respiratory disorder
C. M. M.	51	Parotid cancer	Lost to follow-up	No improvement: unsuccessful cingulotomy, unsuccessful pump implant	None
M. A. T. L.	75	SCC	Death in 1 month	> 50% improvement	Nausea and vomiting
R. M. S.	26	Neuro—bromatosis	8 months	> 80% pain improvement	None
M. A. A.	86	Lung cancer	Lost to follow-up after 1 month	100% improvement no POI, < than 50% improvement after 1 week	Surgical wound infection, nystagmus, eye movement deficit
N. X.	71	Lung cancer	5 months	> 80% improvement	Eye movement deficit
N. M. B.	65	Lung cancer	3 months	> 50% pain improvement	None

Abbreviations: IPP, immediate postoperative period; SCC, squamous cell carcinoma.

spinal trigeminal nucleus, which mediates the painful sensation of a portion of the cephalic segment. The spinal trigeminal nucleus projects to the posteromedial ventral nucleus (PVM) of the thalamus, to the intralaminar nuclei, and to the reticular formation. The thalamic projection of these tracts lies in the ventrocaudal (Vc) nucleus; The cephalic afferent territory is represented in the most medial portion of the Vc (PVM), while the afferent territory for the rest of the body is in the most lateral portion (ventral posterolateral [VPL]).[12]

The medial pathway has been implicated in the affective component of pain. This pathway consists of the innermost

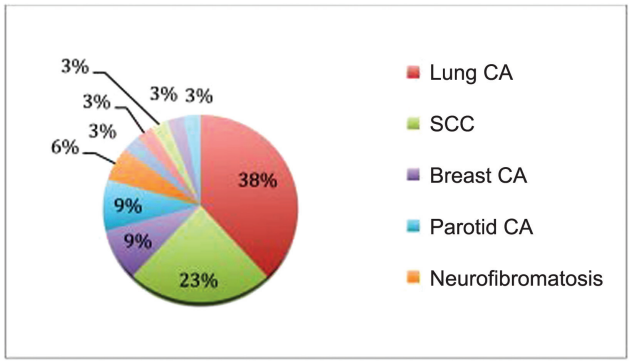

Fig. 5 Preoperative diagnosis of patients submitted to the mesencephalotomy. Abbreviations: CA, cancer; SCC, squamous cell carcinoma.

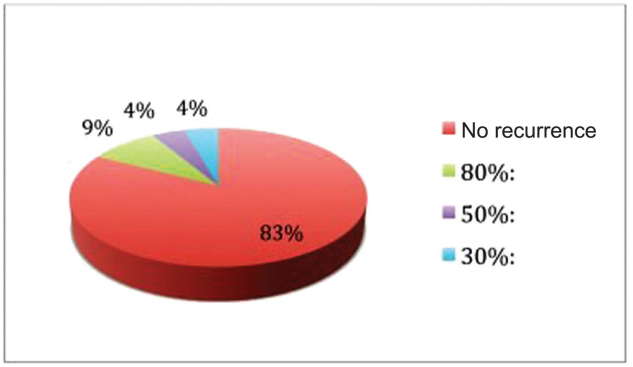

Fig. 7 Percentage of pain recurrence.

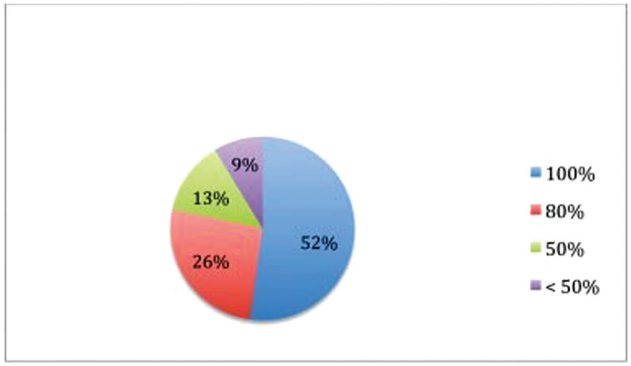

Fig. 6 Visual analog scale at the immediate postoperative period.

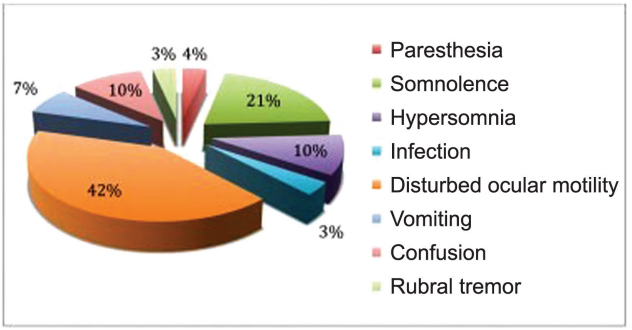

Fig. 8 Postoperative complications.

portions of the spinothalamic and spinoreticular tracts. The medial pathway contains projections for the reticular formation of the brainstem, of the periaqueductal gray matter, of the hypothalamus, of the medial thalamic nuclei (e.g., parafascicular [Pf] and centrolateral [Cl]), and of the anterior limbic structures, such as the anterior cingulate and the insular cortex.[12]

Since 1937, when Papez presented the hypothesis of a reverberant circuit encompassing a large portion of the limbic system, it was shown that these structures were responsible for the memory of pain and for the suffering associated with it.[17–19]

The reverberant idea and its affection are the soul of the perpetuation and of the chronicity of the painful phenomenon, responsible for its progression and refractoriness to the clinical treatment.[17–19]

The lesion of an unspecified medial portion of the spinothalamic and, mainly, of the spinoreticular tracts reduces the suffering sensation not directly connected to nociception through limbic modulation.[5,20]

Chronic pain is associated with a high degree of central and peripheral nervous system sensitization, and it is mostly expressed following neuropathic patterns. Chronicity makes the resolution prognosis rather guarded, and the reverberating component seems to be the big challenge.

The symbology of cancer-induced pain often justifies refractoriness to several treatments. Mutilation, aesthetic changes, social role reversals (from provider to provided, from caregiver to cared), future uncertainty, financial difficulties, and other situations, including acceptance of the diagnosis, interfere with the abstract portion of the suffering and with the perpetuation of pain.

The insufficient analgesic effect obtained with opioids on neuropathic pain forms suggests compliance with the poor results obtained with mesencephalotomy in predominantly neuropathic chronic pain. However, the mixed composition (neuropathic and nociceptive) of the cancer-induced pain found in most cases, and the progressive nature of the disease allow an at least partial relief with the procedure. This is also true for cordotomy, which provides total remission of pain for months, even in cases of clearly neuropathic predominance.[2]

There are few surgeries with analgesic purpose that attenuate two fundamental components of pain, namely the affective and nociceptive components. Cingulotomy and mesencephalotomy are rare examples of such procedures.

Ablative techniques, such as RMM, are associated with lower costs and good analgesic effectiveness. They are economically viable, and therefore accessible to most interventional pain centers. However, the need for thorough knowledge and long training in functional neurosurgery; the risks due to surgical complications; the deterioration of the doctor-patient relationship, and the high demand levels from the part of the patients, of the their representatives, and of the legal consequences; as well as administrative interference of the hospital and funding sources; are factors that resulted in the progressive abandonment of this technique. Less invasive methods are favored, with less associated risks, however with less effectiveness.

Ablative surgeries find a residual niche in the treatment of cancer-induced pain,[21] but they are progressively abandoned due to the irreversibility of possible sequelae; in addition, although they have good effectiveness, they will always carry out cost-benefit struggles.

Mesencephalotomy has advantages over some of these procedures. Except for possible disturbances of consciousness, it can be used in patients with respiratory dysfunction, and, in selected cases, bilaterally at adequate time intervals, as a rule, unlike cordotomy.[1] It addresses both the nociceptive and the reverberant components, unlike cingulotomy, which only deals with the latter.

Its performance still requires specialized centers and a staff also trained in the control of complications, including intensive care support, physical therapy, speech therapy, and orthoptics.

We note that, in our service, the postoperative survival of the patients does not match the reality of most studies.[1,2,10,20,22] However, we believe this is due to a peculiar feature: the excellence of the concomitant care performed by the multidisciplinary group (psychologists, palliatists, neurosurgeons, physicians, nurses, physical therapists, pediatricians, and neurologists) can provide a good quality of life for a long period without the need for invasive procedures. Interventionism is only indicated when all of the conservative alternatives are exhausted.

Conclusion

Stereotactic mesencephalotomy should be performed only in cancer patients, with predominantly unilateral and above nipple level pain, including appendicular distribution and a nociceptive component.[2] The new techniques of virtual image fusion reduce pathways and punctures, resulting in a lower rate of permanent complications. Its cost-effectiveness is quite attractive, and, in ideal technical conditions, it can have lower risks, rendering it a valid therapeutic option.

Conflicts of Interests
The authors have no conflicts of interests to declare.

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Use of an Expanded Polytetrafluoroethylene (ePTFE) Dura Substitute in Glioma Surgeries: A Technical Note

Uso do substituto dural politetrafluoroetileno expandido (ePTFE) em cirurgias de gliomas: Uma nota técnica

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Abstract

Introduction Reoperations are a common scenario among glioma patients. There is crescent evidence of its benefit in low- and high-grade gliomas. Here we discuss our experience with inert expanded polytetrafluoroethylene (ePTFE) dura substitute in glioma surgeries.

Technical note We generally put the ePTFE dura substitute below the dura of the patient, even if it is intact. This membrane should be sutured in place using a tension-free technique, with 4-0 polypropylene. Expanded polytetrafluoroethylene minimizes tissue attachment and fibrosis when performing reoperation in glioma patients.

Discussion Since the literature has shown benefits in survival with reoperation in glioma patients, the use of ePTFE dura substitute can improve surgical time and minimize complications in a second surgery.

Keywords
- reoperation
- glioma
- dura substitute
- surgical complication

Resumo

Introdução Reoperações são comuns entre pacientes portadores de glioma, com crescente evidenência de seu benefício em casos de baixo e alto graus. Aqui discutimos nossa experiência com o substituto dural politetrafluoroetileno expandido (ePTFE) em cirurgias de glioma.

Nota técnica Geralmente colocamos o substituto dural ePTFE abaixo da dura-máter do paciente, mesmo quando intacta. Essa membrana deve ser suturadasem tensão com fio prolene 4.0. ePTFE minimiza aderência tecidual e fibrose, facilitando as reoperações em pacientes com glioma.

Palavras-chave
- reoperação
- glioma
- substituto dural
- complicação cirúrgica

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Introduction

Reoperations for recurrent low-grade gliomas (LGG) should be the standard of care.[1] Concerning high-grade gliomas (HGG), reoperation remains controversial, given the limited life expectancy and the aggressive/recurrent nature of these tumors, but there is crescent evidence of benefits with this treatment strategy.[2] Recent studies have shown that a second operation improves survival in patients with glioblastoma multiforme (GBM), with surgical complication rates similar to single-surgery patients.[3,4]

Reopening the dura mater and releasing it from the cerebral cortex in a glioma reoperation can be difficult and increase the surgical time; besides, it may cause cortical injury. Due to the important role of reoperation in glioma patients, here we discuss our experience with inert expanded polytetrafluoroethylene (ePTFE) dura substitute in glioma surgeries to minimize the difficulties of reoperation.

Technical Note

When planning surgery in patients with suspected gliomas in magnetic resonance imaging (MRI) studies, we routinely use an ePTFE dura substitute. After lesion resection and hemostasis of the tumor bed, we put the membrane below the dura of the patient, even if it was intact, as shown in ►**Fig. 1**. The ePTFE dura substitute should be sutured in place using a tension-free technique. This can be achieved by appropriately sizing the membrane to slightly overlap the dural defect and putting minimal tension on the sutures (►**Fig. 2**). This may avoid unnecessary needle punctures in the material. The substitute is compatible with any nonabsorbable suture with a noncutting needle, such as a taper or piercing point. We used 4-0 polypropylene in all of the cases.

As shown in ►**Figs. 3** and **4**, ePTFE minimizes tissue attachment and fibrosis when performing reoperation in glioma patients, lowering the surgery time and complications.

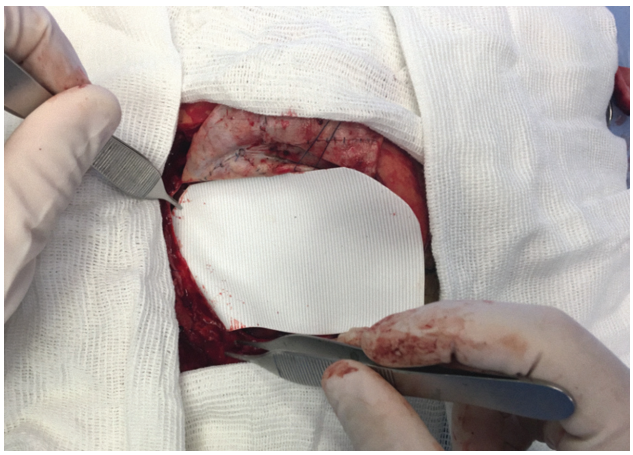

Fig. 1 Expanded polytetrafluoroethylene dura positioning bellow the dura mater of the patient.

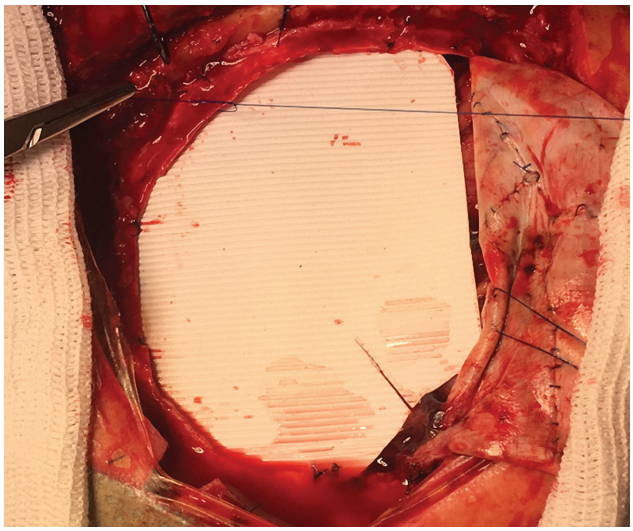

Fig. 2 Expanded polytetrafluoroethylene dura substitute sutured in place with a tension-free technique.

Discussion

Low-grade glioma is a chronic disease of the brain, and should be treated with a personalized and long-term multistage therapeutic approach.[5] The importance of surgery and maximal extent of resection (EOR) is well-established in primary LGG management. There is increasing evidence to support maximal EOR for treating recurrent LGG as well, as it may improve progression free survival (PFS) after recurrence and overall survival (OS).[1] Reoperations of the patients with recurrent LGG have similar risk of neurological complications and sequelae when compared with the initial surgery.[6]

Regarding HGG, Lacroix et al have shown that the EOR improves survival.[7] Predictive factors of good prognosis after a second surgery include young age, high Karnofsky performance status (KPS) score, gross total resection, and longer time interval between operations.[8–11] D'Amico et al showed recently a greater total survival in patients $>$ 65 years old submitted to a second intervention than those submitted to a single surgery.[3] Moreover, systemic, local, or neurological complication rates were not significantly different between the single-surgery group and the reoperation group in that study.[3] Chen et al showed similar results and concluded that, in a select group of patients with recurrent grade IV glioblastomas, repeated craniotomy had a significant survival benefit without severely compromising functionality.[12]

The ePTFE dura substitute is indicated for use as prosthesis for the repair of the dura mater during neurosurgery. It has a porosity of $<$ 1 μ, which provides excellent conformability and handling while minimizing fibrous tissue ingrowth. This dura substitute serves as an inert, watertight, full thickness dural graft that minimizes tissue attachment between the neural structures and other tissues.[13] Another advantage is that it becomes translucent after 3 to 4 months in vivo, which allows visualization of the underlying neural structures in reoperations.[14]

Besides avoiding tissue attachment and fibrosis in reoperation, we did not observe cerebrospinal fluid fistula or meningitis in patients with ePTFE dura substitute. This

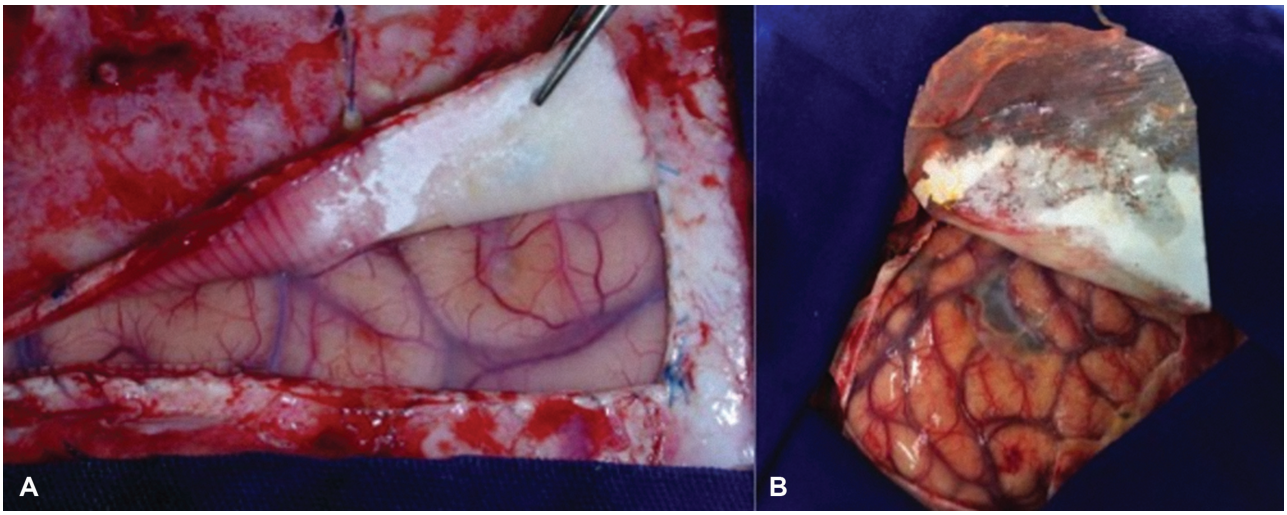

Fig. 3 Brain aspect underneath expanded polytetrafluoroethylene dura.

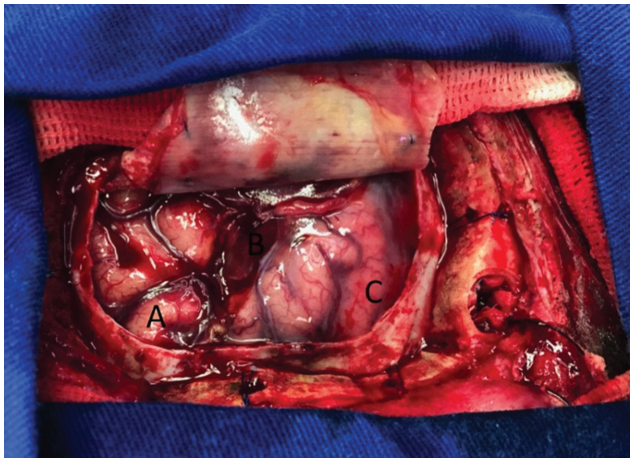

Fig. 4 Comparison of brain surface with and without expanded polytetrafluoroethylene dura substitute in reoperations in a glioblastoma multiforme patient. Tissue attachment and blood vein lesions can be seen in the area with no dura substitute (A), in opposite of preserved anatomy with no fibrosis in tissue covered by expanded polytetrafluoroethylene membrane (C). Between both, previous tumor cavity (B).

membrane has already been shown to be a safe and effective synthetic dura, without the complications observed with other synthetic and biological materials.[15–18]

Conflicts of Interests

The authors have no conflicts of interests to declare.

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Necrotizing Otitis Externa: A Disease Barely Known to Neurosurgeons

Otite externa necrotizante: uma doença pouco conhecida entre os neurocirurgiões

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Abstract

Necrotizing otitis externa (NOE), also known as malignant otitis externa (MOE), is a severe and rare infectious disease of the external auditory canal (EAC). Without treatment, it may progress to skull base involvement. The bacteria *Pseudomonas aeruginosa* is the most common causative agent (~ 90% of the cases), and affects immunocompromised subjects, particularly diabetic patients. Severe chronic otalgia, otorrhea, and cranial nerve palsy are the most common clinical presentations. Patients with NOE are frequently referred to neurosurgery because of the neurological impairment and skull base compromise. The definitive diagnosis is frequently elusive, requiring a high index of suspicion. Several laboratorial tests, imaging modalities, and the histologic exclusion of malignancy may be required. An early diagnosis and aggressive treatment reduce morbidity and mortality. We present four NOE cases to illustrate the spectrum of clinical presentation and complementary exams. According to the literature, more effort for early diagnosis and treatment is required, and neurosurgeons play an important role in this task.

Keywords
- otitis externa
- malignant otitis
- necrotizing otitis
- diagnosis
- cranial base osteomyelitis
- treatment

Resumo

Otite externa necrotizante (OEN), também conhecida como otite externa maligna (OEM), é uma doença infecciosa grave do conduto auditivo externo. Sem o tratamento adequado, pode progredir com acometimento da base do crânio. A bactéria *Pseudomonas aeruginosa* é o agente etiológico mais comum (~ 90% dos casos), e afeta pacientes imunocomprometidos, principalmente diabéticos. Otalgia crônica severa, otorreia, e déficit em nervos cranianos são as apresentações clínicas mais comuns. Pacientes com OEN frequentemente são encaminhados ao neurocirurgião devido ao déficit neurológico e ao comprometimento da base do crânio. O diagnóstico é complexo e exige alto índice de suspeição. Diversos exames laboratoriais, de imagem e exclusão por histologia de neoplasia podem ser necessários. O tratamento precoce e agressivo reduz a morbimortalidade. Apresentamos quatro casos de OEN para ilustrar o espectro de apresentação clínica e exames complementares. De acordo com a literatura, é necessário mais empenho para o diagnóstico e o tratamento precoce, e o neurocirurgião tem importante papel nessas tarefas.

Palavras-chave
- otite externa
- otite maligna
- otite necrotizante
- diagnóstico
- osteomielite da base do crânio
- tratamento

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Introduction

Necrotizing otitis externa (NOE) or malignant otitis externa (MOE) is an infection of the soft parts of the external auditory canal (EAC) that penetrates the skull and can affect the temporal bone and other components of the base of the skull. Its description as a clinical entity dates from 1959.[1] In the 1990s, studies elucidated factors related to its pathogenesis and distinct evolution forms, such as mastoiditis and skull base osteomyelitis (SBO).[2,3]

The pathophysiology of NOE involves an invasive infection that begins in the EAC and penetrates the skull through the Santorini fissure, with *Pseudomonas aeruginosa* as the etiological agent in up to 98% of the cases.[3] Immunity-impairing comorbidities (HIV, pharmacological immunosuppression, diabetes mellitus, etc.), ear irrigation for EAC cleaning, and local alterations (microangiopathy of the EAC and change in the pH of the cerumen in diabetic patients) are the main risk factors.[2,3]

The natural history of the untreated disease is the contiguous involvement of the bones from the base of the skull in several patterns, leading to cranial nerve damage.

The progression to SBO with the involvement of the temporal, occipital, and other bones, although rare, results in great morbidity and mortality.[4] Skull base osteomyelitis can also be triggered by odontogenic or paranasal sinuses involvement, but less frequently when compared with SBO secondary to NOE.[5]

Methodology

Four cases of NOE evaluated and treated at the Neurosurgery Service of the Hospital Felício Rocho are described. A flowchart is proposed to approach and treat this condition.

Case 1

Male patient, 58 years old, with severe otalgia for 30 days associated with neck pain and right temporal headache. Previous history of insulin-dependent diabetes mellitus. Otitis for 11 months with secondary right facial paresis, treated in primary care with topical corticosteroids and oral amoxicillin for 2 weeks.

Physical Exam

Right-sided peripheral facial paresis (House-Brackmann IV). Otoscopy showed perforation of the right tympanic membrane.

Adjuvant Tests

Complete blood count showing discrete leukocytosis with no left shift. Computed tomography (CT) scan of the skull evidenced thickening and enhancement of the dura mater in the lateral wall of the right cavernous sinus, erosion of the right petrosal bone and of the clivus. Magnetic resonance imaging (MRI) of the brain showed the same dura mater alteration and extensive impairment of the soft parts at the base of the skull.

Evolution

Due to the severity of the condition and to the impossibility of excluding an associated neoplastic involvement, material for culture and biopsy was collected through a tympanostomy. The procedure was performed by the otorhinolaryngology team.

The anatomopathological examination revealed a nonspecific inflammatory infiltration, and there was no organism growth at cultures.

Based on the clinical data, the diagnosis of SBO secondary to NOE was made. Antibiotic therapy with ciprofloxacin and intravenous clindamycin was instituted for 10 days, with improvement of pain complaints; next, the treatment was modified to oral ciprofloxacin and sustained for 8 weeks. Facial paresis (House-Brackmann III) partially improved after 6 weeks of antibiotic therapy. Then, the patient was lost to follow-up.

Case 2

Male patient, 80 years old, admitted with otalgia, otorrhea, and right facial paresis beginning more than 40 days before. Associated dysphagia. Insulin-dependent diabetes mellitus as medical history.

Physical Exam

Right peripheral facial paralysis (House-Brackmann VI), right IX, X, XI and XII cranial nerve palsy. Otoscopy showed purulent secretion and perforation of the tympanic membrane.

Adjuvant Tests

A biopsy through tympanostomy was performed, and the secretion was collected for culture. Results showed no signs of neoplasia, and the secretion culture was positive for *P. aeruginosa*.

Evolution

The patient was treated by the otolaryngology team from another service with intravenous (IV) piperacillin plus tazobactam for 12 weeks, and then with oral ciprofloxacin for 8 weeks. Significant improvement of facial paralysis (House-Brackmann II) and dysphagia.

After 12 months, the patient returned presenting with left-sided otalgia, headache, dizziness, and left-sided sensorineural hearing loss. At the examination, there was persistent peripheral facial paresis (House-Brackmann III) on the right side. Laboratory tests showed increased inflammatory activity, and a CT scan of the head revealed significant bone destruction around the right jugular foramen, with veiling of mastoid cells. A brain MRI showed enhancement in the middle third of the EAC with bone and soft tissue involvement extending to the right carotid and to the jugular foramina. A gallium 67 scintigraphy was requested, which evidenced radioactive compound accumulation at the right mastoid, extending to the base of the skull and to the contralateral mastoid (the contralateral involvement was not evident in anatomical imaging scans).

The diagnosis of recurrent, bilateral NOE with SBO was made. An indwelling catheter was implanted for home treatment with piperacillin + tazobactam 4.5 g every 8 hours.

The patient presented improvement of the headache, of the otalgia, and of the vertigo and, after 16 weeks, the inflammatory activity was normalized; then, the antibiotic therapy was terminated, and the catheter was removed.

Case 3

Male patient, 74 years old, complaining of right otalgia and of temporal headache for 8 months. Initially, he was seen by an otolaryngologist in another service, where, due to the diagnosis of chronic otomastoiditis, he underwent a mastoid biopsy evidencing a chronic inflammatory infiltrate and questionable neoplastic cells. At the time, culture was positive for *P. aeruginosa*. The patient was treated with systemic corticosteroids, with partial pain relief. He had no history of diabetes mellitus.

Two months after the initial treatment, the patient presented with hoarseness and hypoacusis ipsilateral to the painful symptoms. Three additional biopsies had inconclusive immunohistochemistry results, and a new MRI evidenced progression of the infiltrative process.

The patient was referred to an oncologist who, due to the suspicion of lymphoma, chose to perform chemotherapy with cyclophosphamide, vincristine, and dexamethasone. During treatment, a lumbar puncture showed an increased level of mononuclear cells at the cerebrospinal fluid (CSF), and, then, intrathecal methotrexate was administered.

Due to the worsening of the symptoms, he was referred for evaluation at the neurosurgery service, with an initial suspicion of skull base lymphoma.

Physical Exam

Right-sided VIII, IX, X, XI and XII cranial nerves dysfunction.

Evolution

Adjuvant tests and the clinical history were reviewed, with the hypothesis of NOE with evolution for SBO. The treatment was initiated with ciprofloxacin, 400 mg IV every 12 hours for 6 weeks, and then modified to 500 mg (oral) every 12 hours for 8 weeks. The patient presented progressive improvement of the neurological deficits, and, 12 months after the treatment, he had subnormal hearing and mild dysphonia, with no other significant deficits. No signs of relapse at the 6-year follow-up.

Case 4

Female, 58 years old, with progressively worsening bilateral otalgia for 40 days. Intermittent serous otorrhea for the previous 12 months. Initially treated with amoxicillin and clavulanate for 14 days, with no improvement, and ciprofloxacin, 500 mg (orally) every 12 hours for 10 days, with partial response.

Medical history of systemic arterial hypertension, insulin-dependent diabetes mellitus, amenorrhea at age 35, and prolactin dosage of 2,000 ng/mL at a previous examination, without further investigation.

Physical Exam

Bilateral sensorineural hearing loss (positive Rinne test and bilateral shortening at centralized Weber test), without other focal neurological deficits. Otoscopy showed bilateral serous secretion and a perforation at the anteroinferior quadrant of the right tympanic membrane.

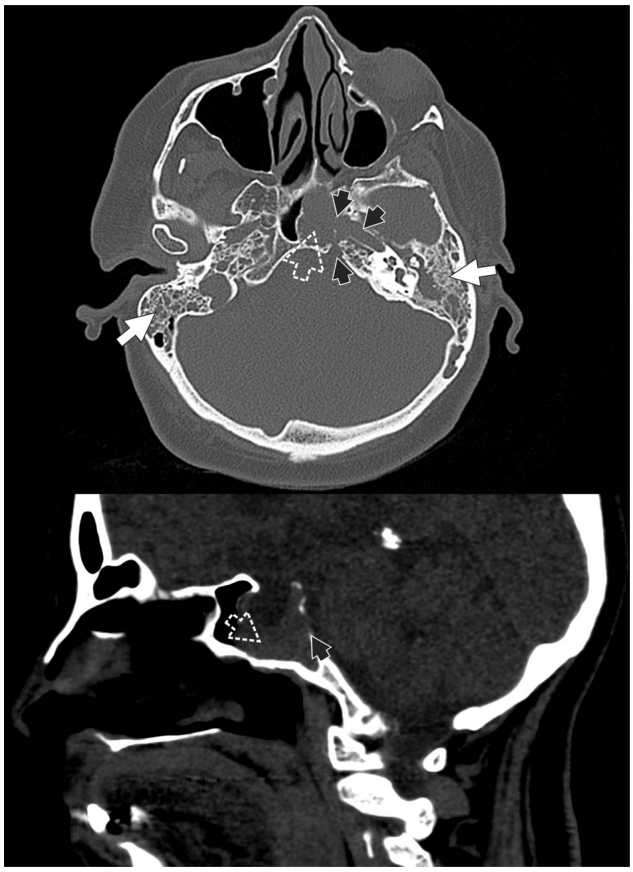

Fig. 1 Computed tomography of the head, axial section, above, and sagittal section, below, case number four. Bilateral mastoid cells (white arrows), erosion of the petrous apex, of the sphenoid sinus wall, of the clivus and of the left carotid canal (black arrows). Expansive lesion with soft tissue density in the sphenoid sinus (dotted arrow).

Adjuvant Tests

A CT of the mastoid showed bilateral cell veiling, and erosion of the petrous apex, of the sphenoid sinus wall, of the clivus, and of the left carotid canal (►**Fig. 1**).

An MRI of the brain showed an empty saddle sign, a bulky lesion centered on the left cavernous sinus surrounding the left internal carotid artery and extending to the sphenoid sinus, measuring 2.4 × 2.1 × 2.5 cm, tangential to the inferior hypophyseal margin and with no well-defined limits between them (►**Fig. 2** and **3**).

C-reactive protein: 63.50 mg/dL (VR < 10).

Prolactin > 2,000.00 ng/mL (test result above the maximum value detectable by the method even after 1:10 dilution).

Endocrinological screening with no other significant changes.

Left ear secretion with no Gram-positive bacteria or growth at cultures.

Evolution

After hospital admission and case discussion with the clinical medicine and otorhinolaryngology teams, the diagnostic hypothesis of uncomplicated NOE with SBO associated to a prolactin-secreting hypophyseal macroadenoma was established. Treatment started with piperacillin and tazobactam,

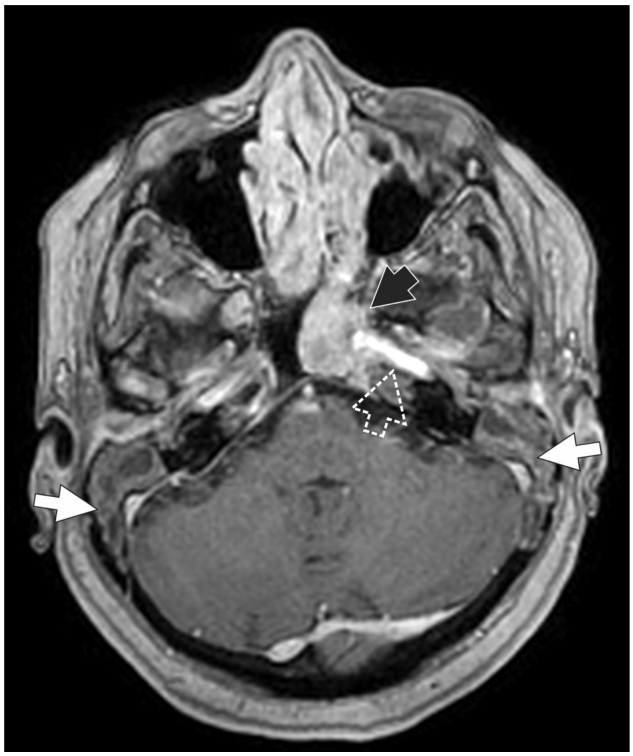

Fig. 2 Magnetic resonance imaging of the brain, axial section, T1-weighted sequence after gadolinium administration, case number four. A large lesion centered at the left cavernous sinus (black arrow) surrounding the left internal carotid artery (dotted arrow), and extending to the sphenoid sinus, measuring 2.4 × 2.1 × 2.5 cm. Bilateral complete obliteration of mastoid cells (white arrows).

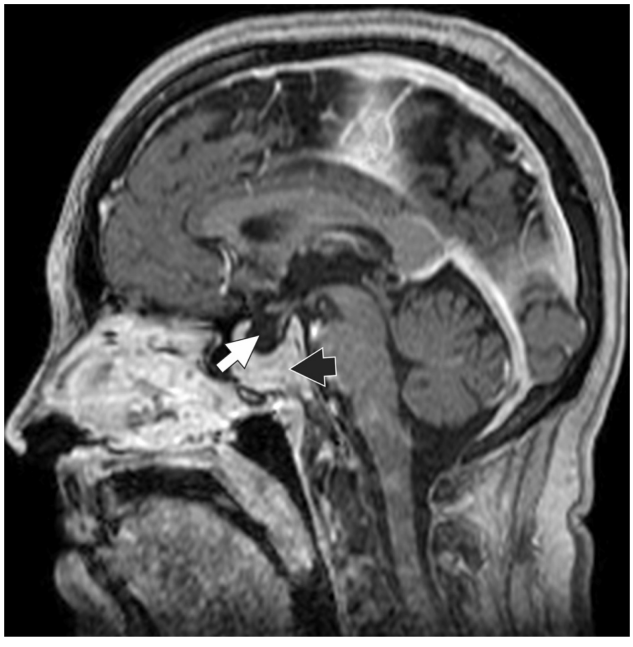

Fig. 3 Magnetic resonance imaging of the brain, midsagittal section, T1-weighted sequence after gadolinium administration, case four. Empty saddle signal (white arrow), massive lesion occupying the sphenoid sinus (black arrow), with homogeneous postcontrast enhancement.

4.5 g (IV) every 6 hours and cabergoline. After 7 days, the patient presented with left-sided peripheral facial paresis (House-Brackmann V), and a mastoidectomy was performed for debridement and collection of biopsy and culture material. The procedure was performed by the otorhinolaryngology team (►**Fig. 4**).

The anatomopathological analysis revealed bone tissue necrosis, with nonspecific inflammatory reaction, and no identifiable fungi or bacteria. No growth or infectious agents were identified at the culture and fungal analysis of the secretion obtained intraoperatively.

Due to worsening during antibiotic therapy and to the absence of identified etiologic agents, the piperacillin and tazobactam regimen was replaced with 2 g of meropenem every 8 hours for 16 weeks.

The patient presented a partial improvement of the peripheral facial paresis (House-Brackmann IV), along with a persistent auditory deficit and diarrhea secondary to prolonged antibiotic therapy. The prolactin level returned to normal after 3 months of cabergoline administration. A single-photon emission computed tomography (SPECT) with gallium 67 was performed at the end of the IV antibiotic therapy and revealed a discrete isotope concentration at the mastoid bone (►**Fig. 5**). Due to the normalization of the evidence of inflammatory activity and of the side effects of the antibiotic therapy, the otorhinolaryngologist decided to discontinue meropenem.

Outpatient follow-up with no clinical signs of relapse within 6 months of treatment.

Discussion

Clinical Picture

Persistent headache, otalgia, otorrhea, and cranial nerve deficits (in advanced cases) are the most common changes. This diversity of signs and symptoms makes the patients seek care of several specialties, including neurosurgery. In addition, the diagnosis is difficult, and, on average, it is made 70 days after the onset of symptoms. Chronic otorrhea unresponsive to topical agents, otalgia of difficult management, and irradiation to the temporomandibular joint are the most characteristic findings. At examination, the presence of granulation tissue at the osteocartilaginous junction of the EAC and an intact tympanic membrane are typical. Most cases do not present systemic signs of infection, such as fever and leukocytosis. The progression to SBO affects, in order of frequency, the facial nerve, the glossopharyngeal nerve, the vagus nerve, the spinal root of the accessory nerve, and the hypoglossal nerve. There is no record of optic nerve involvement.[4,6] Our case series presented clinical symptoms compatible with the literature. Regarding the physical examination, the presence of tympanic perforation in three of the four patients was noted. This finding, not previously described as characteristic, may be justified by the advanced stage at the time of the diagnosis.

Adjuvant Tests

Culture of EAC secretions or from material obtained through surgical exploration too often results in the isolation of *P. aeruginosa*, but recent studies have shown an up to 70%

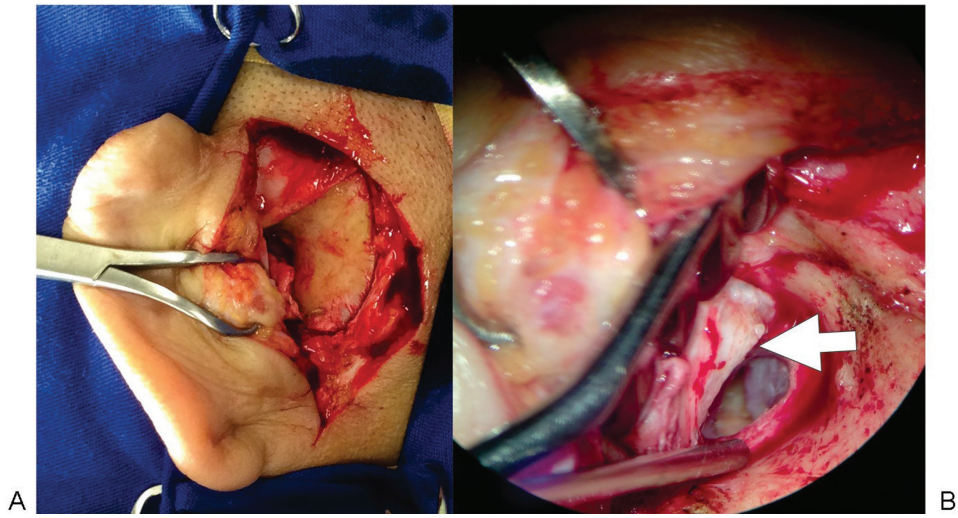

Fig. 4 Intraoperative left-sided mastoidectomy pictures. Retroauricular surgical incision (A). Microscopic view of the facial nerve, 2 x magnification (white arrow), after surgical debridement (B).

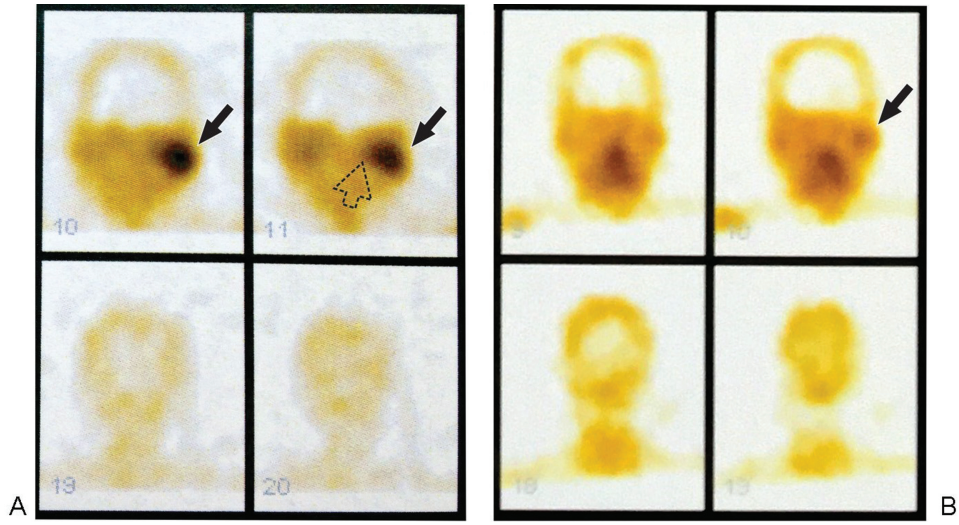

Fig. 5 Single-photon emission computed tomography with gallium 67, coronal sections, before antibiotic therapy (A) and after intravenous antibiotic therapy (B), case number four. (A), Accumulation of the radiopharmaceutical at the left mastoid region (black arrow) and at the left sphenoid and maxillary sinuses topography (dotted arrow). (B), Significant reduction of radiopharmaceutical accumulation compared to the previous examination (A), and persistence of minimal accumulation at the left mastoid bone (black arrow).

negative culture rate. Ideally, collection should be performed prior to the initiation of antibiotic therapy.[4,7] Therefore, the 50% positivity rate in the described cases may have been influenced by the prior use of antibiotics with in vitro inhibition of bacterial growth.

The erythrocyte sedimentation rate (ESR) is markedly increased and can be used as a therapeutic response marker, as observed in other osteomyelites.[6,8,9]

There are no sensitivity and specificity studies comparing different imaging tests in NOE diagnosis and therapeutic control, so their use is guided by the technical advantages and deficiencies of each method.

Technetium-99m methylene diphosphonate bone scintigraphy (MDP – Tc 99m) is the most sensitive method; the accumulation of the radiopharmaceutical compound is related to osteoblastic activity. Because it remains altered in an undefined way and in uncomplicated otitis externa cases, this methodology is not a good option for the differential diagnosis and cure control.

Scintigraphy using gallium 67, which is incorporated into granulocytes and bacteria, has a higher specificity compared with bone scintigraphy with MDP – Tc 99m. Some authors advocate that this scintigraphy can be used for cure control and follow-up; however, there is a report of NOE recurrence with normal gallium 67 scintigraphy findings.[10] Alterations in gallium 67-scintigraphy/SPECT results may precede the bone erosion evidenced in CT by weeks.[11]

Anatomical examinations, such as CT and MRI, allow the accurate topography of the involved area. Computed tomography reveals bone erosion and changes in the adjacent soft parts and in the dura mater (fat blurring, trabecular bone density alteration, and contrast enhancement). Even after satisfactory

treatment, the eroded areas remain unchanged, which limits the use of CT for treatment control. Magnetic resonance imaging is more sensitive than CT for identifying soft tissue changes (hypersignal in T2-weighted sequences and postcontrast enhancement), as well as in identifying alterations in the lipid content of the bone marrow in NOE cases.[4,11,12]

In the presented cases, nuclear medicine methods for diagnostic purposes were dispensable, since CT revealed bone erosion in all of our patients, suggesting the diagnosis of NOE. In patient number four, scintigraphy with gallium 67 was useful for treatment control after the change in the antibiotic therapy.

Surgical biopsy is the only form of differential diagnosis between squamous cell carcinoma and NOE in cases without ESR elevation and negative cultures, as imaging findings may be similar. Although rare, there is a description of the coexistence of both conditions in the same patient.[13,14] It is important to note that, in case number three, whereas the biopsy results showed questionable neoplastic cells, culture was positive for *P. aeruginosa*. In our opinion, this warrants the institution of the antibiotic treatment, since it has a lower risk than the chemotherapy to which the patient was submitted.

Diagnosis

There is no consensus regarding the diagnostic criteria for NOE, and alterations in adjuvant tests along the history of otalgia, of chronic otorrhea and/or of other symptoms is required in a patient with risk factors. Our sample clearly illustrates the

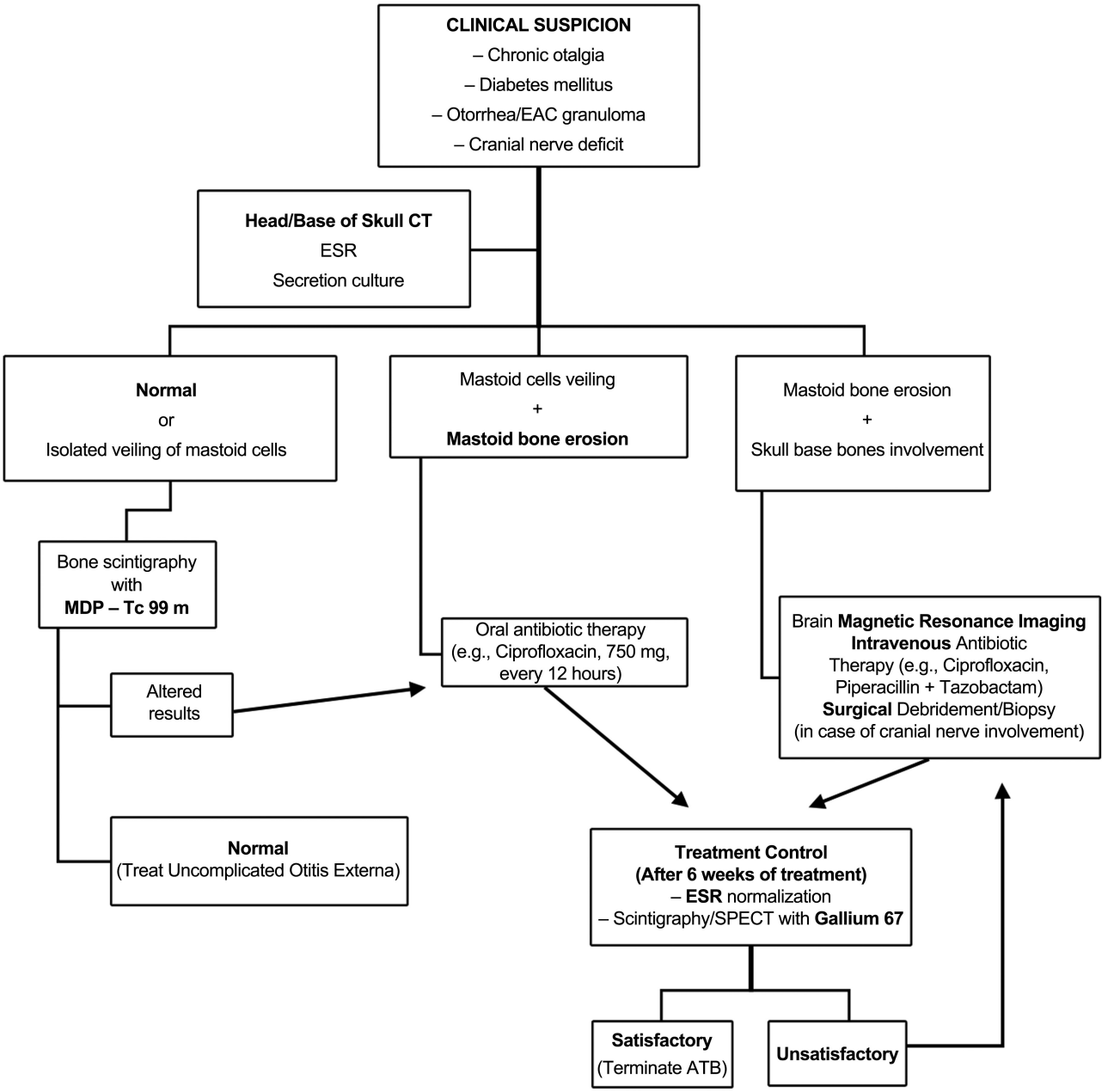

Fig. 6 Flow chart for the diagnosis and treatment of necrotizing otitis externa. Abbreviations: ATB, antibiotic therapy; EAC, external auditory canal; MDP, methylene diphosphonate; SPECT, single-photon emission computed tomography; CT, computed tomography; ESR, erythrocyte sedimentation rate.

variability of presentations, and it is worth noting that case number three did not present any risk factors for NOE, despite the typical clinical picture. The good response to the clinical treatment can be used for diagnostic confirmation, since the cure rate for NOE is $> 75\%$.[4]

Treatment

The use of antimicrobial agents with antipseudomonas spectrum is the first choice. Ciprofloxacin, 750 mg orally every 12 hours, shows good bone penetration and high efficacy in NOE treatment when used for at least 6 weeks. Although isolated studies use drugs for < 4 weeks, there is insufficient scientific evidence to justify this reduction.[4,5] Intravenous therapy, such as ceftazidime 2 g every 8 hours, is recommended in cases with partial response to oral treatment or progression to SBO. Topical medications elicit no response and distort agent isolation in EAC secretion cultures.[4,5] Although no agent resistant to conventional antibiotic therapy was documented, due to the unsatisfactory clinical response of case number four, an antibiotic regimen for multi-resistant *P. aeruginosa* (meropenem) was instituted. There is no consensus on the cure criteria that determines discontinuation of antimicrobial therapy, and the recurrence rate is very similar between the various regimens in uncomplicated cases. The last review found an average recurrence rate of 9.7% in the several series evaluated.[4]

In the rare cases with a fungal etiology (mainly *Aspergillus*), the prolonged treatment (for > 12 months) with amphotericin B is recommended.

Antibiotic therapy restricted surgical treatment to the obtainment of materials for culture or biopsy. Debridement is rarely necessary in cases with cranial nerve involvement or secondary abscesses treatment. As the neural lesion is caused by the cytotoxic effect of the inflammatory response, the decompression of the isolated cranial nerves without debridement is not indicated.[4–6,15,16] Surgical biopsies were performed in all of the cases presented, and a surgical debridement was only required in the last one due to a new cranial nerve deficit during antibiotic therapy.

As previously shown, there is no pathognomonic criterion for the diagnosis of NOE or of its complications, such as SBO.[4,17,18] The insidious progression and difficult diagnosis delay treatment, which can lead to complications and even death.[4,5,8,9] As such, we propose a flowchart, which is currently adopted in our institution and is based on the scientific literature used to prepare the present paper (►**Fig. 6**).

Conclusion

Necrotizing otitis externa is well-documented in the otorhinolaryngological literature, but poorly described in neurosurgical publications. It is a disease with high morbidity, but treatable. A high index of suspicion, the knowledge of adjuvant diagnostic methods, and early treatment reduce the time to diagnosis and avoid complications. Due to the differential diagnosis with skull base tumors and the possible involvement of neural structures, neurosurgeons must be aware of this condition for an early and adequate treatment, in addition to avoid unnecessary surgical procedures.

Conflicts of Interests
The authors have no conflicts of interests to declare.

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Professor Fernando Costa— A Man Ahead of His Time

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Abstract

This article describes the milestones in the life Brazil's greatest neurosurgeons, Professor Fernando Costa. Born and raised in the city of Pelotas, RS, Professor Fernando was an exemplary doctor. As former director and professor at the Catholic University of Pelotas, School of Medicine, his courage as well as his ethical attitude and transparency were the central traits of this masterful teacher. He will be eternally remembered as a great physician, teacher, father, husband, grandfather and friend.

Keywords

- Fernando Costa
- Universidade Católica de Pelotas
- school of medicine
- neurosurgery
- professor

Resumo

Este artigo relata os principais passos da trajetória de um dos grandes neurocirurgiões brasileiros, o Professor Fernando Costa. Nascido e radicado na cidade de Pelotas, RS, o professor Fernando foi exemplo de neurocirurgião. Ex-diretor e professor da Escola de Medicina da Universidade Católica de Pelotas, sua coragem, bem como sua attitude, ética e transparência foram as principais características desse exímio mestre. Será lembrado eternamente como um grande médico, professor, pai, marido, avô e amigo.

Palavras-chave

- Fernando costa
- Universidade Católica de Pelotas
- escola de medicina
- neurocirurgia
- professor

In the early 90s, before we had up-to-the-minute news and information from around the world in the palms of our hands, one of the most valued technical aspects of a medical professor was their encyclopedic knowledge. The ability to cite 15 different diagnoses for a particular symptom during a clinical visit was considered the utmost demonstration of knowledge. Recalling this from memory without referring to a book was a proof of intellectual prowess that students admired (►**Figs. 1–5**).

In 1994, at the Universidade Católica de Pelotas, I had the good fortune of studying under a professor who had this encyclopedic knowledge and also had a unique way of practicing medicine. Three of his habits, in particular, stuck with me. First, he refused to carry an appointment in less than 40 minutes, even in the public health system, and was often criticized for this by managers and bureaucrats, who required him to attend to a far larger number of patients. Second, he committed himself to the care of his patients and refused to pass them off to other doctors. If one needed an exam that was unavailable in the public health system or a procedure with too long of a waiting line, he would explain everything the patient needed to do to get the exam and even who to call on if there was a delay in the process, and all in a clear and understandable manner. Third, when quizzing us medical students on the variety of possible diagnoses for a particular symptom, while on rounds, he would ask our opinion and, before responding, he would say, "I don't know, we have to consult the books." He would then open a book in front of us and the patient and, to the astonishment and admiration of everyone in the room, read aloud all the information necessary to solve the case based on up-to-date literature. Being close to Professor Fernando Costa was never monotonous. This unique teacher could be

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Fig. 1 The childhood of Fernando Costa in the City of Pelotas, next to one of his brothers.

Fig. 2 Graduation of Fernando Costa in 1974.

characterized by three principal traits: courage, empathy, and humility.

In his own way, he directed the hearts and minds of his students to strive for excellence in practice, and in a way that was thoroughly humane. Many of Professor Costa's students followed his example by opting to train as neurosurgeons. This is the story of one of the most dedicated and humanitarian neurosurgeons Brazil has ever produced.

Fig. 3 Prof. Fernando Costa alongside the current Rio Grande do Sul senator, Ana Amélia Lemos, in 2000, discussing and solving problems of the School of Medicine of the Catholic University of Pelotas.

Fig. 4 Prof. Fernando Costa was one of the most honored professors ever in the School of Medicine of the Catholic University of Pelotas.

Fernando Antonio de Oliveira Costa was born on October 12, 1946, in the city of Pelotas, Rio Grande do Sul, and he lived there all his life. He was passionate about his city and proud of it. One of nine siblings, he was born to Irene de Oliveira Costa and the dentist José Bonifácio da Costa. At the age of 17, Fernando Costa lost his father and had to go to work to finance his studies. He began his academic career as a teacher at the Federal Technical School of Pelotas in the chemistry department while still a medical student.

Between 1969 and 1974, he studied medicine at UCPEL and was a volunteer monitor in neurology, biochemistry and anatomy for several years while in school. He started his neurology and neurosurgery medical residency at Cristo Redentor Hospital, in Porto Alegre, under Dr. Mário Cadermatori and finished it in 1977. He had been a graduate and postgraduate professor of Neurology and Neurosurgery at Universidade Católica de Pelotas (UCPeL) since 1978 and had always been very active in research and development.

In 2000, he assumed the position of director of the School of Medicine of Universidade Católica de Pelotas. This was the

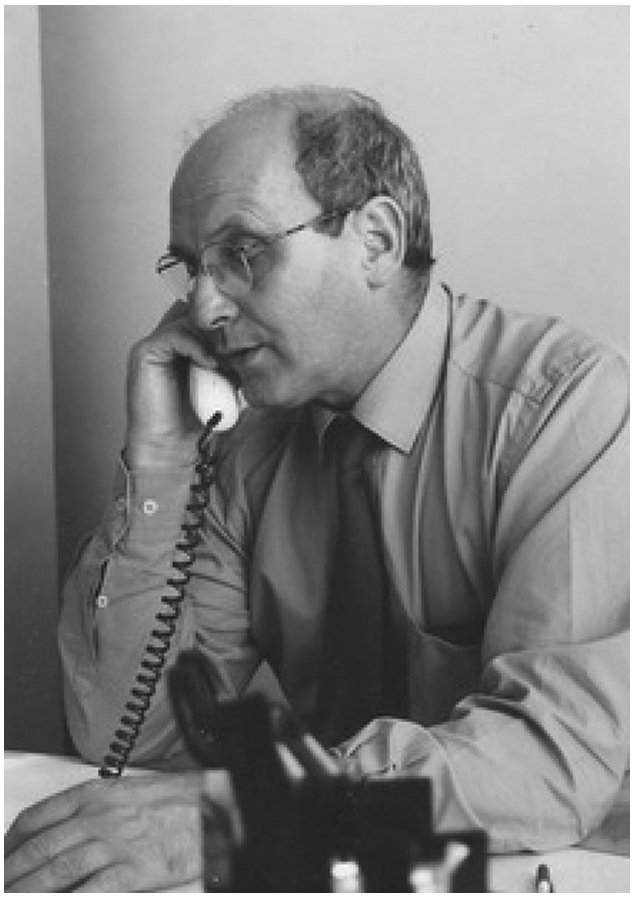

Fig. 5 Prof. Fernando Costa was a constant presence at symposia and events, always encouraging his students to present the results of their research.

most critical period in the school's history as the Ministry of Education (MEC, in the Portuguese acronym) was threatening it with closure due to poor performance. This had national repercussions and caused a great deal of apprehension, not only among teachers, students and patients, but also throughout the region due to the school's economic impact.

In a short period, millions of Reais were invested in the school, the emphasis on community medical service was increased, professors were hired, new pedagogy was introduced, the school's library was expanded, more laboratories and classrooms were built, and the university hospital was renovated and expanded. With all this, the school of medicine overcame its difficulties and was saved. Professor Fernando Costa left his position as director only after the school was returned to a stable condition and ready to move forward without major challenges.

Professor Fernando Costa was chosen by the city of Pelotas as Person of the Year 2000 for his many achievements.

He received his Master's and PhD in Medicine from the Graduate Program in Neurosurgery at the Universidade Federal de São Paulo (UNIFESP) in 1994 and 1999, respectively, with the dissertation "Epidermoid Tumors: Clinical, Diagnostic and Therapeutic Aspects" and with the thesis "Cytogenetics of Meningeomas: Geographical, Topographical and Correlation with Histopathological Study". Fernando Costa actively participated in conferences with lectures and presentations of scientific articles. In the city of Pelotas, he was often invited to give interviews to newspapers and radio stations on current issues relevant to the education and orientation of the population.

He was a founding partner of the department of neurology and neurosurgery of Associação Médica de Pelotas (Pelotas Medical Society) and was a titular member of the Academia Brasileira de Neurocirurgia (Brazilian Academy of Neurosurgery) and Sociedade Brasileira de Neurocirurgia (Neurosurgical Brazilian Society). Professor Fernando Costa had boundless energy, passion for life and for people, and was intensely committed to everything he did. His many qualities as a son, brother, husband, father-in-law, father, grandfather, doctor, professor, director of the school of medicine, friend, and as fellow a citizen were clear. His moral and ethical principles were unwavering and did not tolerate injustice. In his free time, he practiced and followed sports, having played volleyball, soccer and tennis. He enjoyed a rich social life and had many friends. In his professional life, he was adored by his patients and students, and was an Honored Professor of

Fig. 6 Prof. Fernando Costa was a speaker at dozens of conferences.

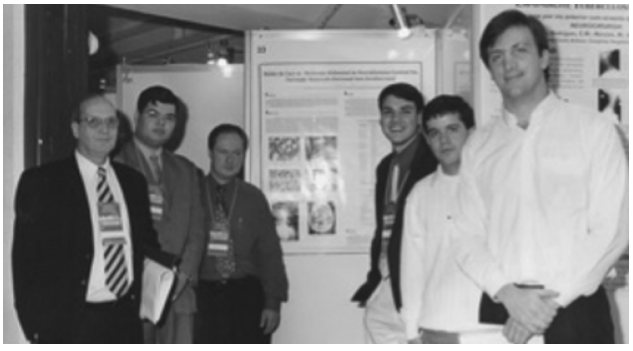

Fig. 7 Prof. Fernando Costa defining the goals that would put the School of Medicine of the Catholic University of Pelotas back on the path of excellence.

numerous classes. Fernando Costa was working intensely in the city of Pelotas together with the well-known doctor Othello Fabião Neto.

He died unexpectedly on June 30, 2018, at Moínhos de Vento Hospital, in Porto Alegre, due to a complication during an elective surgical procedure. He remained vital and active in all aspects of his life until the end. The last project he started, which, unfortunately, was left unfinished, was a book he was writing, in which he reflected on patients' risk, based on his 43 years of experience. We will miss this beloved, caring man and champion of good medical practice.

This text would not have been written without the contribution of Fernanda Costa Svedman MD, PhD, oncologist at the Karolinska University, Stockholm, Sweden

►**Figs. 6** and **7**

The Tale of the Dueling Neurosurgeons. A Contribution to the Neurosciences and Neurosurgery

O duelo dos neurocirurgiões. Uma contribuição para as neurociências e a neurocirurgia

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Abstract

In the present article, we elaborate a critical review of the book "The Tale of the Dueling Neurosurgeons: The History of the Human Brain as Revealed by True Stories of Trauma, Madness, and Recovery", written by Sam Kean. In our opinion, this book can contribute to the dissemination of neurosciences to the lay public, but it can also have an important role: to increase the interest of medicine students in neurosciences and research, since an increasingly lower number of students declare they have this interest. Thus, this book can be an important tool to deal with a pertinent and current issue under debate in the neuroscience research and neurosurgery communities.

Keywords

- neuroscience
- career in neurosurgery
- medicine
- medical education
- career in research

Resumo

Nesse artigo, elaboramos uma resenha crítica do livro "O duelo dos neurocirurgiões e outras histórias de trauma, loucura e recuperação do cérebro humano", escrito por Sam Kean, que, em nossa avaliação, pode contribuir de forma significativa para a divulgação das neurociências ao público leigo, mas que também pode atuar com a importante função de fomentar o interesse de estudantes de medicina para as neurociências e pesquisa, uma vez que um número cada vez menor desses estudantes declaram ter tal interesse. Dessa forma, esse livro pode ser um importante instrumento para uma questão oportuna e atual debatida na comunidade de pesquisa em neurociências e neurocirurgia.

Palavras-chave

- neurociência
- carreira em neurocirurgia
- medicina
- formação médica
- carreira em pesquisa

Many undergraduates who have their first contact with research or scientific initiation may end up forming a misconception of what the profession really is. This occurs because, when participating in these programs, they are usually taken directly into the day-to-day research, which, as a rule, involves repetitive and monotonous activities. The initial stages of discovery, the awakening of curiosity, or the interest in answering questions, which are the pillars of science and the main motivators of researchers and scientists, are usually "skipped" or ignored.

Added to this, there is still a strong financial aspect involved in the vocation for research. Recently, the University of New York (NYU) stated that it would exempt medical students from tuition for the first year of the course. The measure, according to the Board of Directors, is an attempt to reduce the debts that students accumulate throughout the course, which end up influencing the choice of more profitable specialties to the detriment of the vocation itself, and a reflection of this, still according to the university administrators, is the ever-

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decreasing number of students opting for specialties such as Family Medicine, or even scientific research (masters and doctorates).[1]

Certainly, these situations do not occur only in developed countries. Latin-American countries like Brazil have shown the same problem, with a low number of researchers in the medical field. The last study on medical demography in Brazil was conducted in 2018 by Faculdade de Medicina da Universidade de São Paulo (FMUSP, in Portuguese), and it showed that only 0.5% of public-university medical graduates, and 0.3% of private-university graduates, wish to follow a career in research.[2]

In addition, the existence of numerous academic leagues in the different medical fields[3] ends up directing the students in a pre-maturation way to the medical specialty itself, because they are mostly focused on clinical activities, being present at surgeries etc., without opportunizing that the academic knows and or evaluates first its vocations in research or teaching.

In this context, a question becomes more present: What to do to arouse interest in a career in neuroscience research, if the medical specializations (neurosurgery and neurology) seem to be much more financially promising and much more present throughout the undergraduate courses?

The book "The Tale of the Dueling Neurosurgeons: The History of the Human Brain as Revealed by True Stories of Trauma, Madness, and Recovery", written by Sam Kean, addresses historical and technical subjects regarding neurosurgery and neurosciences in general, from the point of view of a professional science writer.

Sam Kean is also the author of other bestsellers that deal with the dissemination of scientific knowledge. In 2009, he was a runner-up for the National Association of Science Writers' Evert Clark/Seth Payne Award for best science writer under the age of thirty.[4] In "The Tale of the Dueling…", he tells stories that he finds curious and interesting about brain functioning, neurosurgery and the evolution of the research in this field.

However, Sam Kean has a peculiar way of spreading science; his stories are dramatic, and generate curiosity and the most varied emotions. It is not enough to say, for example, how the first surgery was performed to prove the closed head injury, the so-called contrecoup brain injury; the author instead takes the reader back to the fifteenth century, to the afternoon when King Henry II decided to take part in a joust that would cost him his life, and how this decision culminated in the meeting of two of the greatest science and neurosurgery geniuses of the time: Andreas Vesalius and Ambroise Paré (p. 36-43)[4]. The authors then describes with detail the research process that led to that surgery and how this fact was extremely important for the advancement of research in the history of the neurosciences.

Another example from the book is set during World War II, amid explosions and piercing shots of surgical precision, when soldiers tried to look outside a trench, and, by exposing their heads, made the skull the part of the body most susceptible to injuries during the war. These are seemingly disconnected and irrelevant facts, but have converged so that the mapping of the complex sensory cortexes of the human brain became possible (p. 107-146)[4].

Another emblematic example occurs when, rather than describing how the cannibalistic habit of a particular tribe caused scientists to understand prions (Kuru disease), the author takes the reader to the wilderness in the mountainous region of Papua New Guinea, telling the intriguing discoveries and daily adventures of a neuroscience pioneer: Carleton Gajdusek (p. 155-179)[4].

Another example from the book tells the story of the assassination of a President of the United States, which is related tothe discovery of chemical synapses (p. 61-75)[4].

In yet another excerpt, a stuck slide may have led to the discovery of cortical maps, with the scientist winning a Nobel Prize (p. 111ff.)[4]. These are only a few examples of the author's talent for capturing attention and arousing curiosity and interest for the subject.

One cannot fail to mention that the book is based on deep and extensive historical and academic research, with references to other books, scientific articles and images, such as to the National Library of Medicine, The San Diego Brain Observatory, the book "De Humani Corporis Fabrica", by Andreas Vesalius, The death of Henry II of France did not publish any Journal of Neurosurgery, among others.

The negative point observed was the general organization of the book, which in our opinion could have been done in descending chronological order, as it would help the reader form a clearer idea of how the historical evolution of the most important events involving the neurosciences occurred, but this does not invalidate the importance and quality of the book as a whole.

Thus, considering the decreasing number of medical students who declare their intention to invest in a career in research, a branch of fundamental importance in this area of knowledge, and considering that the act of arousing curiosity and pleasure for answering questions are essential motivating pillars for any researcher, the importance of this book as complementary literature in the field of medicine becomes clear, especially due to the relaxed and engaging way in which it addresses the subjects, and can act as a mitigator of the current discrepancies in relation to the intention vocational training of these professionals after their formation.

Finally, it would not be risky to think that, even a fully-trained neurosurgeon with many years of dedication to the profession, after reading this book, could even for a moment enter into an internal duel (paraphrasing the title of the book) and imagine a life as a neuroscientist.

Author Contribution

GAS had the original idea and wrote the manuscript. EGS and SGS reviewed the writing and the scientific content of the manuscript, and made suggestions regarding the topics to be approached.

Conflicts of Interest

The authors have none to declare.

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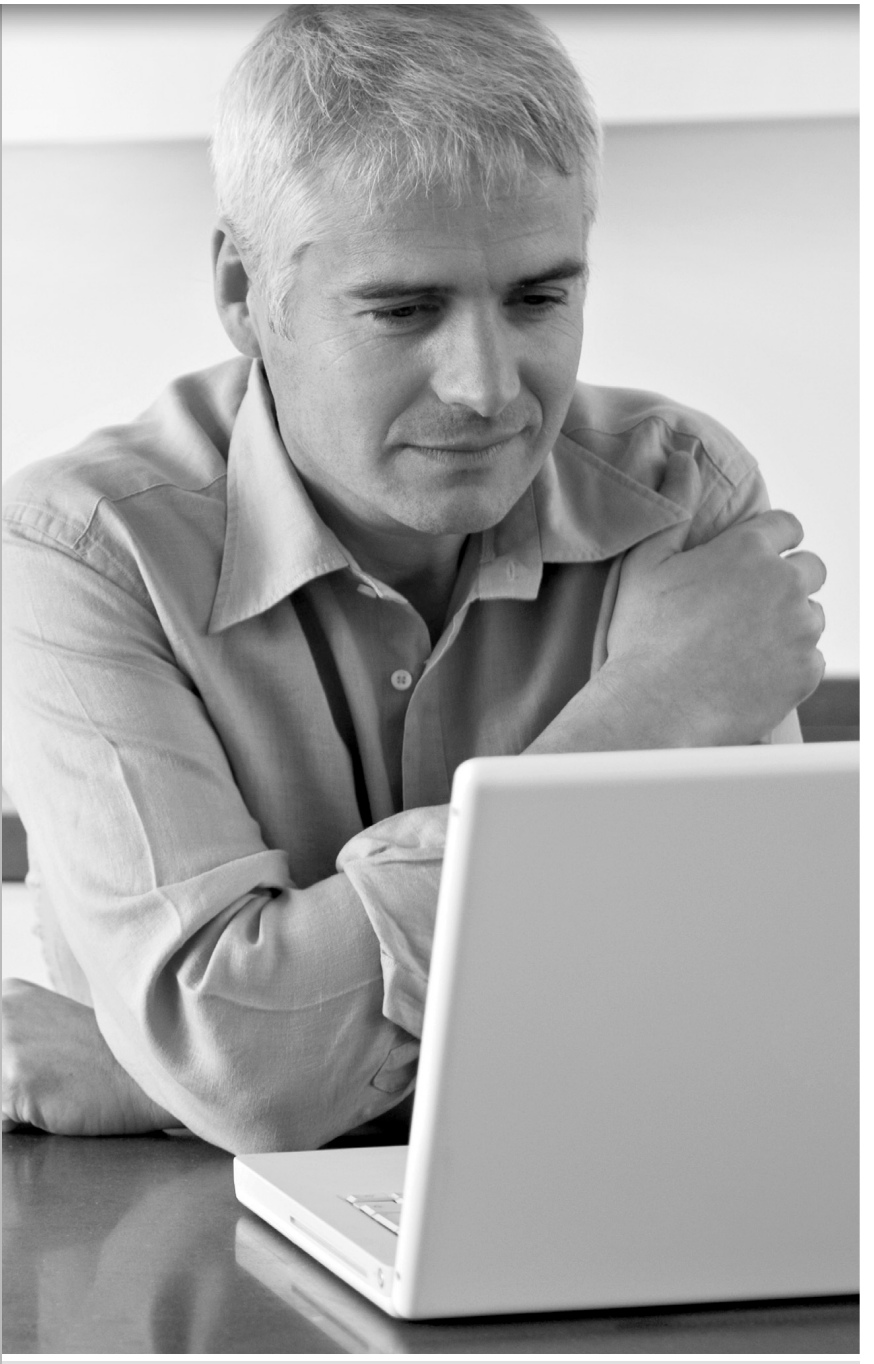

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