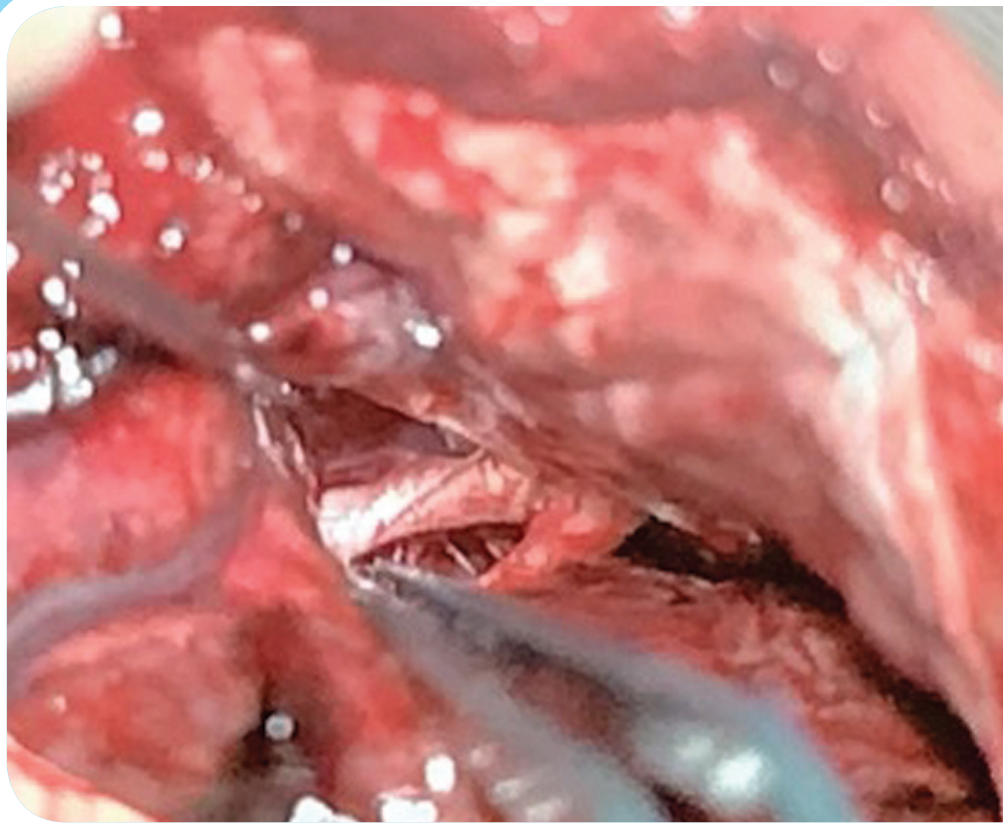
ISSN 0103-5355

Brazilian Neurosurgery

Arquivos Brasileiros de Neurocirurgia

Number 3 • Volume 39 • Pages 155–242 • September 2020



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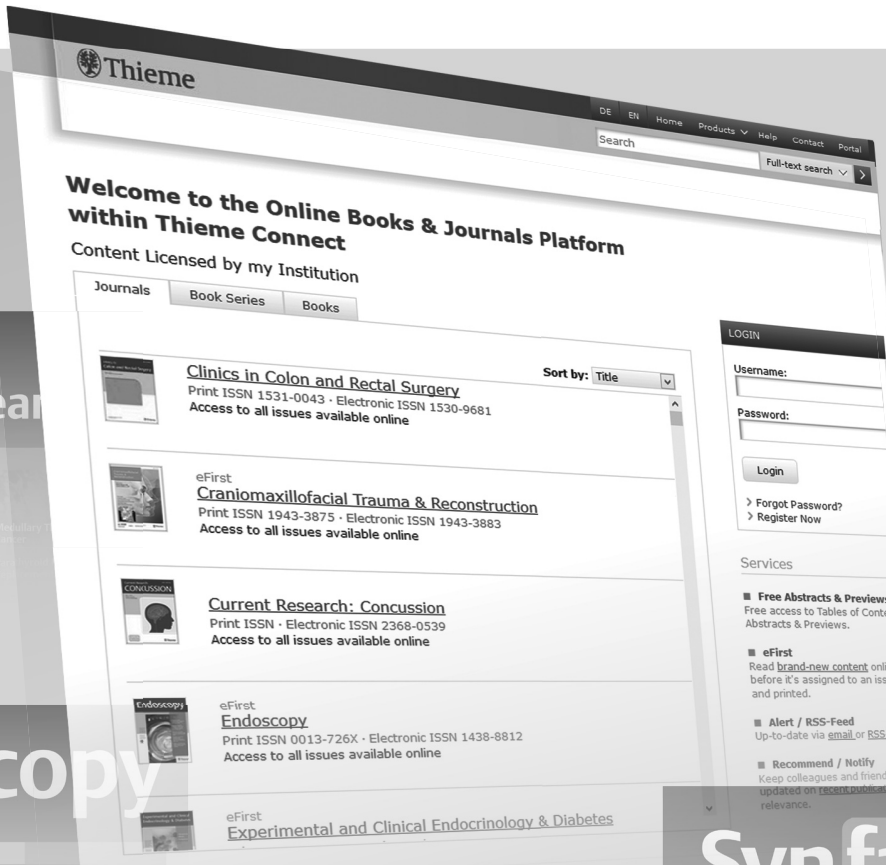

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ISSN 0103-5355

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Volume 39, Number 3/2020

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 Arquivos Brasileiros de Neurocirurgia is published four times a year in March, June, September, and December by Thieme-Revinter Publicações Ltda, Rua do Matoso, 170, Rio de Janeiro, 20270-135, Brazil.

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ISSN 0103-5355

Microsurgical Cisternostomy for Treating Critical Patients with Traumatic Brain Injury - An alternative Therapeutic Approach

Cisternostomia microcirúrgica para o tratamento de pacientes críticos com lesões cerebrais traumáticas - Uma abordagem terapêutica alternativa

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Arq Bras Neurocir 2020;39(3):155–160.

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Abstract

Introduction Traumatic brain injury (TBI) is a major cause of mortality around the world. Few advances regarding surgical approaches have been made in the past few years to improve its outcomes. Microsurgical cisternostomy is a well-established technique used in vascular and skull base surgery and recently emerges as a suitable procedure with lesser costs and morbidity when compared with decompressive craniectomy in patients with diffuse TBI. This study aims to describe the technique, indications, and limitations of cisternostomy and to compare it with decompressive craniectomy (DC).

Methods A prospective study is being conducted after obtaining approval of the local human ethics research committee. Once the inclusion and exclusion criteria are applied, the patients are submitted to microsurgical cisternostomy, pre and postoperative neurological status and brain computed tomography (CT) evaluation. A detailed review was also performed, which discusses diffuse TBI, DC, and cisternostomy for the treatment of TBI.

Results Two patients were submitted to cisternostomy after TBI and the presence of acute subdural hematoma and huge midline shift at admission computed tomography. The surgery was authorized by the family (the informed consent form was signed). Both patients evolved with a good recovery after the procedure, and had a satisfactory control brain CT. No further surgeries were required after the initial cisternostomy.

Conclusions Cisternostomy is an adequate technique for the treatment of selected patients affected by diffuse TBI, and it is a proper alternative to DC with lesser costs and morbidity, since a single neurosurgical procedure is performed. A prospective study is being conducted for a better evaluation and these were the initial cases of this new protocol.

Keywords
- cisternostomy
- traumatic brain injury
- decompressive craniectomy
- hydrodynamics

received
June 25, 2019
accepted
December 2, 2019

DOI https://doi.org/10.1055/s-0040-1701279.
ISSN 0103-5355.

Resumo

Introdução O traumatismo crânio-encefálico (TCE) é causa importante de mortalidade em todo mundo. Poucos avanços em relação a abordagens cirúrgicas foram feitos nos últimos anos com o objetivo de melhorar seus desfechos. A cisternostomia microcirúrgica é uma técnica bem estabelecida usada nas cirurgias vasculares e de base de crânio e que recentemente surgiu como um procedimento com menos custos e menor morbidade quando comparada a craniectomia descompressiva (CD) para pacientes vítimas de TCE. O presente estudo objetiva descrever a técnica, as indicações e as limitações da cisternostomia e compará-la com a CD.

Métodos Um estudo prospectivo está sendo conduzido após obtenção de autorização do comitê local de ética em pesquisa. Após aplicados os critérios de inclusão e exclusão, os pacientes são submetidos à cisternostomia microcirúrgica, sendo avaliados o status neurológico e as tomografias computadorizadas (TCs) de crânio pré e pós-operatórias. Alem disso, uma revisão detalhada foi realizada considerando a discussão sobre TCE difuso, CD, e cisternostomia para o tratamento do TCE.

Resultados Dois pacientes foram submetidos a cisternostomia após TCE com presença de lesão difusa incluindo hematoma subdural agudo e desvio de linha média. A cirurgia foi autorizada pelas famílias (o termo de consentimento informado foi assinado). Os pacientes evoluíram com boa recuperação após o procedimento, e a TC pós-operatória satisfatória. Não foram necessárias outras cirurgias após a cisternostomia.

Conclusões A cisternostomia é uma técnica adequada para o tratamento de pacientes selecionados vítimas de TCE com lesão difusa, e representa uma alternativa à CD, com menos custos e menor morbidade. Um estudo prospectivo está sendo conduzido para melhor avaliação, e esses foram os resultados iniciais deste novo protocolo.

Palavras-chave

- cisternostomia
- traumatismo cranioencefalico
- craniectomia descompressiva
- hidrodinâmica

Introduction

Traumatic brain injury (TBI) has a high incidence and mortality index in all age groups and all around the world. It also has a huge economic impact, mainly in developing countries, because of its direct and indirect costs and, therefore, public health budget commitment.[1] A Brazilian retrospective study has shown an elevated cost associated with decompressive craniectomy (DC) for TBI.[2] In the past decades, the incidence of trauma has significantly increased, and it is predicted that in few years it will surpass the incidence of some chronic conditions, such as vascular diseases.[3] The importance of this theme is clear; nevertheless, few advances have been made in the last years, especially regarding neurosurgical approaches. In many countries, trauma neurosurgery did not have significant advances[3] when it comes to trying to improve the outcomes and minimize the costs.

The knowledge of the mechanism of TBIs helps to understand the pathophysiology of these lesions and how to improve the therapeutic approaches. Traumatic brain injuries can be focal or diffuse. For focal lesions, there are detailed protocols describing intensive care unit (ICU) management and surgery indication according to the type, size, and topography of the injury. However, there are some controversies about the treatment of diffuse injuries.[1] Considering surgical treatment, DC has been used in the past decades, although some large trials have not shown real benefits in the outcomes,[4,5] and, besides, these patients required further surgeries to restore the normal brain hydrodynamic.[6] Thus, DC is associated with elevated costs and few benefits.[2]

In this context, a well-defined technique, previously used in skull base and vascular surgeries, has been proposed to improve cerebrospinal fluid (CSF) flow, brain hydrodynamic and avoid DC.[1] Cisternostomy is a technique in which the basal cisternae are opened, thus helping brain relaxation and, consequently, eliminating the need for DC. It is performed in patients with moderate or severe TBI and diffuse injuries who would classically be submitted to DC.

Methods

A research project was developed, evaluated and approved by the local human ethics research committee. It was also registered at the *Plataforma Brasil* database. All study procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This is a prospective study in which patients affected by TBI, considering the inclusion and exclusion criteria, are submitted to cisternostomy as the main neurosurgical procedure. The initial results are described in this paper, and an extensive review about diffuse TBI, DC and cisternostomy is also performed. This protocol is still being applied for a bigger evaluation.

The inclusion criteria are patients between 18 and 70 years without severe systemic compromise and with diffuse TBI and classic indication for DC. A consent form was signed by the legal responsible, and the procedure performed within a maximum of 6 hours after emergency room (ER) admission. The pre and postoperative neurological exam and computed tomography (CT) were evaluated.

An extensive literature review considering the terms cisternostomy, traumatic brain injury, DC was conducted.

Results

After the local ethics committee approval, two patients were selected for cisternostomy, and they are described below.

Case 1

A 20-year-old male patient fell off a height of 3 m and was associated to TBI. He was admitted to the neurosurgical emergency department presenting with a Glasgow coma scale (GCS) of 12 and isochoric pupils, incapable of providing further information about his past medical history. He was evaluated according to Advanced Trauma Life Support (ATLS) protocol, and no other lesions were found. On his admission brain CT, a left acute subdural hematoma (ASH) with important midline shift was observed (►**Fig. 1**). The Zunkeller index was greater than 5 mm. In this context, a microsurgical cisternostomy (►**Fig. 2**) was proposed and performed within the first 6 hours after admission. The hematoma was drained during surgery; however, despite this, the brain remained swollen. Because of this, microsurgical technique for opening the basal cisternae and the lamina terminalis was performed. After this, a proper brain relaxation and edema decrease could be observed. Therefore, there was no need for a DC. The patient had a good recovery and was alert on the first postoperative day, with GCS of 15 and an adequate postoperative brain CT (►**Fig. 1**), without midline shift. He was discharged a few days after with a Glasgow outcome scale (GOS) of 5.

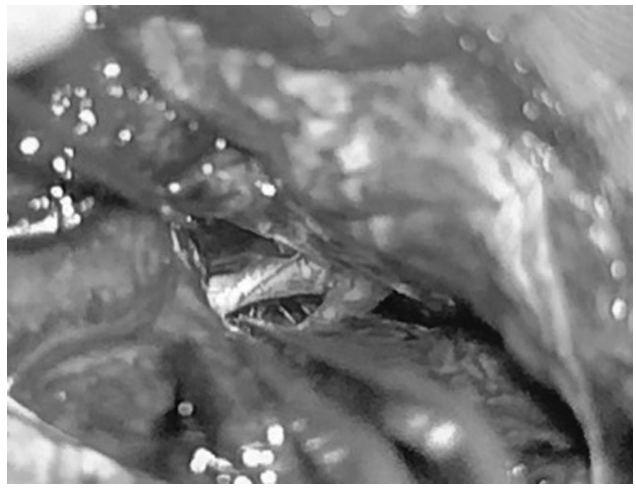

Fig. 2 Opticocarotid microsurgical cisterna opening – Case 1.

Case 2

A 69-year-old female patient presented to the neurosurgical emergency department after a fall from her own height and sudden unconsciousness. She arrived to the hospital with anisocoric (left > right) pupils, with a GCS of 3 and under mechanical ventilation. She did not have other systemic

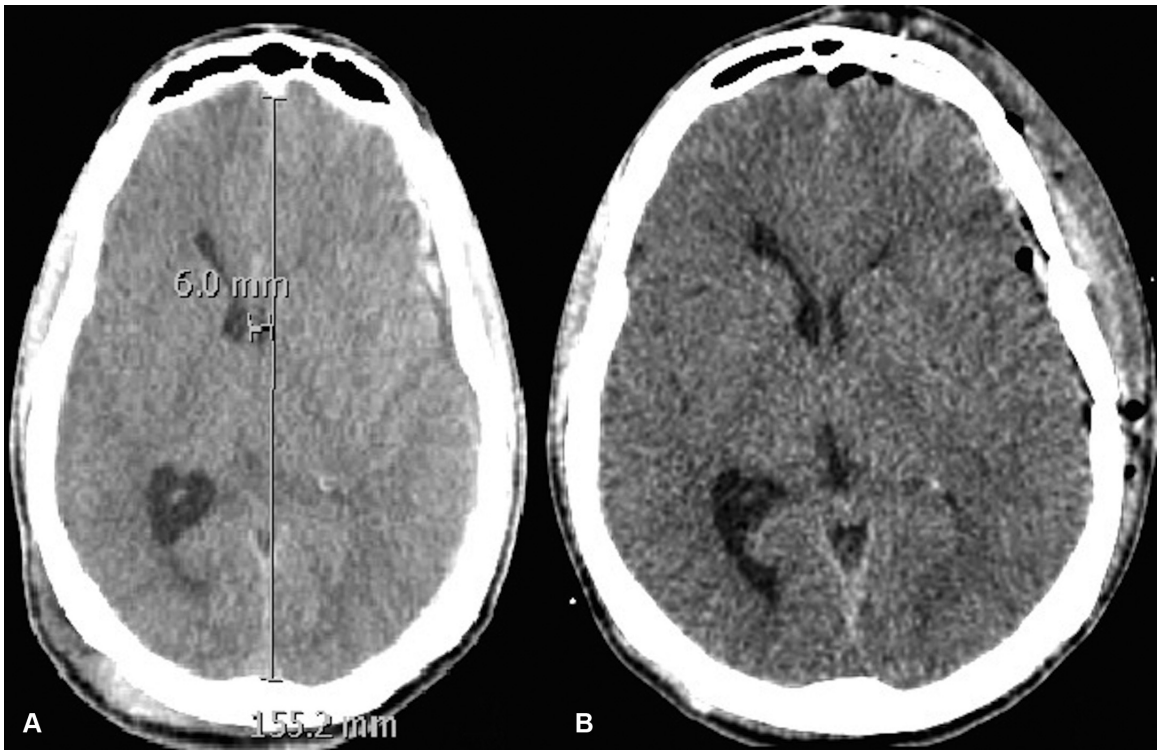

Fig. 1 (**A**) Admission axial brain computed tomography revealing a left subdural hematoma and brain swelling with midline shift; (**B**) 24-hour postoperative computed tomography revealing swelling reduction and no midline deviation.

lesions after evaluation by the ATLS protocol. On her past medical history, it could be noticed that she was previously submitted to a ruptured aneurysm clipping surgery at the same hospital and required a ventriculoperitoneal shunt. After this, she remained with neurological sequelae, especially concerning her cognitive status. She also used drugs for blood hypertension and acetylsalicylic acid due to a previous stroke.

On her admission brain CT, a massive ASH with midline shift (►**Fig. 3**) and a Zunkeller index greater than 5 mm were observed. She underwent a cisternostomy within less than 6 hours after admission (►**Fig. 4**). The hematoma was drained during surgery; however, despite this, the brain remained with noticeable swelling and transcalvarial herniation. Therefore, a microsurgical cisternostomy was proposed through the opening of the basal cisternae and the lamina terminalis. After this it could be noticed a proper brain relaxation, edema decrease and herniation resolution. There was no need for skull removal through DC. She had a slower recovery when compared with the pilot case; however, her postoperative brain CT showed a good surgical result (►**Fig. 3**) and she was discharged a month after the initial procedure with a GOS of 4 and with no need for further surgery.

No other neurosurgical procedures were required for either patient, and they had satisfactory recovery, evaluated through GOS and postoperative CT.

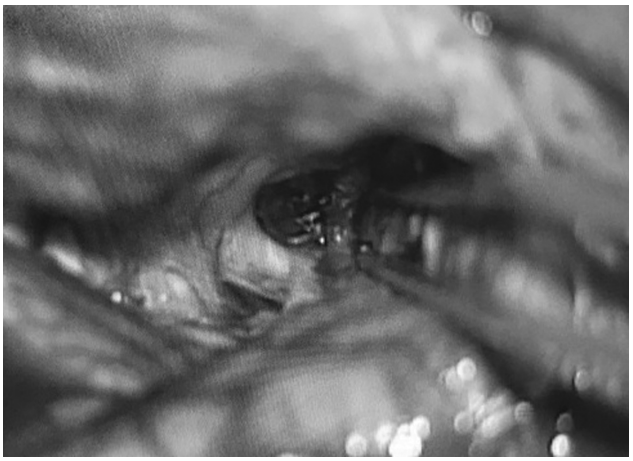

Fig. 4 During microsurgical cisternostomy it could be noticed the presence of an aneurysm clipping (internal carotid artery posterior communicating segment) – Case 2.

Discussion

Traumatic brain injury is a major cause of morbidity and mortality, especially in developing countries.[2] Direct traumas generally cause focal lesions, such as epidural hematomas, brain contusions, and skull fractures.[1] The neurosurgery procedures for draining these hematomas, if they have significant repercussion, are well established in the literature. The Brain Trauma Foundation Guidelines describe these indications.[1,7] On the other hand, due to inertial forces, in some cases, there are diffuse injuries, mainly brain swelling, traumatic SAH, diffuse axonal injury (DAI), and subdural hematomas.[8] These lesions constitute a therapeutic challenging and require a multidisciplinary team for a proper management.

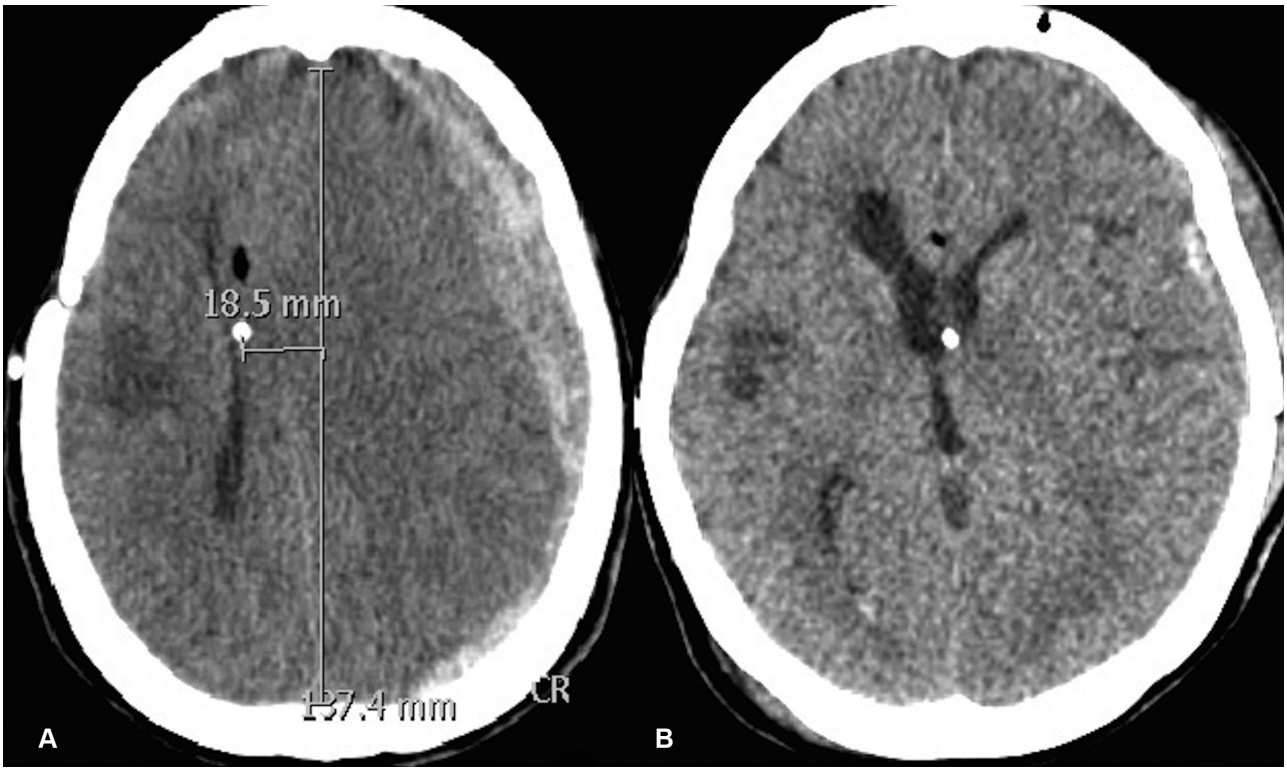

Fig. 3 (A) Preoperative brain computed tomography disclosing huge left subdural hematoma and brain swelling with severe midline shift; (B) 24 hours postoperative brain computed tomography revealing brain swelling and midline deviation reduction.

For diffuse TBI, DC may be an option for decreasing the raised intracranial pressure associated when there is an important brain swelling and midline shift causing brain herniation. However, many huge trials, such as DECRA and RESCUE-ICP, have demonstrated that this procedure has high morbidity and mortality rates.[1,2,9] The technique and indications of DC have been extensively described in previous studies;[4,10] nevertheless, the outcomes and costs are high, and these patients always require at least one more neurosurgical procedure for cranioplasty.

Recently, a Brazilian study had shown elevated costs associated with DC for TBI.[4] Patients who do survive generate greater hospitalization costs, and the majority of them will require future hospitalizations for treatment of clinical complications and other procedures, such as ventricular shunts and cranioplasty. Some studies have demonstrated that the real cost of these patients is $\sim$ 10 to 15 times greater than the cost of the treatment in the acute phase.[4,11,12]

Encephalic hemodynamic is severely altered after skullcap removal, and many complications are associated with this, such as hydrocephalus. In some cases, after DC, a permanent shunt is required in addition to further cranioplasty (with autologous or heterologous bone) to restore hydrodynamics.[13] Cranioplasty is a surgical procedure that requires another hospitalization after the acute phase and offers some risks, such as infection. Besides, it could be expensive, especially if synthetic prosthesis is used. A national population analysis performed in the United States revealed a mean total cost of U$ 94,356, with hospital payments comprising most of this cost at a mean of U$ 82,680.[14]

Recent evidence suggests that in trauma, edema formation is also associated with CSF entrance into the brain parenchyma via the low-resistance para-arterial space or decreased interstitial fluid efflux or a combination of the two processes.[6] There is a hypothesis that the glymphatic removal of excess interstitial fluid decreases new injury, and, therefore, CSF is shifted from the cerebral cisterns to the brain after TBI.[6] The hydrodynamics of the brain is altered after a severe TBI associated with diffuse lesions due to this mechanism.

Because of these principles, anatomy and physiology of the cisternae were studied[4] in the context of trauma. Commonly, the basal cisternae opening is a procedure performed in skull base and vascular neurosurgeries. It is useful for brain relaxation, helping to improve CSF flow and brain hydrodynamics.[6,15] In diffuse TBI, the cisterns are usually compressed, and the CSF flow is altered.[1,3,16] The Marshall Graduation System considers the cisternae status for TBI graduation and mortality estimate. Opening cisterns in a tight brain is a difficult procedure. Nevertheless, after the opening of the interoptic, opticocarotid, and lateral carotid cisternae, the brain become lax. This procedure reverses the cisternal pressure gradient, causing CSF to flow back into the cisterns, thus decreasing the intracranial pressure.[6,15]

Cherian et al[1,3] described a case series of cisternostomy for the treatment of TBI, comparing it with DC, and achieved good results. Cisternostomy presented decreased morbidity and mortality when compared with DC. Cisternostomy has a low cost, same surgical duration and better outcomes. Patients will not require additional procedures, as they do after DC: a cranioplasty is always performed, and, in many cases, patients required ventriculoperitoneal shunt to restore brain hydrodynamics. In this protocol, the lamina terminalis is also opened.

After local ethics committee approval and national databank registration, this technique is being performed at our institution for patients with diffuse TBI to whom DC would be classically indicated (considering established protocols for this surgery). Inclusion and exclusion criteria were applied to perform this study, considering age, time from the trauma until the surgery, the presence of severe major internal organ lesions, and family authorization.

These are the initial results of an extensive protocol that is being applied at our institution.

Conclusions

Cisternostomy was performed in the cases described in the present manuscript as part of this new protocol for the treatment of TBI. A similar study was previously published only by a single center with good outcomes. Patients evolved with a proper functional recovery and did not require further neurosurgical interventions. This technique is an advance in neurotrauma surgery. Low costs, morbidity and mortality are the major benefits of cisternostomy. A case series is being developed at our institution for a better analysis of the results.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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Cerebrospinal Fluid Infection with External Ventricular Drainage: Analysis of the Risk Factors in 110 Patients of a Single Institution*

Infecção liquórica em drenagem ventricular externa: Avaliação dos fatores de risco em 110 pacientes de uma única instituição

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Arq Bras Neurocir 2020;39(3):161–169.

Abstract

Objectives External ventricular drainage (EVD) is extensively used in the neurosurgical practice with the purpose of monitoring the intracranial pressure and draining the cerebrospinal fluid (CSF). Despite its remarkable benefits, the technique is not devoid of risks, notably infections, which have been reported in up to 45% of the cases.

Methods A retrospective analysis of the main risk factors for CSF infection in neurosurgical patients submitted to EVD at a single institution. We recorded and submitted to statistical comparison every risk factor for CSF infection present or absent in each of the 110 EVD patients enrolled, 53 males and 57 females, with an average age of 52.9 years, with different underlying neurosurgical conditions.

Results Infection of the CSF occurred in 32 patients (29%). The rate of mortality related to CSF infection was of 18.7% (6 of 32). The risk factors that showed statistical significance for CSF infection in this series were: emergency surgery; length of stay at the intensive care unit (UCI); duration of the EVD; parenchymal and/or intraventricular hemorrhage; simultaneous infections; time of bladder catheterization; and the use of non-disposable adhesive drapes as part of the preparation of the wound area.

Conclusions Infection of the CSF in patients submitted to EVD is multifactorial and a challenge in terms of prevention. Further studies proposing scores with blended risk factors may be useful to prevent and reduce the morbidity and mortality associated with CSF infection.

Keywords
- external ventricular drainage
- cerebrospinal fluid infection
- risk factors

* *Work developed at the Neurosurgery Service of Hospital de Clínicas, Universidade Federal do Paraná (UFPR), Curitiba, Paraná, Brazil.*

received
February 19, 2020
accepted
May 12, 2020

DOI https://doi.org/10.1055/s-0040-1713917.
ISSN 0103-5355.

Resumo

Objetivos A derivação ventricular externa (DVE) é frequentemente utilizada na prática neurocirúrgica para monitorização da pressão intracraniana e drenagem de líquido cefalorraquidiano (LCR). Apesar dos evidentes benefícios, a utilização do método não é isenta de riscos, notadamente infecção, podendo atingir incidência de até 45%.

Métodos Realizamos análise retrospectiva dos principais fatores de risco para infecção do LCR em pacientes neurocirúrgicos com DVE em uma única instituição. Registramos e analisamos, através de comparações estatísticas, todos os fatores de risco para infecção do LCR presentes ou ausentes em uma série de 110 pacientes submetidos à DVE, onde 53 eram homens e 57 mulheres, com idade média de 52,9 anos.

Resultados Infecção do LCR ocorreu em 32 pacientes (29%). A taxa de mortalidade relacionada diretamente à infecção liquórica foi de 18,7% (6 de 32). Os fatores de risco que se mostraram significantes para infecção do LCR nesta série foram: cirurgia de emergência, tempo de permanência em UTI, tempo de permanência da DVE, hemorragia parenquimatosa e/ou intraventricular, foco infeccioso distante concomitante, uso prolongado de sonda vesical e o uso de campos cirúrgicos não adesivos durante a confecção da DVE.

Conclusões A infecção do LCR em pacientes com DVE é multifatorial e um desafio para sua prevenção. Estudos adicionais, com propostas de escores que combinem vários fatores de risco podem ser úteis na prevenção e redução dos índices de infecção liquórica com repercussão positiva sobre morbidade e mortalidade associadas.

Palavras-chave

- derivação ventricular externa
- infecção liquórica
- fatores de risco

Introduction

Ventricular catheters are essential for the treatment of patients with intracranial hypertension. Besides monitoring hypertension, these devices also play a role in its treatment through cerebrospinal fluid (CSF) drainage. External ventricular drainage (EVD) is frequently used for the treatment of patients with disturbances in CSF circulation. Most patients present subarachnoid or parenchymal hemorrhage. Some patients present acute expansive lesions that require CSF derivation before the definitive treatment. Monitoring the intracranial pressure (ICP) and concomitant CSF drainage have been used more frequently over the past years. However, continuous CSF drainage may increase the exposure of the patients to risks. The main disadvantages of the permanence of these catheters are the potential risk of fatal ventriculitis and/or meningitis, and the mortality rate of the patients varies, reaching up to 45% according to a literature review.[1–4] Continuous monitoring of the ICP,[1,5] and continuous manipulation[1,6–8] and frequent collection of CSF for laboratorial tests[9] are factors frequently related to the contamination of the derivation system of the CSF. Other risk factors are related to the long-term use of the ventricular catheter, such as presence of an infectious site at distance and the surgical technique. Due to the fact that the influence and incidence of such risk factors for CSF infection may vary between groups of patients and regarding different procedures, it is relevant to know the data to improve the results related to CSF infection in patients submitted to EVD as individually as on specialized assistance provided by a neurosurgery service.

The present study aimed to identify and quantify the potential individual risk factors for infection related to the device in a series of patients submitted to EVD, to monitor the ICP or to perform CSF drainage.

Patients and Methods

The present study was performed in the Neurosurgery Service of Hospital de Clínicas, Universidade Federal do Paraná (UFPR). The project was evaluated and approved by the Ethics Committee on Human Beings of the hospital under technical report CAAE N° 0184.0.208.000–08. Out of 142 patients submitted to EVD with registered data, 110 patients whose records had full information related to the study were included. These patients had a ventricular catheter implanted for CSF drainage. Their underlying diseases were cerebral aneurysms, intracranial tumors, hydrocephalies, and strokes. All patients were aged 16 years or older. All of them were submitted to frontal or parietal EVD, and the same surgical technique was used, with catheter exteriorization by counter incision with a subcutaneous tunnel, and always using the same model of EVD system. Patients with active central nervous system (CNS) infection were excluded from the study. The minimum period of follow-up for inclusion in the study was of 6 months.

The potential risk factors associated to CSF infection in patients submitted to EVD were chosen after a review of the world literature and based on the experience of the service, and they were divided into 4 groups for didactical purposes: 1) factors related to the patients submitted to EVD; 2) factors related to the disease/neurological condition of the patients

Table 1 Factors with potential influence on the onset of cerebrospinal fluid (CSF) infection in external ventricular drainage (EVD)*

Group 1–Factors related to the patients submitted to EVD			
Age (110)	Gender (110)	Comorbidities (108)	Distant-site infection prior to the EVD procedure (108)
ICU permanence (104)	Use of prophylactic antibiotics (108)	Use of hormonal anti-inflammatory drugs (108)	Bladder catheter permanence (102)
Group 2–Factors related to the disease/neurological condition			
Surgery indication (108)	Glasgow Coma Scale at admission (109)	Treatment of underlying disease (110)	Intraventricular hemorrhage (102)
Presence of hydrocephalus (100)		Postoperative Glasgow Coma Scale (108)	Postoperative ICP alteration (98)
Group 3–Factors related to the neurosurgical treatment			
Concomitant procedures (108)	Emergency surgery (110)	Surgery time (106)	Anesthesia time (106)
Surgeon experience (110)	Number of surgeons (110)	Operating room (98)	Number of professionals in the operating room (108)
Change of assistants in the operating room (108)	Presence of a technician (108)	Use of surgical adhesive film (110)	Trepanning site (104)
Number of suture plans (110)			
Group 4–Factors related to the EVD device			
Previous manipulation of the EVD system (108)		EVD time (106)	Change of the prophylactic catheter of the EVD (110)

Abbreviations: ICP, intracranial pressure; ICU, intensive care unit.
*The figures in parentheses refer to the numbers of patients used in the specific statistical analysis of each factor.

submitted to EVD; 3) factors related to the neurosurgical treatment to which they were, including the implantation of the device; and 4) factors directly related to the EVD device. ►**Table 1** shows all potential factors for CSF infection investigated in the study subdivided into 4 categories, as well as the number of patients who participated in each individual analysis of the factors.

Epidemiological data about the studied population were obtained, such as age and gender; clinical data such as comorbidity, symptoms and sign of sickness, fever, interval between the onset of the symptoms and the diagnosis, level of consciousness according to the Glasgow Coma Scale (GCS), and location of associated lesions through imaging tests, such as computed tomography or encephalic nuclear magnetic resonance. We also obtained data related to the treatment, such as surgical time, qualification of the professional who performed the procedure, use of disposable surgical adhesive film, number of professionals in the surgical room, and use of prophylactic antibiotics. Laboratorial data obtained from biochemical CSF tests, CSF cultures and hemograms were also recorded. According to literature review,[10] for the purpose of analysis, in the present study the presence of positive CSF culture was considered ventriculitis, this fluid was taken from the ventricular catheter or by lumbar puncture, associated to fever, clinical signs of meningitis, including stiff neck, photophobia, decrease in the level of consciousness, seizures, as well as low levels of glucose, high protein, and CSF pleocytosis. Manipulation and/or changes of catheter were performed only due to demand in specific individuals. In order to analyze each parameter, the patients were subdivided regarding the occurrence or non-occurrence of CSF infection. At the hospital release, the functional state of the patients was evaluated and classified in categories A, B or C according to the Karnofsky Scale, which was adapted by Crooks et al.[11]

The statistical analysis consisted of determining the positive and negative predictable values, the specificity, the sensibility, and the accuracy of several parameters of the study; comparative tests for each risk factor in the study were also applied. Regarding the qualitative parameters, the Chi-squared (χ^2) test and/or frequency distribution tables were used. As for the quantitative parameters, we first observed the prerequisite of normal distribution (Gauss) to later choose the statistical tests (Student *t* test or the Mann-Whitney test). In all of the analyses, p-values < 0.05 were considered statistically significant.

Results

In the present series, the age ranged from 16 to 82 years, with an average of 52.9 years, and the sample was composed of 53 men and 57 women. In total 32 (29%) patients filled the criteria for the diagnosis of CSF infection required by the study. The CSF cultures were positive for *Staphylococcus epidermis* in 59.37% of the patients, followed by *Staphylococcus aureus* in 18.75% of the cases. *Acinetobacter baumanni*, *Enterococcus faecalis*, *Enterobacter cloacae* and *Staphylococcus hemoliticus* were the etiological agents agents of the 7 remaining cases (21,88%).

The most common comorbidity was systemic arterial hypertension in 16 patients, followed by the effects of

smoking in 8 patients, the effects of alcoholism in 4 patients, and type-2 diabetes mellitus in 4 patients. Emergency surgeries were performed in 77% (85 out of 110 patients) of the cases. The average permanence of the EVD was of 10 to 14 days. The trepanning site was predominantly frontal (87 cases). Disposable surgical adhesive film was used in 49 of the 110 patients (44,54%) patients during the surgical procedure. In total, 92 (83%) cases of hydrocephalus were verified. Prophylactic antibiotics were used in 86 (78%) cases, and cefazolin was the most administered drug.

►**Table 2** shows the results obtained in the analysis of the factors related to the patients, with the respective statistical comparison between carriers and non-carriers of CSF infection.

Neither age nor gender or the comorbidities influenced on the onset of CSF infection in the patients submitted to EVD in the present study. Similarly, the use of prophylactic antibiotics or hormonal anti-inflammatory drugs did not show a significant effect. However, the existence of distant-site infection prior to the insertion of the system, the length of stay of the patient in intensive care, as well as the time of permanence of the bladder catheter were factors that potentially had an influence on the onset of CSF infection (►**Table 2**).

►**Table 3** presents the analysis of the factors related to the illnesses that may correlate with CSF infection in the patients submitted to EVD.

In general, the studied aspects of the underlying diseases of the patients submitted to EVD did not influence the onset of CSF infection. However, the CNS hemorrhage links both factors with positive data. Sick patients with hemorrhage in the CNS and/or inside the ventricles are more prone to present CSF infection in case they need EVD (►**Table 3**).

We analyzed many different aspects and characteristics related to the neurosurgical treatment administered to the patients submitted to EVD (►**Table 4**).

Some of the factors evaluated in this study and listed on ►**Table 4** are rarely found in the available literature. What draws attention is that the concomitant execution of other procedures, such as tracheostomy, central venous access, invasive mean arterial pressure monitoring, phlebotomy and cystostomy, did not influence the rate of CSF infection.

Table 2 Factors with potential influence on the onset of cerebrospinal fluid (CSF) infection related to the patients submitted to external ventricular drainage (EVD)

Evaluated factor	Factor distribution among patients with and without CSF infection			Statistical test (univariate analysis)
Age (years)	CSF infection	Average age		Student *t* test
	With	53.88		$p = 0.57$
	Without	52.12		
Gender	CSF infection	Male	Female	Chi-squared test
	With	15	17	$p = 0.97$
	Without	38	40	
Comorbidities	CSF infection	Absent	Present	Chi-squared test
	With	3	29	$p = 0.09$
	Without	20	56	
Previous infection distant from the EVD system	CSF infection	With previous infection	Without previous infection	Chi-squared test
	With	28	4	$p < 0.0001$
	Without	34	42	
Permanence in the intensive care unit (ICU)	CSF infection	Average of days in the ICU		Student *t* test
	With	20.97		$p < 0.0001$
	Without	11.81		
Use of prophylactic Antibiotics	CSF infection	Yes	No	Chi-squared test
	With	25	7	$p = 0.99$
	Without	61	15	
Use of hormonal anti-inflammatory drugs	CSF infection	Yes	No	Chi-squared test
	With	21	11	$p = 0.10$
	Without	35	41	
Permanence of the bladder catheter	CSF infection	Average (days)		Student *t* test
	With	21.25		$p < 0.0001$
	Without	10.71		

Table 3 Factors with potential influence on the onset of cerebrospinal fluid (CSF) infection related to the underlying disease of the patients submitted to external ventricular drainage (EVD)

Evaluated factor	Factor distribution among patients with and without CSF infection					Statistical test (univariate analysis)
Surgical indication	**CSF infection**	**Subarachnoid hemorrhage and brain aneurysm**	**Hemorrhagic stroke**	**Brain tumor**	**Other**	**Chi-squared test**
	With	16	13	0	3	$p = 0.001$
	Without	29	16	8	23	
Glasgow Coma Scale at admission	CSF infection	3 to 8	9 to 14	15		Chi-squared test
	With	18	10	4		$p = 0.50$
	Without	43	18	16		
Treatment of underlying disease	CSF infection	Only EVD	EVD + operation			Chi-squared test
	With	19	13			$p = 0.21$
	Without	37	41			
Intraventricular hemorrhage	CSF infection	Hemorrhage	Without hemorrhage			Chi-squared test
	With	32	-			$p < 0.001$
	Without	51	19			
Presence of hydrocephalus	CSF infection	Yes	No			Chi-squared test
	With	32	-			$p = 0.10$
	Without	60	8			
Postoperative Glasgow Coma Scale	**CSF infection**	**3 to 8**	**9 to 14**	**15**		**Chi-squared test**
	With	**19**	**11**	**2**		$p = 0.10$
	Without	**46**	**15**	15		
Postoperative alteration in intracranial pressure	CSF infection	Yes	No			Chi-squared test
	With	28	–			$p = 0.14$
	Without	62	8			

Curiously, from this specific group of factors, the only ones that showed influence on the onset of CSF infection in patients submitted to EVD were the emergency catheter for the neurosurgical treatment and the lack of use of surgical adhesive films (►**Table 4**).

Since certain aspects and characteristics of the manipulation of EVD systems may also influence the onset of CSF infection, they were also analyzed in the present study (►**Table 5**).

The total amount of time that the EVD system remained installed in the patient had an influence on the onset of CSF infection. Nevertheless, previous manipulation of the system did not have a negative influence, and the prophylactic change of the catheter did not have a positive influence; the patients who remained longer with the EVD system presented a higher rate of CSF infection (►**Table 5**).

Discussion

The most serious and potentially fatal complications of the onset of CSF infection are constituted by meningitis, ventriculitis or both. The concern about the risk factors that can determine CSF infection has grown in the world literature related to this subject. Among the several risk factors that are more frequently mentioned in the literature as relevant to CSF infection in patients submitted to EVD are the continuous monitoring of the ICP,[1,5] frequent manipulation,[1,6–8] collection techniques for regular laboratory evaluations,[9] prolonged permanence of the device,[2–4,7,9,12–14] concomitant infection,[13] the surgical technique used, CSF leak,[2,4,8,13,15] catheter change,[8] underlying diagnosis, as well as the factors related to the neurosurgical procedure of the treatment of the patients.[2,12] Despite the presence of some risk factors on the world literature, there is no consensus about which factors would be relevant, nor about the individual performance of each one of them in the many studies in which the topic is approached.

From the eight factors related to the patients submitted to EVD (►**Table 2**) whose statistical analysis was possible in this study, three of them were considered relevant to CSF infection. We verified that patients with infections in other sites, previous to the installation of the device, as well as those who remained with a bladder catheter for more than three weeks, or in an intensive care unit (ICU) for more than three weeks, developed CSF infection with significant superiority in relation to the others. In this sense, we find recent reports in the literature that support concomitant infection[13] and prolonged hospitalization in an intensive care environment[6,14] as relevant risk factors for CSF infection in patients submitted to EVD.

Table 4 Factors with potential influence on the onset of cerebrospinal fluid (CSF) infection related to the neurosurgical treatment of the patients submitted to external ventricular drainage (EVD)

Evaluated factor	Factor distribution among the patients with and without CSF infection				Statistical test (univariate analysis)
Concomitant procedures	CSF infection	Yes		No	Chi-squared test
	With	25		7	$p = 0.87$
	Without	60		16	
Emergency surgery	CSF infection	Emergency		Non-Emergency	Chi-squared test
	With	30		2	$p < 0.01$
	Without	55		23	
Surgery time	CSF infection	Average (minutes)			Student *t* test
	With	64.69			$p = 0.61$
	Without	74.39			
Anesthesia time	CSF infection	Average (minutes)			Student *t* test
	With	105.16			$p = 0.36$
	Without	128.18			
Surgeon experience	CSF infection	R2	R3/R4	Preceptor	Chi-squared test
	With	20	8	4	$p = 0.83$
	Without	44	22	12	
Number of surgeons	**CSF infection**	**Average**			**Student *t* test**
	With	**1.47**			$\mathbf{p = 0.39}$
	Without	**1.60**			
Operating room	CSF infection	Own surgical service room		Other	Chi-squared test
	With	26		4	$p = 0.46$
	Without	53		15	
Number of professionals in the operating room	CSF infection	Average			Student *t* test
	With	4.56			$p = 0.38$
	Without	4.88			
Change of assistants in the operating room	CSF infection	With change		Without change	Chi-squared test
	With	4		28	$p = 0.97$
	Without	8		68	
Presence of surgical instrument technician	**CSF infection**	**With**		**Without**	**Chi-squared test x^2**
	With	**4**		**28**	$\mathbf{p = 0.19}$
	Without	**20**		**56**	
Use of disposable	CSF infection	With surgical adhesive		Without surgical adhesive	Chi-squared test
Surgical adhesive film	With	2		30	$p < 0.0001$
	Without	47		31	
Trepanning site	CSF infection	Frontal		Parietal	Chi-squared test x^2
	With	25		5	$p = 0.81$
	Without	62		12	
Number of suture plans	CSF infection	Single		Double	Chi-squared test x^2
	With	27		5	$p = 0.64$
	Without	61		17	

Abbreviations: R2, second-year resident; R3, third-year resident; R4, fourth-year resident.

Table 5 Factors with potential influence on the onset of cerebrospinal fluid (CSF) infection related to the external ventricular drainage (EVD) system

Evaluated factor	Factor distribution among patients with or without CSF infection			Statistical test (univariate analysis)
Previous manipulation of the EVD system	CSF infection	Yes	No	Chi-squared test
	With	4	28	$p = 0.97$
	Without	8	68	
EVD time	CSF infection	Average of days with the EVD device		Student *t* test
	With	15.39		$p < 0.0001$
	Without	7.86		
Prophylactic change of the catheter of the EVD system	**CSF infection**	**With change**	**Without change**	**Chi-squared test**
	With	**8**	**24**	$\mathbf{p = 0.09}$
	Without	**8**	**70**	

We did not expect that factors such as age, gender and the comorbidities of the patients submitted to EVD had influence on the onset of CSF infection as shown on literature,[12] neither the number of days of hospitalization before an elective procedure, nor the number of hours before emergency procedures.

The use of prophylactic antibiotics did not have statistical relevance, and the literature is conflicting regarding their use. Some authors did not observe a decrease in the rates of infection with the administration of prophylactic antibiotics to populations who were victims or not of traumas, and they do not recommend their use.[16] The precise medical recommendations for the administration of prophylactic antibiotics are not well-defined, because their indiscriminate use may theoretically result in infections with resistant germs, anaphylactic reaction, prolonged bleeding time, and systemic toxicity. However, recent evidence[16,17] has suggested the use of catheters impregnated with antibiotics in the installation of the EVD device, which is justified by the significant increase in the time of infection-free stay achieved with such devices in comparison to catheters that were not impregnated.

Curiously, after the statistical analysis of the data, two other factors related to the patients submitted to EVD with potential influence on the onset of CSF infection – prolonged time of permanence in the ICU and prolonged time of permanence of the bladder catheter – were statistically significant risk factors for CSF infection. Despite the fact that none of the literature data corroborate these results, we believe that such data, mainly due to the nature of these factors, are related to the long-term manipulation of "multi-invaded" critical patients in ICUs.

In the present study, when we analyzed the potential risk factors for CSF infection that are related to the illness of the patients submitted to EVD (►**Table 3**), two factors that showed possible influence on the onset of CSF infection are linked by their origin – CNS hemorrhage. The patients submitted to EVD whose underlying disease presents hemorrhagic stroke or cause bleeding into the ventricle present higher risk of developing CSF infection. In spite of the fact that some literature reports do not agree with such information,[12,18] there are scientific records favoring the role of those factors in the onset of CSF infection in patients submitted to EVD.[1,2,5,10,14,19]

The presence of hydrocephalus, the fact that the device is installed simultaneously to the neurosurgical treatment of the underlying disease, the alterations in the ICP measurement in the postoperative period regarding the score on the Glasgow coma scale of the patients, when at the admission or after the treatment, did not have an influence on the onset of CSF infection in the present study.

The aspects specifically related to the neurosurgical treatment (►**Table 4**) that may be attributed to the onset of CSF infection frequently arouse the curiosity of specialists. Some of these factors are not very frequently found in the studies, probably due to the difficulty in obtaining records of the data, or due to the presence or absence of these factors in the study samples. Regarding this, we believe that the present study contributed specifically to the knowledge on the topic, since it was possible to raise the data of a series and perform statistical analyses to determine these factors.

There is a tendency to admit that there may be a higher risk of CSF infection in patients who had their EVD device installed at the same time as other surgical procedures were being performed. In the present study, this was not confirmed when the underlying neurosurgical disease was approached at the same time. The same result was obtained regarding other small concomitant procedures that were very prevalent (78%) in our series, such as tracheostomy, cystostomy, central venous access, arterial access, phlebotomies etc.

Another very common trend is to attribute to the emergency neurosurgical procedures with EVD an incidence of CSF infection significantly superior to the one found in the elective procedures in which the device was implanted. In the present study, the cases of emergency surgery associated or not with EVD, at the same time or isolated, presented a higher incidence of CSF infection than the elective surgical procedures with the same characteristics. However, there is always the possibility of interaction of factors that may influence the analysis and the results. A typical example would be the occasional and plausible higher incidence of illnesses involving hemorrhage in the CNS in patients who

underwent emergency surgeries, since the rates of CSF infection are higher in patients submitted to EVD who have illnesses that entail parenchymatous and/or ventricular hemorrhage. However, it is important to consider the simple argument that, in general, during emergency procedures, neurosurgical or non-neurosurgical technical errors, either isolated or in chain, are more likely to occur.

In the present study, we performed a sensible investigation of the occasional occurrence of CSF infection resulting from factors related to the surgical procedures in patients submitted to EVD. We did not find a significant statistical relationship between CSF infection and the following situations: prolonged duration of the surgery and anesthesia; the level of experience of the surgeon and the number of surgeons in the operating room; procedures performed in the operating rooms of specialties other than neurosurgery; procedures performed with a higher number of professionals or with changes of assistants; absence of surgical instrument technicians; frontal or parietal trepanning; and single or double suture plan of the surgical wound.

Curiously, the technical factor related to surgery with relevant results was the use of surgical adhesive films. The rate of CSF infection was higher in patients who underwent neurosurgical procedures without the use of surgical adhesive films. Evidence from recent researches[6,20] shows that CSF infection associated with EVD is acquired more frequently by the introduction of the bacteria during the insertion of the catheter than by the subsequent retrograde colonization. The world literature[3,15,16,21] and the present study ratify the fact that the etiology of this infection is widely dominated by *S. epidermidis*, which compose the cutaneous bacterial flora. Therefore, the use of more efficient physical barriers in the isolation of the surgical site may benefit the patients who need the insertion of the EVD device.

Similarly to other factors that were already discussed, it is valid to argue that the longer an invasive via remains open in the CNS, the higher the probability of CFS contamination and its consequences, mainly if the catheter is frequently manipulated, and if there are not prophylactic protocols regarding catheter change. This means that the technical manipulation of the EVD device should also be adequately analyzed in terms of its role in the development of CSF infection (►**Table 5**).

The present study shows that the rate of CSF infection was significantly higher in patients in whom the permanence of the EVD device was superior to 2 weeks.. Despite the fact that this is the most studied risk factor for CSF infection, it is still an issue that generates debate, and it is not accepted by all of the authors who study the topic. Park et al[18] observed a daily increase in the rate of infection after the insertion of the catheter. In the beginning, the infection is mild, but it worsens daily in a non-linear fashion, reaching its peak on the 4th day, though it may still worsen at rates of 1% and 2% a day until the 14th day. After that, many researchers believe that the infection rates remain stable. Holloway et al[5] also found a daily initial increase in the rate of infection after the insertion of the catheter, but the rate continued to increase by as much as 4.1% and 4.9% on days 12 and 14. But there are other authors who report that there is no relationship between the rate of infection and the time of permanence of the catheter.[19]

Some authors did not report the association between the number of manipulations of the EVD system and subsequent infection using a strictly aseptic technique.[1,13] Other authors reported greater rates of infection with the systematic irrigation of the system with antibiotics or saline solution, frequent handling or collection of samples, and scheduled exchanges.[6–9] In the present study, manipulation of the EVD device was rare (►**Table 5**). In the cases in which manipulation was necessary, we did not observe an increase in the rate of CSF infection.

Due to the reported increase in the rate of CSF infection after the insertion of the EVD catheter, some authors recommend changing the catheter prophylactly. The results of a controlled and randomized study[13] did not show a decrease in the rate infection rates with or without regular catheter changes. Several authors do not recommend changing the prophylactic EVD catheter.[2,10,12] In addition, in a recent study,[6] the authors demonstrated that maintaining an elective change protocol for the drainage system was an independent risk factor, increasing the chances of infection by ~ 4.6 times. We did not observe a protective effect against CSF infection regarding the prophylactic measures followed in this series.

Finally, we believe the present study contributes to a better comprehension of several factors that may influence the onset of CSF infection in patients submitted to EVD, it emphasizes the multi-factorial nature of the issue, and it suggests that recording the behavior of several factors involved in CSF infection in patients submitted to EVD is also relevant to neurosurgery services. We hope that in the future this data may be used to establish the profile of the patients who are more prone to develop infection, so physicians can provide them with attentive care, aiming to reduce the risk morbidity and mortality.

Conclusion

The individualized and detailed analysis of various relevant factors in the onset of CSF infection in patients submitted to EVD enabled us to establish a more probable profile of the patients who are more likely to develop it during the treatment: individuals with CNS disease with parenchymatous and/or ventricular hemorrhage who present previous distant-site infection, operated in an emergency situation without the use of surgical adhesive film, in whom the permanence in the ICU and/or of the bladder catheter is prolonged for more than 3 weeks, and in whom the EVD device is used for more than 2 weeks.

We suggest the performance of more in-depth studies with statistical multivariate analysis of relevant factors to enable a better prediction of the individual risk of developing CSF infection, with the proposal of a risk score; such studies would benefit a large number of patients.

Conflict of Interests

The authors have no conflict of interests to declare.

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Chronic Postoperative Pain: Comprehending It to Intervene

Dor crônica pós-operatória: Compreender para intervir

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Arq Bras Neurocir 2020;39(3):170–180.

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Abstract

It is estimated that between 266.2 and 359.5 million operations were performed in 2012 worldwide, and this number is on the rise. Chronic postoperative pain (CPOP) is the most important and still neglected postoperative complication, with a multifactorial causality, leading to a major impact on morbidity rates, high costs for the public health system, and direct and negative effects on the quality of life of the patients. The present systematic literature review aimed to elucidate the processes of postoperative pain chronification, biopsychosocial factors, risk factors, management of pain, and types of surgical procedures mainly associated with it. The review was based on the methodological recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The following databases were consulted: the Medical Literature, Analysis, and Retrieval System Online (MEDLINE), the Latin American and Caribbean Health Sciences Literature (LILACS), the Scientific Electronic Library Online (SciELO), and the Cochrane Central Register of Controlled Trials (CENTRAL). After reading the selected articles, the following surgical specialties were chosen to be addressed: general, orthopedics, breast cancer, gynecology, obstetrics, and thoracic. In conclusion, a deficient management of acute postoperative pain is the main risk factor for the development of CPOP. To prevent CPOP, training programs for healthcare professionals should be implemented to improve their skills and knowledge of the management of pain before, during, and after surgeries. It is also necessary to conduct more in-depth studies on the evaluation and management of this condition.

Keywords

- postoperative pain
- chronic pain
- pain management

Resumo

Estima-se que entre 266,2 e 359,5 milhões de cirurgias tenham sido realizadas em 2012 no mundo todo, e este número tende a crescer. A dor crônica pós-operatória (DCPO) é a complicação pós-cirúrgica mais importante e ainda negligenciada, com causalidade multifatorial, resultando em grande impacto nas taxas de morbidade, altos custos para o sistema de saúde, e efeitos diretos e negativos na qualidade de vida dos pacientes. Esta revisão sistemática da literatura teve por objetivo elucidar os processos de cronificação da dor pós-operatória, os fatores biopsicossociais, os fatores de risco, o manejo da dor, e os principais tipos de intervenção cirúrgica associados a ela. A revisão foi realizada com base nas recomendações de "Preferred Reporting Items for

received
June 7, 2019
accepted
October 22, 2019

DOI https://doi.org/10.1055/s-0039-3402489.
ISSN 0103-5355.

Systematic Reviews and Meta-Analyses (PRISMA)". As bases de dados consultadas foram: Medical Literature, Analysis, and Retrieval System Online (MEDLINE), Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS), Scientific Electronic Library Online (SciELO) e Cochrane Central Register of Controlled Trials (CENTRAL). Após a leitura dos artigos selecionados, as seguintes especialidades cirúrgicas foram escolhidas para abordagem: geral, ortopédica, mastológica, ginecológica, obstétrica e torácica. Em conclusão, o manejo deficiente da dor aguda pós-operatória é o principal fator de risco para o desenvolvimento da DCPO. Para prevenir a DCPO, é aconselhável implementar programas de treinamento para os profissionais da saúde de modo a melhorar suas habilidades e conhecimentos no que concerne o manejo da dor antes, durante e após procedimentos cirúrgicos. Também é necessário desenvolver estudos mais aprofundados acerca da avaliação e do manejo da DCPO.

Palavras-chave
- dor pós-operatória
- dor crônica
- manejo da dor

Introduction

It is estimated that between 266.2 and 359.5 million operations were performed in 2012 worldwide, and this number is on the rise.[1] Surgical procedures, like any type of aggression to the body, trigger immunological and metabolic responses to trauma as part of the adaptive response to the survival of the organism. The patient then reacts with anxiety and fear, feelings that may be present before, during, and after surgeries.

Pain persistence after surgical procedures is an important patient complaint. The International Association for the Study of Pain (IASP) defines pain as any unpleasant sensory and emotional experience associated with a present or potential tissue injury or described as this by the patient.[2] Therefore, pain is evidenced as a complex phenomenon that encompasses sensorial-discriminative and affective-motivational components.[3]

Despite the advances in the medical field, postoperative pain is still neglected and not properly treated. The consequences include decreased quality of life and increased morbidity and mortality rates. The acceptance of pain as a natural and predictable phenomenon after surgery corroborates healthcare professional negligence in spite of the patients' complaints. As a result, the patient sometimes stops complaining. Adequate management of acute postoperative pain (APOP) relieves suffering and favors early mobilization, thus shortening the average length of hospital stay and reducing costs. However, chronic postoperative pain (CPOP) is likely to occur after an episode of APOP that was not adequately treated.[4] The consequences of CPOP are of great importance, because in addition to causing suffering for patients and reducing their quality of life, it is also a burden on the health care and social support systems worldwide.

In summary, CPOP is a syndrome with its own characteristics, which may result from an isolated inflammatory process, neural damage, or a combination of these factors.[5] An up-to-date definition of CPOP includes the following criteria: pain developed after a surgical procedure or increased in intensity after it; pain should last at least 3 to 6 months and significantly affect the patient's quality of life; pain is a continuation of APOP or has developed after an asymptomatic period; pain is located in the surgical field, projected to the innervation territory of a nerve located at the site of the incision, or referred to a dermatome; other causes of pain should be excluded.[6]

Nevertheless, these criteria are usually not followed by healthcare professionals, since they have not been prepared to observe them. This deficiency in training makes recording the real incidence of CPOP almost impossible. In spite of this, it is well accepted that CPOP is the main surgical complication of APOP.[4,5]

Therefore, the present systematic literature review aimed to elucidate the processes of postoperative pain chronification, as well as the biopsychosocial factors, risk factors, management of pain, and types of surgical procedures mainly associated with it.

Materials and Methods

A systematic literature review was conducted based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The following databases were consulted: the Medical Literature, Analysis, and Retrieval System Online (MEDLINE), the Latin American and Caribbean Health Sciences Literature (LILACS), the Scientific Electronic Library Online (SciELO), and the Cochrane Central Register of Controlled Trials (CENTRAL). The search descriptors employed, associated with Boolean operators, were as follows: *postoperative chronic pain*, *postsurgical pain*, and *chronic pain*.

During article selection, the following inclusion criteria were adopted: 1) full-length original articles; 2) articles published within the past five years; 3) observational studies, randomized studies, or guidelines; and 4) articles written in Portuguese, English, or Spanish.

The exclusion criteria elected for the current review were: 1) studies involving animals; 2) studies involving children (under 18 years of age); 3) publications such as letters, comments, unpublished manuscripts, dissertations, government reports, and classes; 4) definition of chronic pain not meeting that of the IASP; 5) comparisons of medications, anesthetics, and/or surgical techniques; 6) studies with a

restricted focus on specific populations and/or regions; 7) prior use of opioids; and 8) previous chronic pain.

Results

During the literature review, a total of 25 papers were selected (►**Fig. 1**, ►**Table 1**). After reading the selected articles, the following surgical specialties were chosen to be addressed: orthopedic, gynecologic, obstetric, breast cancer, general, and thoracic.

Physiopathology of CPOP

The patients submitted to surgery present with tissue injury, which in turn locally releases chemical mediators that modify the environment where the nociceptors are located. This changes the depolarization threshold and causes a hyperalgesic response after the procedure. The C and Aδ fibers are sensitized, leading to non-evoked pain. Several factors contribute to the sensitization of nociceptors after surgery, such as pH reduction, lactate elevation, reduction of local oxygen tension, and activation of acid-sensitive ion channels.[4]

Sensitization is an increase in the effectiveness of synaptic driving. It manifests locally-peripherally with the release of chemical mediators of injured tissue and immune system cells that activate receptors of the neural membrane of the primary afferent of the C and Aδ fibers. Thus, chemical, mechanical, or thermal stimuli are transformed into electrical stimuli. Synapses are formed between these fibers and neurons from the posterior horn of the spinal cord, and they conduct the painful stimulus through the lateral spinothalamic tract to the nuclei responsible for the cognitive evaluation of cerebral cortex pain. The nociceptive impulse leads to an increase in the neuronal excitability of the central nervous system (CNS), generating central sensitization. Thus, the persistence and intensity of the painful stimulus lead to a decrease in the excitatory threshold of the nociceptor, which may cause allodynia or hyperalgesia. Subsequently, a repetitive activation of C fibers and a feedback of this process, added to sensory information processed in an atypical way, causes an alteration in peripheral and central neuroplasticity. This can last a long time after the initial lesion has healed, resulting in years of pain, characterizing the process of pain chronification.[5]

Risk Factors for CPOP

Chronic postoperative pain is associated with several preoperative, intraoperative, and postoperative risk factors, which

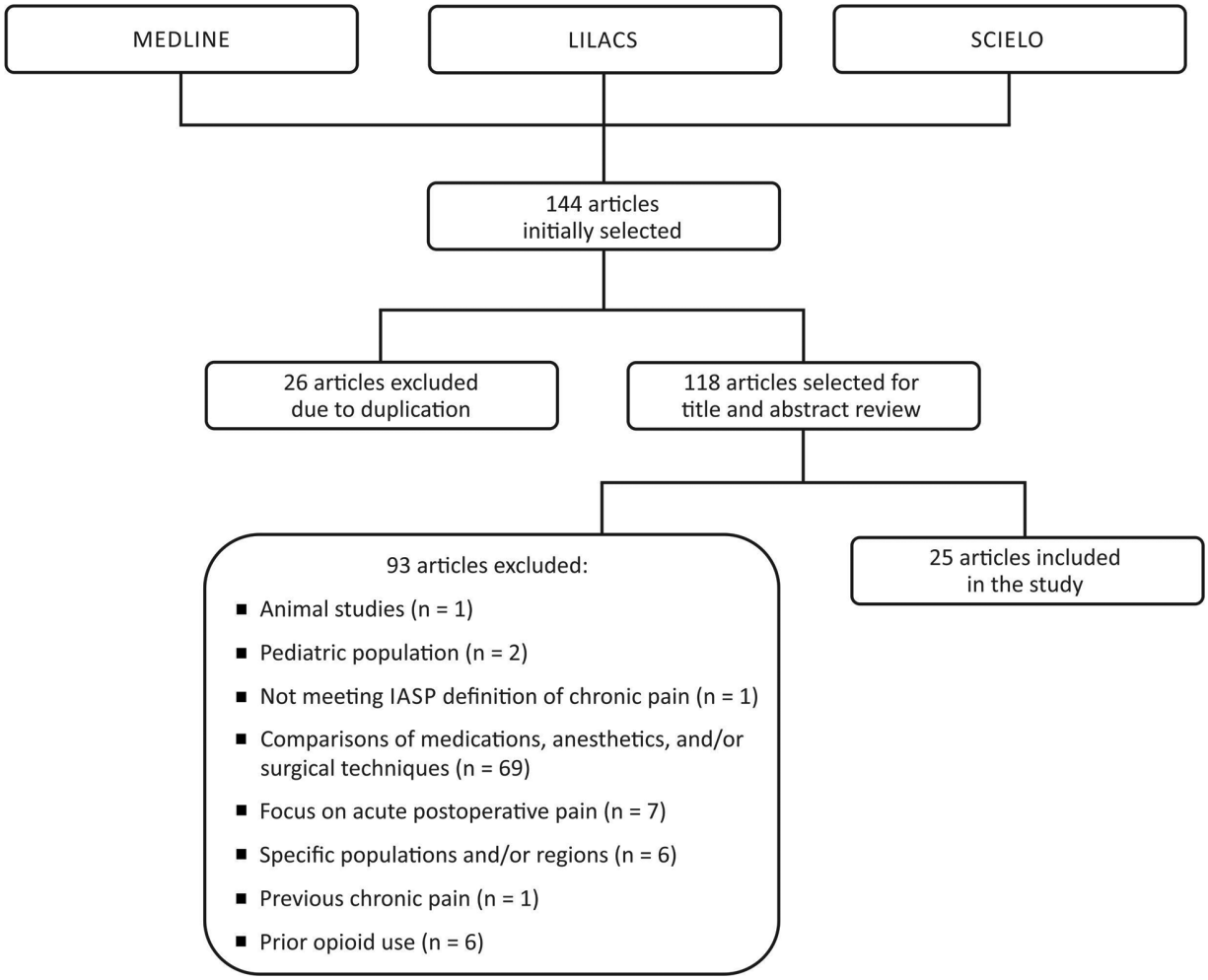

Fig. 1 Data collection during this systematic literature review.

Table 1 Articles selected in this systematic literature review

Design	Procedure	Sample	Follow-up	Conclusion	Reference
Retrospective study	Laparoscopic/open nephrectomy, laparoscopic/open prostatectomy, adenomectomy, cystectomy, prostatic cystectomy, laparoscopic hernia, open surrenalectomy, orchidectomy, renal transplant, pelvectomy, laparoscopic promontofixation	523 patients	3 months after surgery	Preoperative pain reported by 8% of the patients; chronic postoperative pain (CPOP) reported by 24% (6 months after surgery); neuropathic pain reported by 36%. Patients with CPOP had significantly more preoperative pain and increased morphine use in the postoperative period. Postoperative administration of non-steroidal anti-inflammatory drugs (NSAIDs) led to lower levels of persistent pain.	Artus et al[7]
Prospective cohort	Surgical excision of tumor with or without removal of axillary lymph nodes	406 women recruited: 338 with full preoperative data; 308 eligible for analysis at 4 months; 293 eligible for analysis at 9 months	Preoperative, 1 week, 4 months, and 9 months after surgery	210 out of 308 (68%) women reported chronic pain at 4 months, and 184 out of 293 (63%), at 9 months. Nine variables were included in the multiple logistic regression models, predicting chronic pain at 4 and 9 months. The adjusted analysis evidenced that younger women, those with greater preoperative psychological vulnerability and decreased psychological robustness, and those with higher acute pain scores at rest in the first postoperative week were more likely to have chronic pain at 4 months.	Bruce et al[8]
Retrospective study	Thoracotomy	320 patients	–	Almost 1 in 4 patients undergoing thoracic surgery may develop CPOP, 1/3 of them accompanied by a neuropathic component. Early prevention and aggressive treatment are important for high quality of life of patients with CPOP after thoracic surgery.	Peng et al[9]
Editorial	–	–	–	Re-evaluation of the criteria that make up the definition of CPOP.	Werner and Kongsgaard[6]
Prospective cohort	Surgical excision of breast tumor	537 patients	Preoperative, 3 days after surgery, 1 week after surgery, 6 months after surgery, 1 year after surgery	Both patient-related and treatment-related risk factors predict CPOP. Younger patients with preoperative locoregional pain, treated with axillary lymph node dissection and high intensity of acute postoperative pain (APOP) and signs of neuropathic pain in the acute phase of the postoperative period are at high risk.	Andersen et al[10]
Review	–	–	–	Government, colleges, and patients gathered to discuss chronic pain. Many risk factors are known, but few measures for prevention are taken. They propose to carry out studies on basic models of pain, among them CPOP, to study it and its prevention. Surgeries with higher rates of CPOP: mastectomy, thoracotomy, amputation, inguinal hernia repair.	Gewandter et al[11]
Prospective longitudinal cohort	Elective surgeries	908 patients	1 week before surgery, 4 days and 1 year after surgery	Prevalence – moderate to severe preoperative pain: 37.7%; acute postsurgical pain: 26.7%; and CPOP: 15.3%. Risk factors for the development of CPOP: surgical specialty; preoperative	Hoofwijk et al[12]

(*Continued*)

Table 1 (*Continued*)

Design	Procedure	Sample	Follow-up	Conclusion	Reference
				pain; use of preoperative analgesics; APOP; surgical fear; lack of optimism;, and poor preoperative quality of life. Prevalence of poor global recovery: 22.3%.	
Review	–	–	–	Five predictors contribute to CPOP: preoperative pain in the area to be operated on; CPOP elsewhere in the body, such as in the spine or hip; acute postoperative pain; capacity overload; and comorbid stress symptoms such as anxiety, rumination, magnification, and helplessness. Chronic pain may require a prolonged course of analgesic medication, specifically opioids.	Lavand' homme and Thienpont[13]
Observational study	Total knee replacement (TKR)	78 patients with knee osteoarthritis (OA), with no other associated local diseases	Preoperative, 2 months, and 12 months after surgery	Preoperative pain intensity and temporal summation (TS) correlated with 12-month postoperative pain intensity and showed a trend toward independence. The TS of pain may be a mechanistic preoperative predictor of the development of CPOP in patients with knee OA after TKR surgery.	Petersen et al[14]
Review	–	–	–	Chronic pain is frequent; it affects ~ 20% of people worldwide, and accounts for 15% to 20% of physician visits. Chronic pain should receive greater attention as a global health priority because adequate pain treatment is a human right, and it is the duty of any health care system to provide it.	Treede et al[15]
Review	–	–	–	The treatment of perioperative pain has significantly developed in the past 20 years. Detection of new clinical entities such as CPOP and the negative consequences of the excessive use of opioids have redefined the treatment. The goal is a high-quality perioperative analgesia that minimizes the use of opioids and thereby enables rapid rehabilitation.	Beloeil and Sulpice[16]
Prospective cohort	Ventral hernia repair	887 patients	Preoperative 1, 6, and 12 months after surgery	Patients who have preoperative pain are significantly more likely to have chronic pain 1 month after surgery.	Cox et al[17]
Prospective cohort	Cesarian section	527 women	3, 6, and 12 months after surgery	In women undergoing Cesarian section, CPOP was not uncommon. Patients with more intense postoperative pain in the movement, preoperative depression, and longer surgical time presented a higher risk for CPOP postoperatively.	Jin et al[18]
Randomized controlled trial	Traumatic tibial fracture repair	359 patients	6 weeks after surgery	Out of 267 tibial fracture patients with data available for analysis, 55.1% reported CPOP 1 year after surgery. Applying the Somatic Pre-Occupation and Coping (SPOC) scores, the	Khan et al[19]

Table 1 (*Continued*)

Design	Procedure	Sample	Follow-up	Conclusion	Reference
				CPOP was of 37.6%, 54.1%, and 81.7% among patients with low (≤40), intermediate (41–80), and high (> 80) scores respectively. The patients' coping and expectations of recovery, measured by the SPOC questionnaire, are an independent predictors of CPOP and pain interference one year after traumatic tibial fracture.	
Prospective cohort	Elective surgical interventions including joint (hip arthroplasty, knee), back (nucleotomy, spondylosis) or urologic (cystectomy, prostatectomy, nephrectomy) surgeries.	644 patients	2 days and 6 months after surgery	A significant number of patients suffer from pain and need analgesic medication, even opiates, up to 6 months after surgery.	Laufenberg-Feldmann et al[20]
Review	–	–	–	Based on the pathophysiological discussion and the risk factors that contribute to the chronification of postoperative pain, topics are suggested that still need studies to be performed to contribute to better pain management.	Pozek et al[21]
Observational study	Knee arthroplasty (partial or total)	104 patients	3 and 6 months	Several pre- and postoperative features could be used to facilitate the identification of patients at high risk for CPOP after knee surgery. All therapeutic strategies that decrease APOP, such as controlling anxiety or performing a knee replacement before pain, have serious effects on walking ability, and may help reduce the risk of CPOP.	Thomazeau et al[22]
Review	–	66 World Health Organization member states with data available	2005 to 2012	266.2 to 359.5 million operations were performed in 2012. This represents an increase of 38% over the previous 8 years. The largest increase in operations was in very-low- and low-expenditure Member States. Surgical data were lacking for many Member States.	Weiser et al[1]
Prospective observational	Thoracotomy, video thoracoscopy, thoracoscopy	206 patients	3 days and 6 months after surgery	No difference was found in the incidence and severity of chronic pain 6 months after surgery in patients undergoing thoracotomy versus thoracoscopy. Unlike other postsurgical pain conditions, none of the preoperative psychosocial measurements were associated with chronic pain after thoracic surgery.	Bayman et al[23]
Observational cohort	Inguinal hernia repair	108 patients	15 days and 2 months after surgery	Chronic postsurgical pain is frequent in this type of surgery. The use of perioperative analgesia along with prevention and management of pain in the first postoperative weeks help to prevent the development of chronic postsurgical pain. General anesthesia may increase the risk of it. Similar studies conducted on a larger scale could help	Hermida et al[24]

(*Continued*)

Table 1 (*Continued*)

Design	Procedure	Sample	Follow-up	Conclusion	Reference
				identify other associated factors.	
Review	–	–	–	Chronic postsurgical pain may occur regardless of the type of procedure, although some surgeries carry a higher risk in relation to the degree of tissue damage and the potential for a major inflammatory reaction or nerve injury. CPOP resolves over time. Of all patients with CPOP 6 months after surgery, 55.8% will be pain-free at 12 months, whereas 2.9% of patients without pain at 6 months will report some pain at 12 months. Mental health has an important impact on the patient's ability to recover after surgery.	Lavand' homme[25]
Editorial	–	–	–	Early identification of patients at risk will help reduce the percentage of patients who develop CPOP.	Tawfic et al[26]
Review	–	–	–	Chronic pain in general has an association with difficulty in coping, socioeconomic aspects (poverty, access to health/medication), and comorbidities (anxiety, depression, alcoholism, opioid dependence).	Borsook et al[27]
Prospective cohort	Hysterectomy (any technique)	170 women	24 hours, 48 hours, 4 months and 5 years after surgery	Pain trajectory: 51.8% of the women without pain at 4 months; 31.2% with pain at 4 months, but not at 5 years; 17.1% with pain at 4 months and at 5 years. Major risk factors: preoperative anxiety, emotional repercussions of the disease, catastrophization. Greater postoperative anxiety and frequency/intensity of acute pain after surgery have a worse trajectory of pain. Acute variables had a greater impact 5 years after surgery, and should be treated properly with APOP.	Pinto et al[28]
Review	–	–	–	An optimal postoperative pain management requires evidence-based guidance from published guidelines and clinical experts, and must consider individual patient values and preferences.	Manworren et al[29]

have been increasingly studied and identified in scientific research within large surgical fields. Therefore, the professionals dedicated to each surgical specialty seek to obtain parameters that can improve patient care.

The risk factors for CPOP can be grouped into five major domains: clinical, demographic, psychological, surgery-related, and pain-related.[28] Thus, based on the knowledge of the variables that may predispose patients to the onset of CPOP, it is important to identify the susceptible individuals to take measures that positively interfere in the postoperative result in the short and long terms,[18] since a range of factors can intertwine and impact on patient evolution.

The age of the patient has been correlated with the process of postoperative pain chronification in several studies. Younger patients are more likely to present with CPOP,[8,17,19,21,26] especially those under the age of 60 years.[9]

The influence of gender as a risk factor has also been observed,[4] since females are more affected by CPOP.[9,17,19,21,26] In relation to ethnicity, non-Caucasian patients have been more associated with CPOP than other patients after hernia repair.[17] Genetic peculiarities have also been shown to participate in the genesis of CPOP, a field of study that has been slowly growing.[10,16,21,26]

Socioeconomic characteristics,[4] such as having higher education[22] and a job,[24] have been recognized as risk factors. The lifestyle habits of the patients also matter, inasmuch as sedentary adults who underwent orthopedic surgery have had more CPOP.[22]

The presence of psychological changes prior to the surgical procedure is a risk factor for CPOP.[4,8,13,16,18,19,25] Associations between depression,[8,10,21,26,28] anxiety,[10,13,21,22,26,28] and difficulty coping with pain have been identified as risk factors for CPOP.[19,22,27] Even the patient's expectations regarding the surgery to be performed may become a risk factor for chronic pain.[4]

Psychological factors are so important for CPOP that led to the inquiry on the role of pain catastrophizing by the patient, a process by which the individual has a negative response exacerbated by an adverse stimulus.[8] The use of the Pain Catastrophizing Scale in patients that underwent breast cancer surgery revealed a greater presence of CPOP four months after the procedure in those who had suffered from catastrophic pain. This finding has been corroborated in different surgical specialties.[19,21,28]

The incidence of pain prior to surgery, in any part of the body, is also a well-known risk factor for CPOP.[13,15,16,22,25,27,28] It is also known that algic syndromes such as fibromyalgia and migraine play a role in the predisposition for CPOP, although their magnitude is yet to be revealed.[13,21,30]

The surgical procedure itself involves a large dimension of risk factors. Several studies have indicated the type of surgery as a major predisposing factor for CPOP.[4,10,16–18,21,26,28,31] Variations in CPOP incidence may depend on the duration of the surgery,[18,21] the experience of the surgeon, and the anesthetic technique used during the surgical procedure.[12,21,24]

Postoperative events should also be monitored, since the role of acute pain in this period has long been well-established. High risk factors for CPOP are the high intensity of acute pain,[18,20,21,24–26,28,29] the lack of analgesia approach, or its inefficiency.[4,9,21,24,32,33]

In each surgical specialty, the management of CPOP should be optimized, since each procedure has its own peculiarities. The maintenance of postoperative chest tube drainage for at least 4 days after thoracic surgeries[9] and the administration of more than 6 mg of morphine in the first 48 hours after urological surgeries[7] have been identified as predictive factors for CPOP. Postoperative complications also predispose to pain chronification, as demonstrated in breast and orthopedic surgical procedures.[8,22]

CPOP in Orthopedic Surgeries

Due to the increase in human longevity and the development of health resources, more orthopedic procedures are needed and performed around the world every year. About 500,000 total knee arthroplasties are performed in the United States a year, and up to 20% of these patients develop CPOP. In a study with 78 patients submitted to this procedure, 22% had moderate to severe CPOP.[14]

Another study performed with 104 patients submitted to knee arthroplasty found that 10% to 34% of them had CPOP, and 28.8% remained with pain 6 months after surgery. Additionally, the intensity of pain in the first four postoperative days was strongly associated with pain chronification.[22]

Among patients who underwent knee arthroplasty, 15% to 20% were dissatisfied with the result due to the occurrence of pain,[13] with a great negative impact on their lives. A total of 55.1% of the patients who underwent surgery for traumatic tibial fracture reported moderate to severe pain 1 year after the procedure, culminating in negative impact on the daily activities in 35.2% of the cases.[19]

CPOP in Gynecologic, Obstetric, and Breast Surgeries

The most common gynecological surgery performed in the West is hysterectomy. A review of 11 2-year follow-up studies showed that 5% to 32% of hysterectomized patients had CPOP.[28] The study encompassed a sample of 170 women who were evaluated from 24 hours to 5 years after surgery, and almost half of them reported pain after 4 months; of these, 17.1% still felt pain 5 years after the hysterectomy.

In obstetrics, the focus is Cesarean section, a procedure that has been increasingly performed worldwide, despite the ideal rate of 10% to 15% of the total deliveries accepted by the international healthcare community since 1985.[34] In China, for example, up to 80% of births are Cesarean sections.[18] However, despite the number of these procedures, there are few data available that address the presence of CPOP in these women.

A total of 527 patients submitted to Cesarian section included in an observational cohort study[18] were followed up from the preoperative period up to 12 months postoperatively. Pain was reported by 18.3%, 11.3%, and 6.8% of the patients 3, 6, and 12 months after the procedure respectively. The impact on the lives of these patients was evident, because 3 months after the Cesarian section 84.4% of the patients with pain revealed that they had impairments in their daily activities. At 6 and 12 months, they complained of mood disorders and reduced joy of living caused by chronic pain. Long-term analgesic use after Cesarian section has also been reported by 21.9% of the patients with CPOP 12 months after the procedure.[18]

Approximately half of the women who underwent breast cancer surgery reported CPOP after 3 years. The pain complaints may persist for up to 12 years, which decreases their quality of life. Up to 23% of the patients submitted to breast cancer surgery have reported unbearable pain 4 months after the procedure.[8] Of 537 women that participated in a prospective cohort study,[10] between 25% and 60% complained of reduced physical functioning, and 7% reported pain when moving even 1 year after surgery.

CPOP in General Surgeries

An estimated 360,000 ventral and incisional hernioplasties are performed each year in the United States. Chronic postoperative pain has been referred by up to 39% of the patients submitted to ventral repairs,[17] and by around 50% of the cases of inguinal hernia surgeries, of which 11.5% may have pain that persists for up to 1 year after hernioplasty.[24]

A total of 887 patients who underwent ventral hernioplasty (through the open or laparoscopic techniques) were followed up for 1 month, 6 months, and 1 year to assess quality of life

and functionality after the procedure.[17] Among the patients who did not have preoperative pain, 14.6% had pain at 6 months, and 12.6%, at 1 year. Those who already had pain before surgery exhibited more alarming outcomes: 37.2% reported pain at 6 months, while 34.7% complained of pain at 1 year. These findings corroborate the importance of the presence of preoperative pain in the development of CPOP.

In relation to inguinal hernioplasties, the prevalence of CPOP has been associated with the surgical method applied: after open approaches, up to 7.3% of the patients complain about it, while after videolaparoscopic approaches this rate is reduced to 5%.[24]

CPOP in Thoracic Surgeries

Thoracic surgeries greatly contribute to the development of CPOP, including thoracoscopy. The emergence of chronic pain is present among 14% to 83% of the patients submitted to thoracic surgical procedures.[9] Regardless of the technique, 27% of the patients evaluated 6 months after thoracic surgeries had CPOP, and 8.2% of them had limitations in daily activities.[23]

In a large scale study[9] that included a sample of 1,284 patients who underwent thoracotomies and video-assisted thoracotomies, the authors concluded that 24.9% of them had CPOP. The patients' quality of life declined, especially among those who reported severe pain (4.3%), reinforcing the damage caused to their lives.

Proper Management of CPOP

No consensual definition of what constitutes proper perioperative pain management has been reached so far. This gap reflects a lack of well-established criteria and of agreement on the parameters that may support the multidisciplinary team in the conduction of the patient.[35] Thus, no ideal analgesia and no gold standard therapy have been recommended yet, because each case should be planned and analyzed individually.[36] Based on the literature review and on the fact that CPOP is the main surgical complication of APOP that is not adequately treated, its proper management should target preventing pain chronification with actions performed before, during, and after surgery (►**Fig. 2**).

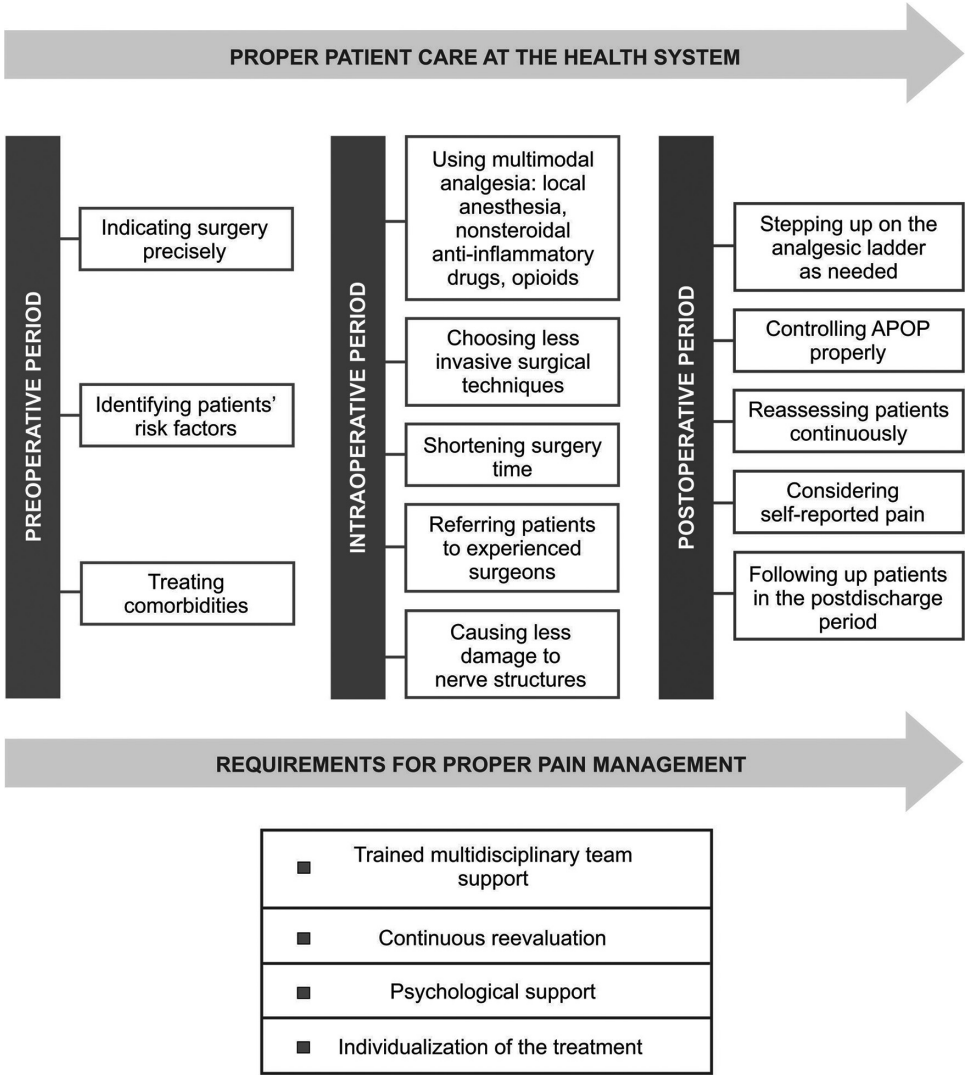

Fig. 2 Proper approach of patients undergoing surgery.

Preoperative Period

To properly manage CPOP, in the preoperative period it is necessary: 1) to identify the risk factors for chronic pain in advance, observing patients who may require special attention for the control of APOP; 2) to integrate pain control into other aspects of preparation and recovery of surgery, such as patient education, mobility, or nutrition and fluid intake; 3) to take into account the differences between patients in terms of experience and how they report pain; 4) and to organize the control of pre-, intra-, and postoperative pain according to an appropriate context and availability of the health system to improve treatment quality and safety.[35,37,38]

Preemptive analgesia is initiated before the surgical procedure to prevent pain in the early postoperative period, even before the surgical incision or any other painful procedures. It is effective, because it reduces the need for painkillers in the postoperative period.[39]

Intraoperative Period

A multimodal approach adopted to manage CPOP in the intraoperative period combines various types of medications such as anti-inflammatory drugs and local anesthesia to reduce dependence on a single agent. In addition, the individualized choice of anesthetic technique associated with peripheral or neuroaxis blocks optimizes the therapeutic plan for a better control of postoperative pain.[36–38] It represents the possibility of action at various levels of pain pathways, enabling the insertion of other drugs and procedures, simultaneously improving the quality of the postoperative period.[39]

Another important step for the prevention of CPOP is to raise surgeon awareness of the use of measures to avoid intraoperative neural injury and the control of symptoms by treating them and changing the neuroplasticity induced in the central nervous system (CNS) with such an injury. Thus, multimodal treatments should be used to act in the progression of the mechanisms triggered by pain.[33]

Postoperative Period

An investigative approach has been designed to reduce acute pain during or shortly after a painful stimulus to decrease the potential development of chronic pain: the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT). The recommendations of IMMPACT include the evaluation of pain intensity and physical and emotional response as a central result in chronic pain tests. It is recommended to emphasize pain outcomes, such as presence and severity, to illustrate several methodological issues in the prevention setting.[11]

Almost all types of pain after surgery can and should be managed to optimize the patients' emotional function. The intensity of pain at rest and with movement should be assessed, which is relevant to adapt pain therapy to rehabilitation needs. Additionally, the continuous assessment of the patient after discharge is highly important to recognize and treat persistent pain and any other unwanted surgical consequences as soon as possible.[37,38]

The evaluations of pain aim to recognize the initial functional recovery through the patient's report on the intensity of pain, interference in activities of daily living, presence and severity of adverse effects, and the patient's perception of the treatment received. The targets should, whenever possible, include pain no worse than mild and minimal interference with function and treatment. A graphical representation of pain intensity scores during the observational period, compared with a single pain score, draws attention to the speed at which pain relief begins, the consistency of this improvement, and the total amount of relief achieved.[35]

Healthcare Team Training Program

An important measure to achieve adequate management of APOP is to enable healthcare professionals to understand pain as an avoidable and unnatural phenomenon, recognizing it as the fifth vital sign, which is influenced by the psychological and social aspects of the individual.[39,40] Since the academic background in pain has been greatly neglected in most healthcare curricula, postoperative analgesia remains inadequate.[33] Consequently, the dedication of healthcare professionals to the adequate management of postoperative pain is a humanitarian act, fundamental to achieve quality in patient care in a global scenario of inadequate management of pain.

It is recognized that the treatment of pain should become a medical subspecialty due to the growth in knowledge and specialized techniques such as regional anesthesia.[37] This targeted approach can reduce or avoid the adverse effects of undertreated APOP, such as increased risk of maintenance or transition to CPOP.[38]

Conclusion

Chronic postoperative pain is a clinical disease with a major impact on morbidity rates in Brazil and in the world, which implies high costs for the health system. With multifactorial causality, it is still much neglected by healthcare professionals, and it is sometimes ignored in their training programs, directly reflecting on the quality of life of the patients after surgical procedures. Therefore, the management of APOP becomes deficient, making it the main risk factor for the development of CPOP.

It is necessary to improve the training of healthcare professionals in the management of pain symptoms before, during, and after surgeries. In addition to this, more in-depth studies should be performed for the evaluation and management of this condition. It is worth mentioning that the multimodal approach should take place pre-, intra-, and postoperatively based on the individualization of the treatment.

Conflict of Interests

The authors have no conflict of interests to declare.

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Operative *versus* Non-Operative Management of Traumatic Thoracolumbar Injuries according to the AO Spine Thoracolumbar Spine Injury Classification System

Tratamento cirúrgico versus conservador das lesões traumáticas toracolombares segundo o Sistema de Classificação AOSpine das Lesões Toracolombares

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Arq Bras Neurocir 2020;39(3):181–188.

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Abstract

Introduction The AOSpine Thoracolumbar Spine Injury Classification (AOSTSIC) system has been proposed to better characterize injury morphologies and improve the classification of thoracolumbar (TL) spine trauma. However, the indications for surgical treatment according to the AOSTSIC system are still debated. Additionally, the proposed Thoracolumbar AOSpine Injury Score (AOSIS) is quite complex, which may preclude its use in daily practice. The objective of this review is to discuss the AOSTSIC system and its indications for initial nonoperative versus surgical management of acute TL spine trauma.

Methods We analyzed the literature for each injury type (and subtype, when pertinent) according to the AOSTSIC system as well as their potential treatment options.

Results Patients with AOSTSIC subtypes A0, A1, and A2 are neurologically intact in the vast majority of the cases and initially managed nonoperatively. The treatment of A3- and A4-subtype injuries (burst fractures) in neurologically-intact patients is still debated with great controversy, with initially nonoperative management being considered an option in select patients. Surgery is recommended when there are neurological deficits or failure of nonoperative management, with the role of magnetic resonance findings in the Posterior Ligamentous Complex (PLC) evaluation still being considered controversial. Injuries classified as type B1 in neurologically-intact patients may be treated, initially, with nonoperative management, provided that there are no ligamentous injury and non-displacing fragments. Due to severe ligamentous injury, type-B and type-C injuries should be considered as unstable injuries that must be surgically treated, regardless of the neurological status of the patient.

Conclusions Until further evidence, we provided an easy algorithm-based guide on the spinal trauma literature to help surgeons in the decision-making process for the treatment of TL spine injuries classified according to the new AOSTSIC system.

Keywords
- AOSpine
- thoracolumbar
- surgery
- non-operative
- classification
- treatment
- fracture

received
August 4, 2019
accepted after revision
August 21, 2019

DOI https://doi.org/10.1055/s-0039-1700578.
ISSN 0103-5355.

Introduction

In 2013, the AOSpine Trauma Knowledge Forum published the AOSpine Thoracolumbar Spine Injury Classification (AOSTSIC) system (►**Annex 1 -** Available online).[1] This new classification of Thoracolumbar spine traumatic injuries was made by an international group of academic spine surgeons in an attempt to improve the previous Thoracolumbar Injury Classification System (TLICS) and to incorporate morphological characteristics of the Magerl classification, such as grading injuries severity in a crescent manner.[2,3]

A systematic review by Abedi et al on the reliability and validity of the AOSTSIC system was recently published.[4] The authors reported that there is moderate evidence for good intraobserver reliability among injury types and moderate evidence of poor interobserver reliability when all subtypes were included. For injuries modifiers, such as indeterminate injury to the tension band based on magnetic resonance imaging (MRI) findings and patients' comorbidities, the reliability is unknown. Based on this review, we can conclude that grouping injuries according to type may improve reliability, facilitate communication among health care providers and allow for comparison of surgical results in different spinal centers with better validity than assessment of injury subtypes.

In 2016, Kepler et al reported the results of a spine survey to develop the AOSTSIC system.[5] They proposed that injuries should receive 1 point for A1, 2 points for A2, and 3 points for A3 subtypes. For A4 and B1 subtypes, the injury should receive 5 points. For B2 subtype, 6 points, 7 for B3 subtype, and 8 for C subtype. Regarding the neurological status, no points for intact (N0), 1 for transient neurological status (N1), 2 for radicular symptoms (N2), and 4 points for incomplete (N3) or complete (N4) neurological deficits. For patients with an indeterminate posterolateral ligamentous complex injury (M1), 1 additional point was counted. According to the authors, the score was not a proposal of a treatment guideline. Although very interesting, we personally believe that such a complex way to score injuries may result in low clinical application. Differently from the TLICS, which is much simpler, this new score system would require a deep knowledge of the AO system and a lot of time to be applied in daily practice.

Considering that, the AOSTSIC is the most recent and widespread classification for traumatic thoracolumbar (TL) injuries, and, due to the lack of studies proposing treatment guidelines according to injury types, we performed this review in an attempt to offer the best management for acute TL spine trauma considering injury type and the neurological status of the patient.

Methods

A narrative review of the spine trauma literature using manual searches in the Medline database (National Library of Medicine) was performed to subsidize the specific treatment of each injury described in the AOSTSIC. We searched specifically for articles related to cases series reporting the treatment for each injury type (and subtype, when pertinent) proposed by the AOSTSIC system. The reason for including only case series in our search was that, with exception of burst fractures without neurological deficits, comparative studies on the outcomes of different traumatic injuries are missing in the spine literature. Articles related to the manuscript that discussed the AOTSIC system were also included, according to the purpose of our review.

Results

Independently of their neurological status, patients with AOSTSIC subtypes A0 to A2 (compression injuries) are initially managed nonoperatively, except if they have some soft tissue compressing the neural tissue that can lead to neurological deficits, such as a traumatic disc herniation, which requires further radiological investigation.[6–9] Using the TLICS score, these injuries were given zero, 1, or 2 points, receiving conservative treatment in cases series previously published with reasonable outcomes.[6–8]

Type A – Subtypes A0–1-2

Neurologically Intact (N0 and N1)

Minor compression injuries are mechanically stable, and many clinical series reported successful treatment with nonoperative management.[6–9] However, some patients may still have chronic pain after the treatment of these fractures, despite being mechanically stable.[10]

Neurological Deficits (Radicular – N2, Incomplete – N3 and Complete – N4)

It is quite unusual for types A0, A1, and A2 (minor bone fractures, compression fractures and split fractures) to have neurological deficits, even in large case series.[7] In this setting, further MRI investigation may be necessary as well as dynamic radiological exams to detect soft tissue compression (such as a disc herniation leading to radicular symptoms) or occult ligamentous injury and inadequate injury classification.[9,11]

►**Fig. 1** illustrates the decision-making process of type A (subtypes A0, A1, and A2 injuries) according to the neurological status of the patient.

Types A3-A4 (Incomplete and Complete Burst Fractures)

Neurologically Intact (N0 and N1)

Burst fractures without neurological deficits are the most controversial issue in the management of acute thoracolumbar spine fractures. Some authors propose surgical treatment when there are burst fractures with segmental kyphosis (greater than 20°), when there is loss of more than 50% of vertebral body height, or when at least 50% of the canal is compromised by posterior wall fragments.[12–15] Although this criteria for surgery may be adopted in many centers around the world, with regional variations, the lack of solid evidence about specific radiological parameters to guide treatment still persists. Unstable burst fractures, with posterior ligament rupture characterized by dislocation of the facet joints, diastasis of the spinous process, and subluxations, should be considered as B2

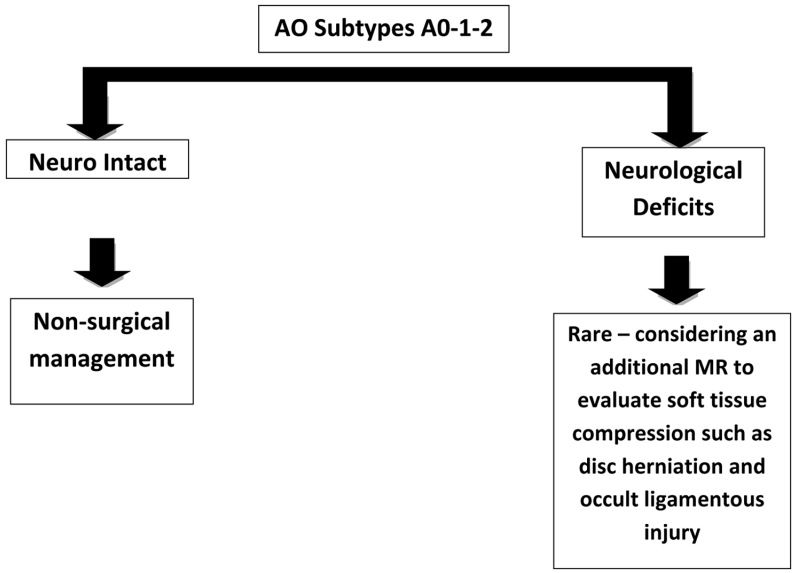

Fig. 1 Management of AO subtypes A0, A1, and A2 according to the neurological status of the patient. Abbreviation: MR, magnetic resonance.

injuries (flexion-distractive mechanism) with a burst component.[7,15–17] Finally, another question that needs further investigation is if there is any difference in the outcome of incomplete (A3) versus complete (A4) burst fractures, which have been evaluated together in the spinal trauma literature until the advent of the AOSTSIC. As far as we know, there is no specific radiological characteristic of a burst fracture in a neurologically intact patient that may guide operative versus nonoperative management.[14]

Systematic literature reviews of the conflicting results of randomized studies comparing operative versus nonoperative management of burst fractures reported that there is no evidence to support one treatment over the other, with potentially lower complication rates and less costs with conservative management.[19–21] Based on this, we propose that an initial nonoperative management should be offered to these patients with very close clinical and radiological follow-up.[11,19] In our practice, we routinely perform an MRI scan and standing plain radiographs before discharging patients to our outpatient facility with the diagnosis of an occult posterior ligamentous injury, as proposed by Mehta et al.[22] Additionally, patients that are not able to ambulate with the help of pain medication may be referred for surgical treatment.

Neurological Deficits (Radicular – N2, Incomplete – N3 and Complete – N4)

Surgical treatment is well accepted for burst fractures with neurological deficits.[2,19,23] Anterior, posterior, and combined approaches have been described, although posterior approaches present potentially less complications.[2,19,23] We did not find any recent study proposing nonoperative management for burst fractures in neurologically-compromised patients. With few exceptions, a mild radiculopathy (N2) associated with a burst fracture may be treated nonoperatively.[24]

Of note, Roberts et al reported in 1970 that the nonoperative management of 7 patients with complete neurological deficits and burst fractures resulted in spinal deformity, suggesting that surgery is advisable despite a poor neurological outcome to avoid posttraumatic kyphosis.[25]

►**Fig. 2** illustrates the decision-making process of type A3 and A4 injuries according to neurological status.

Subtype B1 - "Chance" Fractures or Monosegmental Osseous Failure of the Posterior Tension Band Extending into the Vertebral Body - Pedicular Bone Fractures

The first description of this type of fracture was in 1948 by Chance GQ, in the upper lumbar spine.[26] It is usually the consequence of a flexion-distraction injury and associated with seatbelt use, the pure bony injury extending from posterior to anterior through the spinous process, pedicles, and, finally, the vertebral body, generally associated with visceral injuries, such as bowel rupture.[26]

Neurologically Intact (N0 and N1)

Nonoperative treatment of neurologically-intact patients with only osseous fractures is accepted in non-displaced fractures without moderate or severe kyphotic angulation.[27–29] However, late neurological deterioration and kyphosis have been reported after non-operative management.[29,30] In the majority of the cases series reported in the literature, operative management is preferentially offered to this group of patients, providing early stability. This is the same opinion of this author (AFJ). A posterior approach with instrumentation is sufficient to restore stability, and percutaneous fixation is an option in cases in which neural decompression is not necessary.[28]

Neurological Deficits (Radicular – N2, Incomplete – N3 and Complete – N4)

For patients with B1 injuries and neurological deficits, surgical treatment is well accepted in the majority of the cases to improve neurological outcome and avoid deformities.[8,29]

►**Fig. 3** illustrates the decision-making process of subtype B1 injuries according to neurological status. In ►**Fig. 4**, an illustrative case of a B1 fracture is presented.

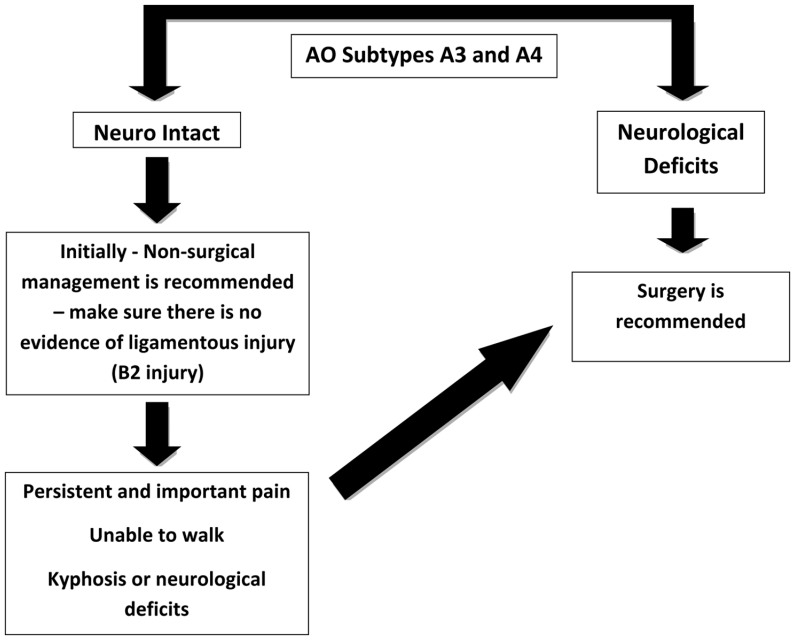

Fig. 2 Management of AO subtypes A3 and A4 (burst fractures) according to the neurological status of the patient.

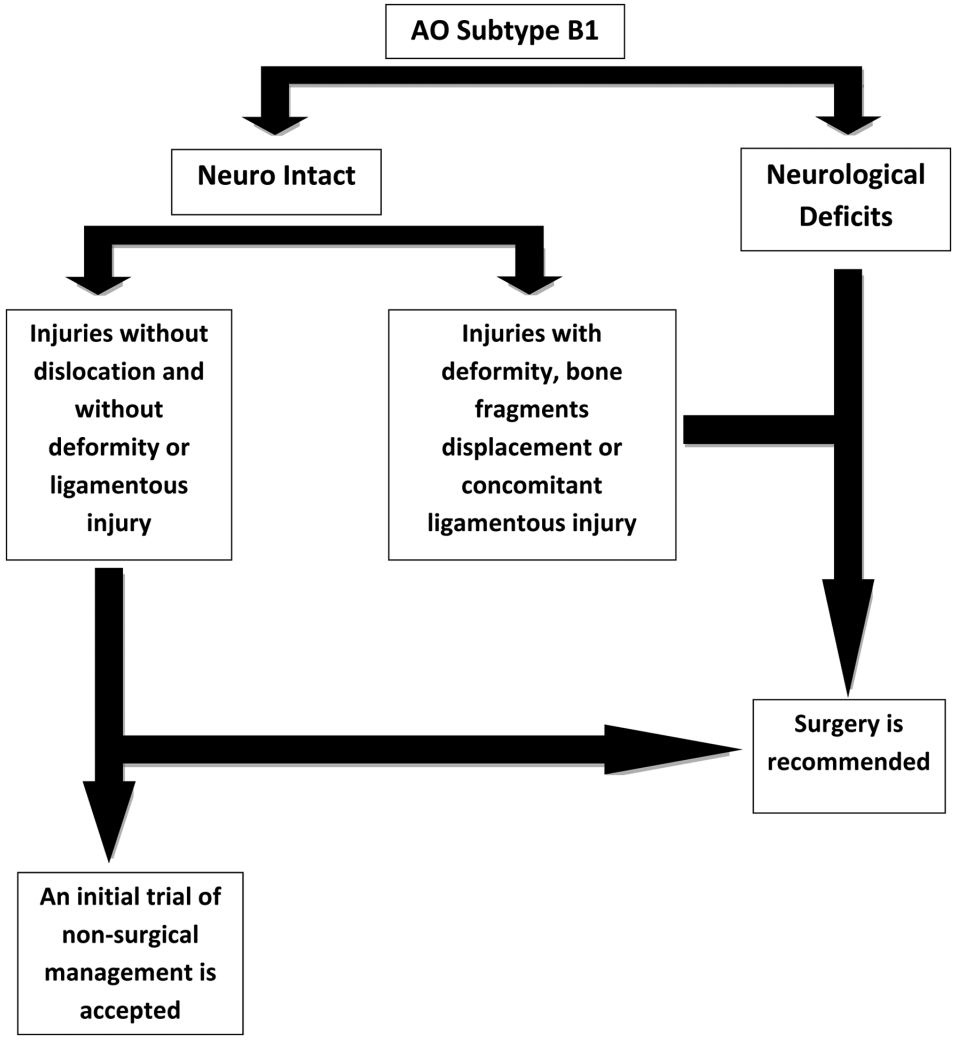

Fig. 3 Management of AO subtype B1 according to patient's neurological status.

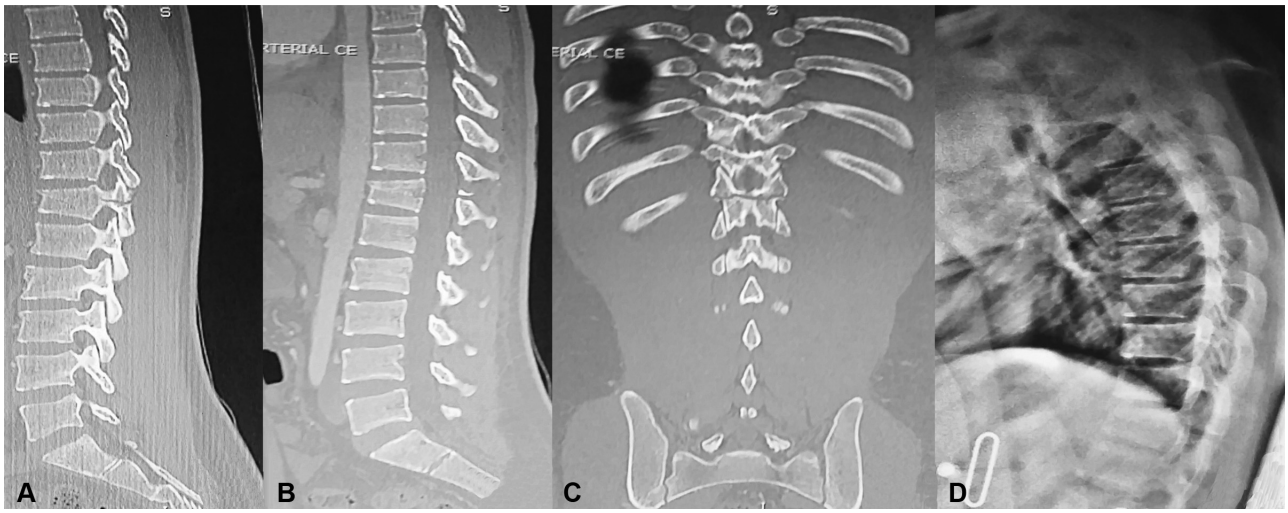

Fig. 4 Sagittal computed tomography scan of a T12 subtype B1 (Chance) fracture showing pedicle fracture (**A**) and some vertebral body compression (**B**) at T12. Coronal CT scan showing a compression fracture from pedicle to pedicle passing through the lamina of T12. The patient was walking with mild pain and no neurological deficits, asking for a trial of non-operative management. Standing lateral thoracic plain radiograph with a brace (**D**).

Subtypes B2, B3, and Type-C Injuries

These types of injury present severe ligamentous damage, and, thus, surgical treatment is recommended, regardless of the neurological status of the patient (N0 to N4), in order to avoid nonunion and late kyphotic deformities.[31–33]

For neurologically-intact patients, surgery is indicated to restore spinal stability. For patients with neurological deficits, surgery is recommended not only to restore stability but also to decompress the neural tissue and optimize the spinal cord recovery, potentially improving neurological outcomes. Nonoperative management of ligamentous injury is associated with severe pain, spinal deformity, and late neurological deterioration.[31–33]

►**Fig. 5** illustrates the decision-making process of subtypes B2-B3 and type C. In ►**Fig. 6**, an illustrative case of a type-C fracture is presented.

Discussion

In this article, we describe in a simplistic way the treatment of injuries classified according to the AOSTSIC system and neurological status. Due to the lack of prospective studies to validate our proposed management, we used the current available literature knowledge to propose the treatment of classic injury patterns that were included in the AO system. Of course, a less comprehensive evaluation may infer in treatment bias in some unusual cases, but clinical judgment is of paramount importance in spinal trauma treatment. Additionally, surgeons experience and regional characteristics should be taken into account in the decision of one treatment over the other. Finally, once the reliability of the system decreases with complexity (such as injury subtype), a more general overview is necessary instead of a detailed one,

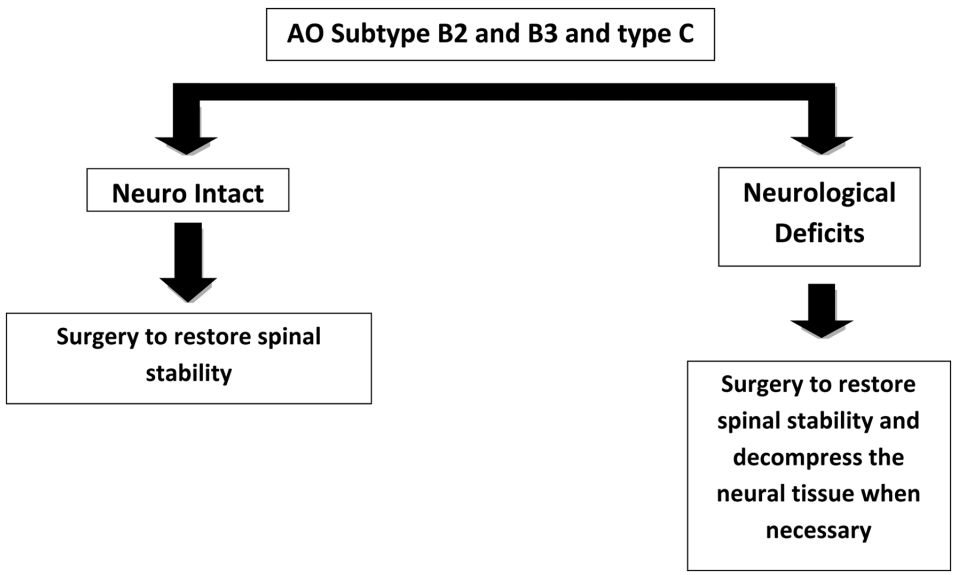

Fig. 5 Management of AO subtype B2 and B3 and type C injuries according to the neurological status of the patient.

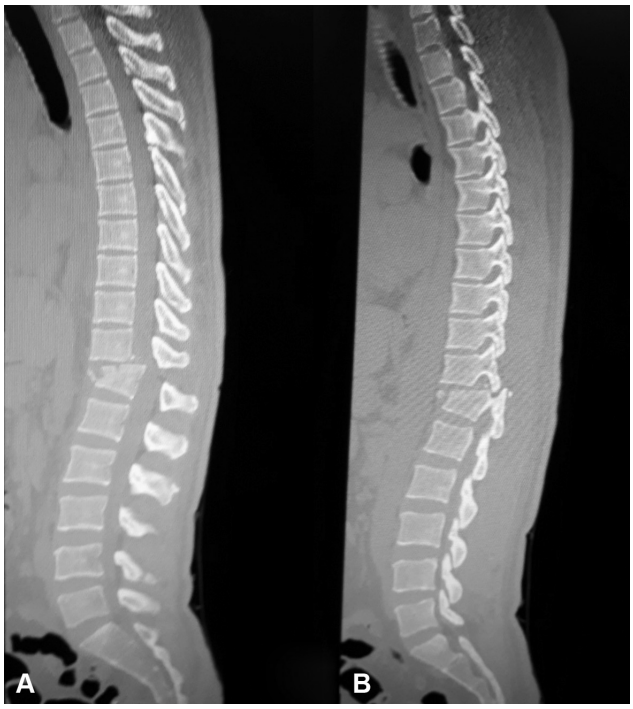

Fig. 6 Sagittal computed tomography scan of a patient with T11–12 thoracic fracture-dislocation with canal compression (**A**) and clear facet luxation (**B**). The patient had complete neurological deficit. This is a type C injury requiring surgical treatment to restore spinal instability and decompress the spinal canal.

but there is no reliable classification, such as the old Magerl system.

Most of the classification systems proposed for TL spine trauma were based on expert opinion—which is characterized by a low level of evidence.[2,3] Interestingly, a new classification is generally based on previous systems, in an attempt to improve previous failures or limitation of the predecessors.[34] Unfortunately, the lack of comparative treatment studies for different injuries generally requires recommendations based on case series. With the exception of burst fractures without neurological deficits, which have some randomized trials with conflictive results, all the remaining injuries management were based on case series and expert opinion.[20,21]

Compression fractures (type A0, A1 and A2 injuries) generally heal well in patients without osteoporosis. In a retrospective study of 458 trauma patients with thoracolumbar fractures, 310 patients treated non-surgically with compression injuries were treated non-operatively, without need of late surgery.[7] Pain and some degree of disability may persist in some cases.[10] Comparative studies randomizing operative and nonoperative stable injuries are necessary to evaluate the benefits of pain control and the level of disability.

Probably, the most controversial problem in the management of TL fractures is the treatment of burst fractures without neurological deficits.[35] Vaccaro et al reported the results of an international survey designed by the AOSpine Trauma Knowledge Forum to establish an algorithm to accompany the AOSTSIC system. They defined that injuries with less than 30% of surgeon-recommended surgical intervention should undergo a trial of initial nonoperative management, whereas injuries in which more than 70% of surgeons would recommend surgery should be operated. They reported that great controversy exists in a case, for instance, with a burst fracture (A3) with transient neurological deficits (N1) and an indeterminate PLC injury (M1)—a gray zone due to the inability of the surgeons to agree on the integrity of the PLC. The use of MRI in the evaluation of the PLC and its clinical role in the outcome should be further studied. The failure of the literature in separating A3 from A4 was an issue identified by the present study, with some surgeons from Europe, for example, having a higher tendency to recommend surgical treatment for burst fractures. Only 17.2% of the surgeons believed surgery was necessary for compression fractures (A2) without deficits, whereas for flexion distraction injuries (B2) with radicular symptoms, 81.3% of the surgeons recommended surgery. They emphasized that a potential advantage of the AOSTSIC system over the TLICS is the better characterization of type-A fractures, which may explain some geographical variability in treatment. An ongoing study sponsored by the AOSpine Trauma Knowledge forum will prospectively evaluate the outcome of A3 and A4 fractures by comparing different treatment modalities.

For more severe ligamentous injuries' patterns (all type B, with rare B1 exceptions, and type C injuries), independent of any neurological deficits, surgical treatment is recommended when there is no systemic clinical contraindication. Historical treatment of fracture-dislocation injuries with prolonged bed rest ($\sim$10–13 weeks on average), generally results in residual deformity and pain syndromes.[33] Compared with modern case series, cases of fracture-dislocation, without neurological deficits, that are surgically treated generally have very satisfactory outcomes, most of the times with the patients returning to their normal activities.[33] Additionally, for patients with neurological deficits, some neurological improvement is documented, especially in those patients with incomplete spinal cord injuries.[8,31]

Our review is limited, once it is based on results of case series and, thus, there is a lack of comparative treatment modalities. Additionally, pain and functional status are not commonly assessed in the spinal trauma literature. Clinical modifiers, such as patients' comorbidities, indeterminate posterior ligamentous injury, and specific osseous diseases, such as ankylosing spondylitis or diffuse idiopathic skeletal hyperostosis, were not considered, requiring a case-by-case decision. Another important factor not taken into account is spine injury location—potentially, multiple levels of fractures, injuries at the thoracic kyphosis apex, low lumbar spine, transitional TL region and middle thoracic spine may have different outcomes and biomechanical behaviors, requiring further investigation.[36] However, despite all these shortcomings, our review provides useful and practical guidance for the management of TL fractures classified according to the AOSTSIC system.

Conclusions

Patients with types A0 to A2 according to the AOSTSIC system are initially managed nonoperatively. Treatment of A3 and A4 fractures (incomplete and complete burst fractures) in

neurologically-intact patients is still debated, with initial nonoperative management being considered after further radiological evaluation. Surgery is recommended in the setting of neurological deficits or failure of nonoperative management. Subtype B1 in neurologically-intact patients may be considered for nonoperative management, when there is no ligamentous injury and non-displacing injuries in selected cases. Due to severe ligamentous injury, type-B (with some rare exceptions B1) and type-C injuries should be considered unstable, independent of the neurological status of the patient, and surgically treated

Conflicts of Interest
The authors have no conflicts of interest to declare.

Acknowledgments
Acknowledgement of AOSpine and the Knowledge Forums' work. AOSpine is a clinical division of the AO Foundation—an independent medically guided nonprofit organization. The AOSpine Knowledge Forums are pathology focused working groups acting on behalf of AOSpine in their domain of scientific expertise. Each forum consists of a steering committee of up to 10 international spine experts who meet on a regular basis to discuss research, assess the best evidence for current practices, and formulate clinical trials to advance spine care worldwide. Study support is provided directly through AOSpine's Research department and AO's Clinical Investigation and Documentation unit.

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Intracranial Hypertension and Intra-abdominal Pressure. Is it Worth Measuring?

Hipertensão intracraniana e pressão intra-abdominal. Vale a pena mensurar?

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Arq Bras Neurocir 2020;39(3):189–191.

Abstract

Patients with refractory intracranial hypertension who have already undergone all the measures recommended by the current guidelines can benefit from having their intra-abdominal pressure monitored since its increase generates hemodynamic repercussions and secondary elevation of intracranial pressure. In this context, a bibliographic research was performed on PubMed with the terms *intra-abdominal pressure*, *abdominal compartment syndrome*, *intracranial pressure, intracranial hypertension*. Altogether, 146 articles were observed, 87 of which were from the year 2000, and only 15 articles were considered relevant to the topic. These studies indicate that patients with refractory intracranial hypertension can benefit from the measurement of intraabdominal pressure, since there is evidence that an increase in this pressure leads to organic dysfunctions with an indirect impact on cerebral venous return and, consequently, an increase in intracranial pressure. In those who underwent decompression laparotomy, direct effects were observed in reducing intracranial hypertension and survival.

Keywords
- intra-abdominal pressure
- abdominal compartment syndrome
- intracranial pressure
- intracranial hypertension

Resumo

Pacientes com hipertensão intracraniana refratária que já foram submetidos a todas as medidas preconizadas pelas diretrizes atuais podem se beneficiar do monitoramento da pressão intra-abdominal, uma vez que seu aumento gera repercussão hemodinâmica e elevação secundária da pressão intracraniana. Nesse contexto, realizou-se uma pesquisa bibliográfica no PubMed com os termos "*intra-abdominal pressure*," "*abdominal compartment syndrome*," "*intracranial pressure*"; "*intracranial hypertension*." Ao todo, foram observados 146 artigos, dos quais 87 eram a partir do ano 2000, e apenas 15 artigos foram considerados relevantes ao tópico. Esses estudos indicam que pacientes com hipertensão intracraniana refratária podem se beneficiar da medida da pressão intra-abdominal, uma vez que existem evidências de que o aumento desta leva a disfunções orgânicas com impacto indireto no retorno venoso cerebral e, consequentemente, no aumento da pressão intracraniana. Naqueles que foram submetidos à laparotomia descompressiva, observou-se efeitos diretos na redução da hipertensão intracraniana e sobrevida.

Palavras-chave
- pressão intra-abdominal
- síndrome do compartimento abdominal
- pressão intracraniana
- hipertensão intracraniana

received
April 3, 2020
accepted
May 12, 2020

DOI https://doi.org/10.1055/s-0040-1713593.
ISSN 0103-5355.

Introduction

The intracranial content is composed of brain tissue (80%), cerebrospinal fluid (10%), and blood (10%). The maintenance of intracranial pressure (ICP) at its typical values depends on the preservation of intracranial volume. Any situation that causes an intracranial component to increase in volume requires a decrease in the other components so that there is no increase in ICP. The compensation process often occurs at the expense of decreasing the volume of liquor and blood, since the brain mass is less compressible. About 30% of the capacity to decrease the intracranial volume is represented by cerebrospinal fluid, which can be displaced into the subarachnoid spinal space or absorbed by arachnoid granulations. When compensation mechanisms are exhausted, ICP increases as a consequence. The increase in ICP, in turn, can cause a decrease in tissue perfusion, leading to an increase in cellular damage due to ischemia. An average ICP measurement ranges from 0 to 15 mm Hg, and values above 15 mm Hg can be considered intracranial hypertension (ICH). However, not all patients have the same tolerance for increased ICP.

Intracranial hypertension is a clinical condition that affects many patients in the intensive care unit. Intracranial pressure monitoring provides information that facilitates interventions to prevent cerebral ischemia.[1–3] Intra-abdominal pressure (IAP) is defined as the pressure inside the abdominal cavity, resulting from the interaction between the abdominal wall and the viscera inside it. Physiologically, the pressure undergoes slight oscillations according to the respiratory phase and the resistance of the abdominal wall. The physiological value in adults is up to 5 mm Hg; however, in patients with altered conditions without pathophysiological significance, such as obese individuals, it can range from 10 to 15 mm Hg; in critically ill patients, it is considered between 5 to 7 mm Hg.[3–6]

Intra-abdominal hypertension (IAH) is considered when an increased IAP ($>$ 12 mm Hg) is registered after three measurements at intervals of between 4 and 6 hours. Since it is gradual, it can progress to abdominal compartment syndrome (ACS), when IAP is maintained at levels higher than 20 mm Hg, associated with changes or organ failure.[4,6] This topic was chosen because, despite all the available technology that is applied to care within an intensive care unit, several times, we come across this environment with patients presenting multisystemic aggravations. Among them, head and abdominal trauma and many times, these patients are in clinical condition with a progressive increase in ICP, which does not decrease with either surgical intervention or pharmacological measures (sedation with neuromuscular blocker associated with osmotic diuretics).

Methods

A bibliographic research in the online database PubMed was used to identify the correlation between the increase in IAP) with the increase in ICP) In the initial search, the titles and abstracts of the articles were considered for the broad selection of probable works of interest, highlighting the abstracts (of the articles that did not have accessible text) and the full texts of the articles, using the keywords as terms: *intra-abdominal pressure*, *abdominal compartment syndrome*, *intracranial pressure*; *intracranial hypertension*. The inclusion criteria were the texts that approached the topic (aiming to bring the discussion closer to our context), and texts published between 2000 and 2019. At the end of the research, 146 articles were found; after filters were applied for dates from 2000 to 2019, 87 articles remained; complete texts were available for 21 articles, and after excluding those that did not contain information relevant to the topic, a final sample of 15 articles were included.

Discussion

Through the analysis of the literature, it can be found that several physiological changes occur in neurologically severe injuried patients, both in clinical e polytrauma scenarios. These changes have a direct impact on various systems, both neurological and abdominal, which is the focus of this study. However, most of these articles bring the treatment of each system in isolation, not establishing a correlation in which the excessive increase in IAP can increase the increase in ICP, which, in turn, causes neurological damage that is often irreversible.[2,4,7]

The literature shows us that acute IAH)causes an increase in ICP due to increased pleural pressure, thus preventing venous return. The increase in chest pressure leads to an increase in central venous pressure (CVP), which increases the intrajugular pressure, consequently decreasing the venous return of the brain and increasing, even more, the ICP.[8] This association between IAP and ICP is essential. It should be considered when treating patients with IAH at risk for brain injury. Cerebral perfusion pressure (CPP) will decrease due to an obstruction of cerebral venous flow caused by increased intrathoracic pressure (ITP) due to cranial displacement of the diaphragm in combination with reduced systemic blood pressure resulting from decreased preload and cardiac output.[9–11]

The acute increase in IAP causes a significant increase in ICP, and the CPP can be significantly reduced. Mechanisms proposed to explain this change include reduced blood flow to the lumbar venous plexus (leading to increased pressure in the cerebrospinal fluid [CSF]), increased pressure of carbon dioxide (PaCO2), and reduced cerebral venous return by the jugular system.[12–14] This hypothesis meets and underlies the Monro-Kellie doctrine, in which states that the intracranial volume is equal to the volume of cerebral blood (3–10%) plus the volume of CSF (8–12%) plus the volume of brain tissue, which consists of more than 80% water. While the total intracranial volume remains identical, the ICP remains constant. There can be no increase in the volume of one of these components without a compensatory decrease in the two others. Thus, whenever there is an increase in IAP, there will be an increase in intrathoracic pressure, which reduces cerebral venous return through the jugular system, leading to an increase in cerebral blood volume and intracranial hypertension.[8,11,12] In a study conducted by Joseph et al, they have monitored parameters of patients ($n = 29$) with head

Table 1 Parameters before and after abdominal decompression

	MAP (mm Hg)	ICP (mm Hg)	CVP (mm Hg)	CI (L/m/M^2)
Predecompression	29.5 ± 5.3	30.0 ± 4.0	20.9 ± 6.6	4.6 ± 1.2
Postdecompression	27.5 ± 5.3	17.5 ± 3.2	18.9 ± 6.1	4.7 ± 1.4
P-value	NS	< 0.0001	NS	NS

Abbreviations: CI, cardiac index; CVP, central venous pressure; ICP, intracranial pressure; MAP, mean airway pressure.

trauma and sustained increase in ICP, even with surgical (decompressive craniectomy) and pharmacological (barbiturates) management. In their study, these patients were evaluated before and after performing decompression laparotomy, resulting in the data shown in ►**Table 1**.

Through the monitoring analysis, it can be seen that after decompression laparotomy there was a slight reduction in mean arterial pressure, central venous pressure, and cardiac index; however, what calls attention is a 41.55% drop in the mean ICP value, demonstrating that abdominal surgical intervention in these patients was an impact factor for reducing ICP.[9] A similar result was demonstrated by Dorfman et al, who, in his case report, submitted a 17-year-old patient with head trauma and subdural hematoma to laparotomy due to ICH refractory to decompressive craniectomy, use of barbiturates and mannitol. After abdominal decompression, there was an improvement in both ICP and ventilatory values and measurement of renal function.[15]

Conclusion

Based on the selected articles, it was possible to identify several systemic complications due to the increase in IAP. Among these complications, there was a direct correlation between the increase in IAP and the increase in ICP. Some studies direct the measurement of IAP when there are findings of ICP refractory to usual treatments such as decompressive craniectomy and pharmacological measures, thereby emphasizing the intervention of decompressive laparotomy as an adjunct in the treatment of refractory ICH. What is also evident is the reflection that we may be underestimating patients with refractory ICP because we are not measuring IAP.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Tribute to Theodor Kocher: Far Beyond an Anatomical Reference

Homenagem a Theodor Kocher: Muito além de uma referência anatômica

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Arq Bras Neurocir 2020;39(3):192–196.

Abstract

We know Kocher's name as an anatomical reference in neurosurgery. In fact, Theodor Kocher was a Swiss general surgeon, and his contributions were such that Kocher was honored in 1909 with the Nobel Prize in Medicine and Physiology, and he was the first surgeon to receive this honor. Kocher participated in the initial scientific phase of medicine, living with names that are in history, as well as him; Langenbeck and Virchow, Lucke, Billroth, Horsley, Lister, Halstedt, Pasteur, Osler, Lawson Tait, Verneuil, and a long list and other icons of the time. The present account rescues the many important facets and contributions of the Swiss surgeon Theodor Kocher, and his relationship with several of them. Kocher's memory, surgical instruments and literary production are preserved in a small wing of the University of Bern. The present article highlights how intense Kocher's dedication to the medical field was.

Keywords
- history of Medicine
- history of the twentieth century
- surgeons
- historical Aspects of NLM Neurosurgery

Resumo

Conhecemos o nome de Kocher como um referencial anatômico em neurocirurgia. Na verdade, Theodor Kocher foi um cirurgião geral suíço, e suas contribuições foram tantas que Kocher foi honrado em 1909 com o Prêmio Nobel de Medicina e Fisiologia, sendo o primeiro médico a deter esta honraria. Kocher participou da fase científica inicial da Medicina, convivendo com nomes que ficaram na história, assim como ele; Langenbeck e Virchow, Lucke, Billroth, Horsley, Lister, Halstedt, Pasteur, Osler, Lawson Tait, Verneuil, e uma longa lista e outros ícones da época. O presente relato resgata as várias e importantes facetas e contribuições do cirurgião suíço Theodor Kocher, e a sua relação com vários deles. A memória de Kocher, seus instrumentos cirúrgicos e produção literária estão preservados em uma pequena ala da Universidade de Berna. O presente artigo evidencia quão intensa foi a dedicação de Kocher à Medicina.

Palavras-chave
- história da Medicina
- história do século XX
- cirurgiões
- aspectos históricos da Neurocirurgia

Introduction

The year of 2017 celebrated 100 years of the death of Theodor Kocher. Time is relentless, and historical events often interfere with due recognition to individuals who extrapolate their time.

Kocher was born in Bern, Switzerland, on August 25, 1841, and at the age of 4 years old attended school, accompanying his brother a year older. At the age of 17, he was already enrolled at the University of Bern, and developed in this period great skills and anatomical knowledge, which made

received
December 5, 2019
accepted
April 22, 2020

DOI https://doi.org/10.1055/s-0040-1713592.
ISSN 0103-5355.

him years later to be recognized worldwide for having contributed to so many surgical techniques. After his board graduation in 1865, Kocher spent a year visiting and studying at other European universities; Langenbeck and Virchow in Berlin, Billroth in Vienna, Lister in Edinburgh, and Pasteur and Verneuil in Paris. Upon his return to Vienna, he became Lucke's assistant and in the same year became a Professor. In 1872 Kocher assumed the chair of Surgery at the University of Bern, and began 45 years of continuous, persistent surgery-focused work; he literally established a new school of surgery.

Kocher was also a member of the German Society of Surgery, and was elected President of that Society in 1902. In 1908 he was elected the first President of the International Society of Surgery and in the following year, in 1909, was awarded the highest possible honor, the Nobel Prize of Medicine and Physiology in recognition for his work on the thyroid gland. He has been invited to take up numerous positions at various European Universities, but has always refused to leave Berne. Kocher was a reserved, religious man who devoted himself to tennis and painting in his free time. On his seventieth birthday, he declined from any public demonstration by the University. While Horsley was a surgeon and politician, Virchow was a pathologist, anthropologist and a political dynamo, Kocher was devoted to surgery and surgery alone. Kocher is also considered one of the precursors in organ transplants, as he tried in 1883 to implant human thyroid tissue in patients undergoing total thyroidectomy. World War I disrupted Kocher's international contacts, and his writing in German also contained recognition of his achievements soon after the War.

Kocher and the General Surgery

Kocher's anatomical knowledge has defined a new surgical technique that has become a model for thyroid surgery, reducing mortality levels from 18% to 1%, percentages that are still difficult to overcome. Bern became the Mecca for patients with thyroid disorders who came from every corner of the planet. Kocher has performed over 9,000 thyroid surgeries. He was the first surgeon to emphasize the importance of hematological changes and coagulation time as a means of early diagnosis and prognosis in both hypo and hyperthyroidism.

Knowing the experiences of McDowell and Lawson Tait, he was one of the first surgeons to successfully perform gynecological techniques such as ovariotomy, hysterectomy, and aseptic hysteropexy as currently employed.

Maintaining good scientific and surgical relationships with Billroth, Kocher has contributed significantly to making gastrointestinal surgery a science. He created different suture points for bowel loops, duodenum mobilization methods after pyloric resection, contributed to rectal cancer resection methods known today as the Kraske method (1897), as well as simplified surgery for inguinal hernia.

For him, teaching was a science and an art. The history and clinical examination of the patient performed by him was unsurpassed. For him, exploratory surgery was the equivalent of a misdiagnosis.

His lectures and publications were always based on his personal experience and touch. He published his first book "Texbook of Operative Surgery"[1] in 1892, which had five editions and was a great success; Undoubtedly, the first was the most striking, because it was written with Kocher's dedication and personality only.

Kocher and Trauma

Kocher's name is often associated with his method of reducing acromioclavicular joint dislocations. The method was demonstrated at the Billroth Clinic in 1870, at a time before radiology. His knowledge of fractures and hemorrhages contributed to his rapid rise in the military career as well. In 1866 he was Lieutenant of the Swiss Army; during the Franco-Prussian War (1870) he taught other colleagues in rescue techniques. He became First Lieutenant at this time. By 1875 he was a colonel and in 1877 he became chairman of the Military Pension Commission, a position he held until his death. With such involvement, it is natural that he was interested in the effects of gunshot wounds and bleeding, increasing the surgical time for meticulous hemostasis. Kocher also spent considerable time understanding firearm and ballistic wounds. Fackler and Dougherty[2] published an excellent text on the subject.

Kocher and the Genitourinary Tract Surgery

In 1874 Kocher wrote the chapter "The Testicle and its Tunic, the Epididymis, the Cord, and the Seminal Vesicles in Billroth's Surgery Book, Textbook of General and Special Surgery" The chapter was considered a masterful description of the subject, and 13 years later Kocher published an even more elaborate review in "Deustche Chirurgie" under the title "Male Genital Organ Diseases."

Kocher and Neurosurgery

The use of meticulous hemostasis (Kocher clamping), intravenous saline application based on animal experiments by Kronecker, Bern physiologist, were also adopted by an American surgeon who became friends with Kocher, William Halsted of John Hopkins., and shortly thereafter by George Crile.

Kocher published the first complete graphics or drawings of human dermatomes (1896). He also wrote a monograph on brain surgery (1901) using experiments on intracranial pressure performed in Bern by a Halsted collaborator, Harvey Cushing, who was also very interested in Kocher's measures of asepsis, hemostasis and intraoperative control.

Hildebrandt et al[3] listed Kocher's contributions in chronological order:

1879: About nerve traction in trigeminal neuralgia.

This year, Kocher published his experience in two patients with trigeminal neuralgia.[4] The treatment consisted in traction of the exposed peripheral branches of the trigeminal in the pain region. In both cases, there was complete reduction of pain.

1880: Specific surgery of the head and the face

A. Vogel[5] described manually in a notebook a course during the summer of 1880 by Kocher, where he lectured on soft tissue trauma to the head, head fractures including skull base

fractures, cranial suture diastases, and comminuted fractures. He discussed causes of brain compression and described the clinical signs of intracranial hypertension. He also commented on "brain commotion" and "brain bruise."

1881: London

Kocher attends the 5th International Medical Congress in London[6] David Ferrier[7] (1843–1928) presented a hemiparetic monkey after a precise ablation of the motor cortex. The contributions of that event first defined a rational consensus on the function and organization of the human brain, based on participants such as William Osler (1849–1919), John Jackson (1835–1911), William Keen (1837–1932), William MacEwen (1848–1924), Rickman Godlee (1849–1925), Victor Horsley (1857–1916), Joseph Lister (1827–1912), Rudolph Virchow (1821–1902), and Louis Pasteur (1822–1895) among others, emphasizing the idea of creating a universal map of the human cerebral cortex. The period of philosophical speculation in neuroanatomic publications was over, and Kocher actively participated in this historical moment.

Kocher and the Craniometer

After the 1881 Congress, various instruments were developed to aid the pre-surgical location of the cranio-cerebral topography. These instruments were given different names according to the country, such as Wilson's cirtometer, Kroenlein's cephalometer and Kohler, Broca's craniograph; They all had the same purpose: to allow the target to be located three-dimensionally from the external characteristics of the skull. And of course, they all had limitations. In 1889, Kocher read a thesis described by Ludwig August Müller, and he then came to the realization that target location faults were related to the effect of different cranial shapes. Müller suggested including numerical coefficients in the metal handles, and Kocher also introduced movable handles, explaining in his 1911 compendium, Textbook of Operative Surgery, that the 60-degree anterior motion allowed the exact location of the structures of the region prior to the pre-central gyrus, and the posterior rotation of 60 degrees allowed to limit the borders between the temporal and occipital lobes (►**Figs. 1–7**). The device was also cited by Quervain, Krause and Cushing, among others. Krause[8] used it and gave detailed information about its use in his book "Surgery of the Brain and Spinal Cord"; Cushing devoted 6 pages on craniocerebral localization in his chapter "Surgery of the Head" written for Keen's compendium, "Surgery." Therefore, Kocher[9] invented a craniometer that became one of the first popular objects of neurosurgical navigation.

1887: Cafe Roth, Bern

Kocher presented an epileptic patient treated for eight years, who had undergone various surgical procedures. Kocher performed a craniotomy on the left occipital lobe, finding and resecting a 2 cm-diameter brain tumor. Pathological evaluation by Langhans revealed "bone tissue" within the tumor. The presentation protocol does not mention the patient's clinical course.

1892: Surgical Texbook

In his first compendium, Kocher[1] describes soft tissue surgery of the head, the relationship of the gyrus with the skull, and the 23-page trepanning technique, the 15-page viscerocranium surgery, and showed and cited the technique described by Wagner,[10] temporary cranial resection, later referred to as osteoplastic trepanation (craniotomy). In this compendium, he also emphasized the need to anatomically distinguish motor sensory functions using requested figures manually drawn by Victor Horsley.

1896: Spinal cord injuries in spinal trauma

Kocher[11] described his experience in diagnosing and treating trauma and spinal disease on 245 pages, with data derived from 78 patients in his clinic. He even proposed a classification of the lesions in 1. Partial (contusion and distortion of the vertebral body) 2. Isolated fractures of the vertebral arch and spinous process, 3. Isolated dislocation of the articular facets, 4. Isolated fractures of the vertebral body and 5. Traumatic total dislocation. He stressed the relevance of spinal contusion in the genesis of hematomyelia and valued the decompression laminectomy technique. This experience and perhaps the accumulated experience of the Franco Prussian War led him to publish what Hildebrand[3] regarded as Kocher's greatest contribution to neurology and neurosurgery, which was the first figurative correlation of dermatomes ever published (►**Fig. 6** page 1111 of reference [3]). In 1917, in his last year of life, Kocher considered the sterile injection of a platelet concentrate (named coagulum) into spinal cord injuries.

1899: About the surgical cure of epilepsy

Kocher firmly believed that the genesis of epilepsy was intracranial hypertension, and that cure could be achieved through dural cleavage or permanent subcutaneous cerebrospinal fluid drainage. In 1896 Hayazo Ito of the University of Tokyo stayed in Bern developing experimental models in epilepsy. His publication contained over 420 references, and when he returned to Japan, he performed several dozen epileptic surgeries. Kocher described his experience in 175 patients at the 28th German Congress of Surgery in Berlin in April 1899. Due to the weight of his name's authority, he initially had many followers, but was confronted in 1910 by Krause and others during the 39th German Congress with several reports of unsatisfactory results through the technique proposed by him. In fact, by 1901 Bier[12] had already shown that intracranial hypertension was a concomitant sign of epilepsy, but not the causative factor. Surbeck[13] reports in detail Kocher's relationship with epilepsy.

1900: Kocher, Hayazo Ito and Harvey Cushing in Bern[14]

Ito was the first Professor of the Second Surgical Department at Kyoto University, Japan, from 1900 to 1924. He remained for 3 years as a research fellow with Kocher and engaged in experimental studies on the relationship between intracranial hypertension and epilepsy, object of interest to Kocher. Ito demonstrated in his experimental studies that saline-induced intracranial hypertension caused a disturbance in blood pressure, translated as "strong and high pulsations" that could be recorded on a kimograph. During his time in Japan, Ito performed 182 Kocher surgeries for epilepsy.

Harvey Cushing worked with Halsted at John Hopkins in Baltimore. Halsted was enthusiastic about the European methodology of university research and suggested to Cushing to spend a year visiting some European centers. Cushing

visited Bern one year after Ito's departure and stayed for 5 months, conducting an intensive study on intracranial hypertension as a suggestion of Kocher.[14] Next, Cushing stayed for 4 weeks in Turin at Angelo Mosso's[15] laboratory. An important event is the fact that Cushing became acquainted in Pavia with the Riva-Rocci device, which was one of the first sphygmomanometers in existence. Cushing then returned to Bern where he stayed another 4 weeks to complete his work, and it is presumed that he carried a sphygmomanometer with him.[14]

Cushing himself describes in one of his monographies (date of 1926) his relationship with Kocher and his influence: "My own interest in the dynamics of the intracranial chamber was first aroused while engaged 25 years ago in the Hallerianum in Berne on a problem suggested by the late Theodor Kocher, who was preparing a monograph on cerebral compression for Nothnagel's Speziellle Pathologie, wherein he laid much more stress on the results of my research during that happy year than they might otherwise have deserved. Cushing returned to Baltimore and founded the Neurosurgery Department at John Hopkins in 1901, taking with him Kronecker and Kocher's fundamentals of volume replacement, asepsis (Lister), and meticulous hemostasis.

1901 In the same year, Kocher published his experience, knowledge, and theories on the anatomy and physiology of cerebral perfusion and various surgical procedures. The monograph was published as the 9th volume of the Spezielle Pathologie und Therapie series and consisted of 457 pages, with H. Nothnagel as editor.[16] Giving credit to visiting physicians, Cushing and Ito, Kocher made his considerations on the pathophysiology of hypertension. taking into account Cushing's observations of what would later be Cushing's reflex.[17] In addition to theoretical considerations, Kocher addressed the issue from a surgical standpoint, describing ventricular puncture, artificial respiration, and trepanation methods in the early stages of intracranial hypertension in detail. On 69 pages, he described the indications for trepanations and the different methods existing at the time.[16]

1909: Kocher and the Hypophysectomy

Kocher performed his first hypophysectomy in 1909,[18] joining an elite at the time of only 5 surgeons who had performed this procedure at a time when patients with pituitary tumors were treated with medieval remedies such as eye compresses, alcohol, "stay for four weeks in a dark room". Radiology was in its infancy, there were no hormonal laboratory studies, no diathermy, aspiration (suction), microscope, or antibiotics. Kocher's publications[18] show how meticulously he and his team prepared this surgery. They studied the literature available at the time, following the publication of Schloffer,[19] who performed the first transnasal approach to the pituitary, developed specula and other instruments before the procedure was performed,[2] and were at the forefront of the pathophysiology of pituitary problems certainly influencing Harvey Cushing[20] to elucidate the cause of acromegaly and other conditions of pituitary function. Cushing performed his first transnasal approach two months after Kocher and recognized and adopted Kocher's approach because of its better cosmetic outcome.

1909 In the same year, Emil Theodor Kocher was the first surgeon in history to receive the Nobel Prize in Physiology and Medicine for his achievements in the fields of physiology, pathology and surgical treatment of the thyroid gland.

Kocher has always been a general surgeon, a visionary, and despite the large amount of accumulated and published information (249 articles and books), curiously he has never had followers or students who dedicated themselves to neurosurgery.[1,2,21] In 1921, a book in his honor was published with more than 1,000 pages.[22] The book contained 35 contributions from his former collaborators and colleagues, and there was only one contribution with anatomopathological reference in the neurosurgical field. It took another two decades for Hugo Krayenbühl to create Switzerland's first neurosurgery department in Zurich.

Theodor Kocher was a pioneer in many ways, a visionary who kept his mind open for new knowledge and techniques until the end of his life.

Conflict of Interests

The authors have no conflict of interests to declare.

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Historical High Complexity Neurosurgery Development of One of the Poorest Brazilian Regions

Desenvolvimento histórico de neurocirurgia de alta complexidade de uma das regiões mais pobres do Brasil

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Arq Bras Neurocir 2020;39(3):197–200.

Abstract

Human development rates in the Vale do Jequitinhonha, state of Minas Gerais, Brazil, called "Misery Valley," are among the lowest in the country, not to mention the often precarious psychosocial realities that daily contact with these families reveals. The history of neurosurgery at the Neurosurgical Reference Center at the Vale do Jequitinhonha e Mucuri dates from 2004, when the first neurosurgical procedures were performed in the recently organized Section of Neurosurgery. The historical surgical series shows the positive impact of the service. In 2007, the average was 3 neurosurgeries/month. In the last year, 2018, service growth boosted the record to 34.83 neurosurgeries/month. In addition to performing elective surgery, the neurosurgery team supports the emergency team by performing some neurosurgical procedures. The service number of patients operated since the development of the service is nearly 3,000. Neurosurgery at the Santa Casa de Caridade from Diamantina has been made comparable to the best national neurosurgery services.

Keywords
- history
- faculty
- medical schools
- neurosurgery

Resumo

As taxas de desenvolvimento humano no Vale do Jequitinhonha, Minas Gerais, Brasil, denominado "Vale da Miséria," estão entre as mais baixas do país, sem mencionar as realidades psicossociais, muitas vezes precárias, que o contato diário com essas famílias revela. A história da neurocirurgia no Centro de Referência Neurocirúrgica do Vale do Jequitinhonha e Mucuri vem de 2004, quando os primeiros procedimentos neurocirúrgicos foram realizados na recém-organizada Seção de Neurocirurgia. A série

* *These authors did the same work.*

received
December 21, 2019
accepted
May 12, 2020

DOI https://doi.org/10.1055/s-0040-1713920.
ISSN 0103-5355.

Palavras-chave
- história
- faculdade
- faculdades de medicina
- neurocirurgia

histórica de cirurgias mostra o impacto positivo do serviço. Em 2007, a média foi de 3 neurocirurgias/mês. No último ano de 2018, o crescimento do serviço elevou o recorde para 34,83 neurocirurgias/mês. Além de realizar cirurgias eletivas, a equipe de neurocirurgia apoia a equipe de emergência executando alguns procedimentos neurocirúrgicos. O número de pacientes operados desde o desenvolvimento do serviço é de $\sim$ 3,000. A neurocirurgia na Santa Casa de Caridade de Diamantina foi comparada aos melhores serviços nacionais de neurocirurgia.

Introduction

Neurosurgery is one of the most specific medical clusters, whose professionals treat many neurological disorders, like brain tumors, brain trauma injury, spinal cord injury, as other neurosurgery issues. After medicine graduation, neurosurgery residents have to pass through 5 years of training to graduate as a neurosurgeon, and after that have to exercise more than 3,000 hours in an operative room to occupy the place of experienced neurosurgeon.[1–4]

Brazilian Neurosurgery: A Brief History

In Brazil, neurosurgery emerged from Luis Gomes Ferreyra, a doctor born in Portugal who practiced medicine in Sabará and Vila Rica (Ouro Preto, nowadays), who performed the first known neurological surgery procedure in Brazil, in 1710, at a little town located in the countryside of Minas Gerais state (Sabará city). The patient was a slave who presented a brain trauma injury after a falling from a tree branch. Seeing this, Luis Gomes Ferreyra removed the fractured bone fragments and covered the bone defect with a piece of calabash shell until bone healing occurred. After that, the patient returned to work with a mild sequela, characterized as an expressive dysphasia.[5,6] Brandão Filho was a general surgeon interested in brain surgery. In 1924, he performed the first ventriculography in Brazil, and in 1928 he performed America's first cerebral angiography. Despite the first performed neurosurgery procedure in 1710, Brazilian neurosurgery just grew up from 1928 with two general surgeons: Alfredo Monteiro and José Ribes Portugal.[5–8]

Neurosurgery Assessment Countrywide

Brazilian neurosurgery has increased in number as also in complexity and worldwide visibility. Nevertheless, according to the National Registry of Health Facilities, in 2018, there were almost 1,200 neurosurgeons in the whole national territory. It shows a small number of professionals to attend plenty of neurosurgical diseases. Furthermore, the majority of these professionals are allocated in the Southern region, one of the more prosperous regions of the country.[9] The primary health system in Brazil is the Brazilian Unified Health System (SUS, in the Portuguese acronym), which is one of the largest public health care systems in the world and provides a wide range of services, including neurosurgery services, divided into two groups: high-complexity assistance units (HCAUs) and high-complexity neurosurgical reference centers (HCNRCs).[5,6,10] The first one is characterized as hospital units that have technical conditions and human resources available to assist those patients that require high-complexity neurointervention and neurosurgical procedures.[3–8,10,11]

High-complexity Neurosurgical Reference Center Development at the Vale do Jequitinhonha e Mucuri

Human development rates at the Vale do Jequitinhonha e Mucuri region (called "Misery Valley") are among the lowest in the country, not to mention the often poor psychosocial realities that daily contact with these families reveals.

In Diamantina, allocated at the Vale do Jequitinhonha e Mucuri region, with a predicted population of 50,000 inhabitants, one of the unique High-complexity Neurosurgical Reference Center was developed in a county with $<$ 100,000 inhabitants. Although Diamantina is in Minas Gerais, Brazil's southeastern region, the wealthiest region countrywide, it remains with poor health access and low economical rates. This situation explains the history question of Diamantina and the whole Vale do Jequitinhonha e Mucuri region. The Jequitinhonha that we have today still suffers the consequences of the colonization process and slavery. Diamantina still has some difficulties at health access from some counties due to the distance or even the shortage of transport to bring those patients with neurosurgical issues.

Transport logistics from patients to Diamantina are highly complex. Individuals with a variety of neurological sequelae often have to leave the house on foot or on the back of an animal at dawn to be able to overcome the arduous stages to the outpatient clinics in the late afternoon. Such a situation significantly increases the chances of prehospital complications of trauma and other neurological disorders, for apparent reasons. All of these factors further expand the need for a systematically humanized approach to these poor Brazilians and become a powerful enabler for dealing with delicate medical situations.

The Santa Casa de Caridade de Diamantina is an institution almost entirely funded by the SUS. About 90% of the patients treated at the hospital are SUS users, and virtually all improvements in their physical structure, guaranteed by funds from the Ministry of Health, which are invariably honestly allocated.

Particularities of the scenario demonstrate the consent of the political entities by our work philosophy. Diamantina, whose estimated population in 2010 was 45,884 inhabitants,

is the only Brazilian city with < 150,000 inhabitants to have a SUS-accredited High Complexity Neurosurgery service. For the perfect functioning of such a service, the availability of state-of-the-art diagnostic tests is indispensable. At the Santa Casa de Diamantina, in partnership with the private sector, a state-of-the-art Netherland magnetic resonance imaging (MRI) (Philips Achieva 1.5T MRI, GE Health Care, Best, The Netherlands) equipment is in operation, which has enabled the rapid and accurate diagnosis and optimal treatment of the most diverse pathologies of the nervous system. This equipment is the only one in Brazil, in cities with a population of < 100,000 inhabitants, which has accreditation to perform examinations by the SUS.

Moreover, technological resources are available, some unusual in public services, such as:

- Zeiss OPMI Vario/S88 operating microscope (Jena, Germany);
- Aesculape pneumatic craniotome (Center Valley, PA, USA);
- Integra Cusa Dissectron ultrasonic cleaner (Priceton, USA);
- Aesculape Neuroendoscope (Center Valley, PA, USA);
- Micromar stereotaxis kit (Toledo, Spain);
- Micromar Radiofrequency Device (Toledo, Spain);
- General surgical equipment: Philips surgical arch (Best, The Netherlands), articulated electric surgical tables Sismatec and Barrfab (Rio Grande do Sul, Brazil), Dixtal and Takaoka anesthesia machines (São Paulo, Brazil), and Deltronix digital electric scalpels (Ribeirão Preto, Brazil).

Therefore, all neurosurgical patients have full access to Computed Tomography (CT) in the Santa Casa de Caridade de Diamantina. Adding to this, in front of the surgical ward is the Intensive Care Unit (ICU) with 20 beds highly prepared to assist neurosurgical patients and those with other health issues. Services guarantee the coverage of the neuro hemodynamic service in the municipality of Belo Horizonte, capital of the state of Minas Gerais. Patients are referred for diagnostic tests and complicated treatments in neurointervention, such as endovascular obliteration of aneurysms and other cerebral vascular malformations, as well as stent implantation in the cervical and cranial arteries.

The historical series of performed surgeries shows the positive impact of the service (►**Fig. 1**). In 2007, the average was 3 neurosurgeries/month. In the last year, 2018, the service growth boosted the record to 34.83 neurosurgeries/month, as illustrated in ►**Fig. 2**. These data show that neurosurgical resolution has increased by an impressive 1,000% since service delivery began 12 years ago.

Far more important than numbers, surgical outcomes have been a constant stimulus to life-saving investments. Morbidity and mortality rates < 5% are close to those in the international literature, translated into low permanence, minimized costs, and high internal and external customer satisfaction rates.

Emergencies Service

In addition to performing elective surgery, the neurosurgery team supports the emergency team by performing some neurosurgical procedures (polytraumatized patients and patients with other neurological complaints, signs, or symptoms) and access to ICU, if necessary.

Resolution of the Elective Neurosurgical Demand of the Region

The team organized the neurosurgical subspecialties among its professionals (oncological and skull base, vascular, endoscopic, spinal, functional, stereotactic, pediatric, peripheral nerve, and neurointervention neurosurgery), achieving continuous and highly specialized improvement. The company

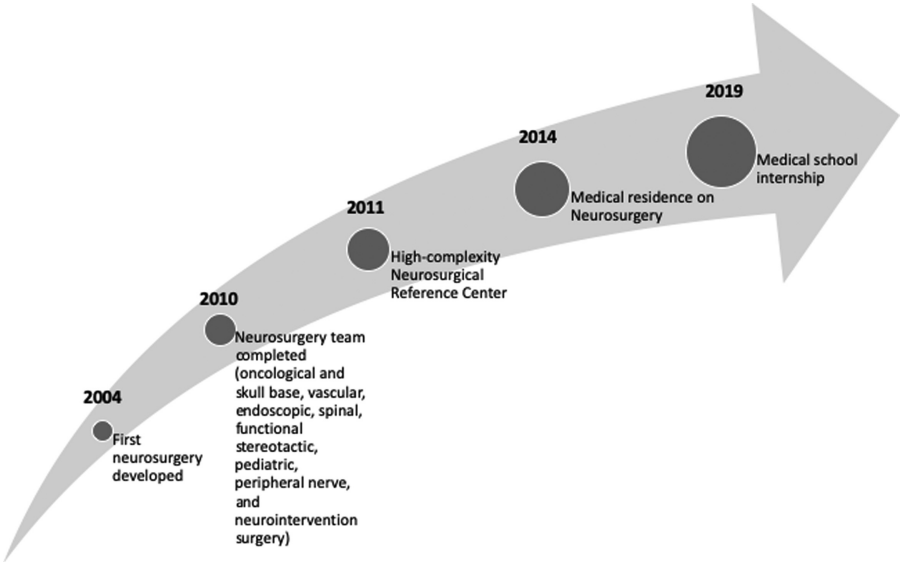

Fig. 1 Timeline of the main events of the neurosurgery service since its foundation.

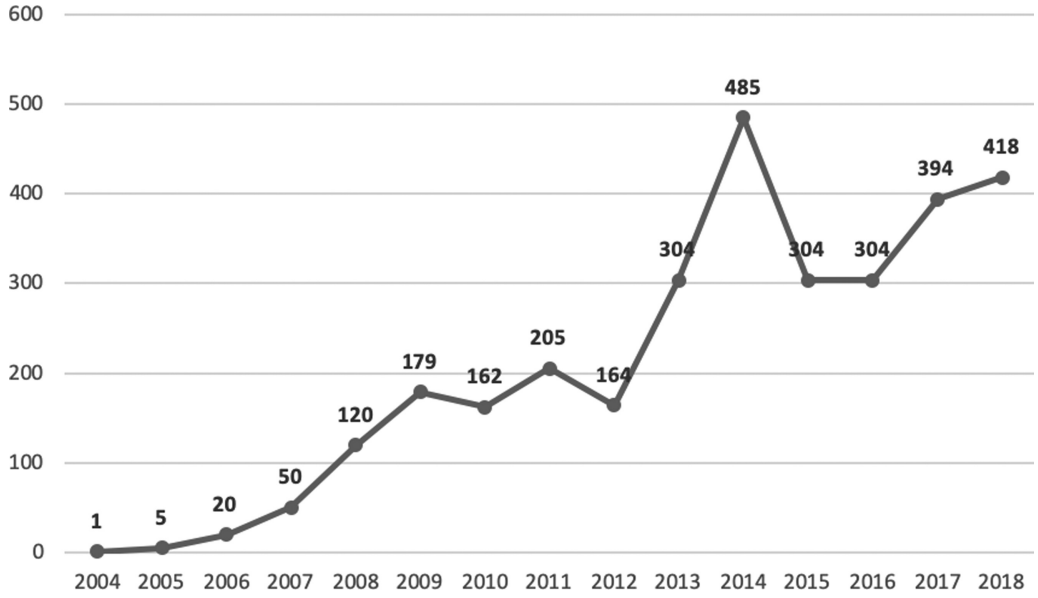

Fig. 2 Number of neurosurgeries since the implementation of the High-complexity Neurosurgical Reference Center at the Vale do Jequitinhonha e Mucuri.

resolves any elective neurosurgical situation in a large and exclusive operating room.

Neurosurgery at the Santa Casa de Caridade de Diamantina has been made comparable to the best national neurosurgery services.

Currently, nearly 3,000 patients have been operated on since the service has been implemented. The service admits one resident a year for training. Nowadays, the discipline of neurosurgery of the Santa Casa de Caridade de Diamantina forms young surgeons who indeed will become some of the future leaders of neurosurgery in Brazil and in the Vale do Jequitinhonha.

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Pure Endoscopic Excision of Parenchymal Brain Tumors: Feasibilty, Risks, Advantages and Realities - A Beginners Perspective

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Arq Bras Neurocir 2020;39(3):201–206.

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Abstract

Background Neuroendoscopy is gaining popularity and is reaching new realms. Young neurosurgeons are exploring the various possibilities associated with the use of neuroendoscopy. Neuroendoscopy in excision of parenchymal brain tumors is less explored, and young neurosurgeons should be aware of the realities. The present article is an approach to put forward the difficulties faced by a young neurosurgeon and the lessons learnt.

Objective To report the experience of surgical excision of parenchymal brain tumors, in selected cases, using pure endoscopic approach and to discuss its feasibility, technical benefits, risks and comparison with conventional microscopic excision.

Method Eight patients of variable age group with parenchymal brain tumors were operated upon by a single surgeon and followed up for a period varying from 6 months to 2 years. Data regarding operating time, illumination, clarity of the field, size of craniotomy, blood loss and course of recovery was evaluated. All of the tumors were resected using rigid high definition zero and 30° endoscope.

Results Out of eight cases, seven had lesions in the supratentorial and one in the infratentorial location. The age group ranged from 27 to 74 years old. Near to gross total resection was achieved in all except two cases. All of the patients recovered well without any significant morbidity or mortality. Hospital stay was reduced by 1 day on average.

Conclusion Excision of parenchymal brain tumors via pure endoscopic method is a safe and efficient procedure. Although there is an initial period of learning curve, it is not steep for those already practicing neuroendoscopy, but the approach has its advantages.

Keywords
- clarity
- illumination
- learning curve
- magnification
- neuroendoscopy

Introduction

Neuroendoscopic excision of intraventricular and sellar tumors is a well-established neurosurgical technique, but the use of this approach for parenchymal tumors has not gained popularity. Several surgeons have tried combined open and endoscopic approaches with success.[1–4] However, pure endoscopic resection of parenchymal brain tumors is not routinely in vogue, the possible reasons being unfamiliarity with the technique and apprehension of incomplete resection at the depth. Although the open microscopic excision procedure is perceived to be better due to the availability of high end microscopes, advanced magnetic resonance imaging (MRI) sequences and support of neuronavigation, the latest neuroendoscopes offer better clarity of vision.[5] Contrarily, the endoscopic approach for parenchymal brain

received
November 30, 2019
accepted
December 23, 2019

DOI https://doi.org/10.1055/s-0040-1702975.
ISSN 0103-5355.

tumor excision is a safer alternative as it allows easy entry to the tumor through the parafascicular corridor of white matter, offers better clarity of image because of the proximity of the endoscope to the brain and tumor surface.[5] Also, the smaller size of craniotomy and the narrow corridor of entry is sufficient to allow bimanual manipulation of the tumor with clear visibility of the hidden corners. The technique therefore is minimally invasive and strictly adheres to proven microsurgical principles.[6–8] Eight patients with parenchymal brain tumors were operated upon using the pure endoscopic method. Comparison on various parameters was done with the purely microscopic approach. The feasibility of this approach along with associated risk, benefits and misconceptions are discussed.

Summary

A total of 8 patients (►**Table 1**), with age ranging from 27 to 74 years old, with a follow-up period of 2 months to 2 years are presented. These include three females and five male patients, out of which seven had supratentorial and one had infratentorial location of the lesions. We were able to achieve near to gross total resection in all the lesions except in two, as one lesion had close proximity to the vessels and there was misleading frozen section report in the other. Three lesions were low grade, four were high grade and one was a hemangioblastoma. Only one patient had significant deficit in the postoperative period in the form of opposite side weakness with aphasia, which recovered with time. None of the remaining patients developed any remarkable postoperative deficits.

Operative Technique

All of the patients underwent contrast-enhanced MRI under neuronavigation protocol. Following standard neuroanaesthetic technique for induction, the heads of the patients were positioned and fixed with the help of a Sugita head frame (Head support of OT table company name, Mizuho, Made in Japan, Made in Japan). Using stealth navigation system, the position of the tumor was confirmed and a limited craniotomy was planned centering on the main bulk of the lesion. Although the initial two cases had a slightly larger craniotomy as a precautionary learning curve measure, the subsequent exposures were reduced to almost half the size of standard exposures. Dural openings were similar to cruciate exposure. The site of cortisectomy was decided based on neuronavigation guidance depending upon the shortest route of entry and eloquence of structure(s) in the vicinity. Cortisectomies were tailored to the optimal space requirement for the introduction of the endoscope and maneuverability of the operating instruments. The initial debulking was performed using a zero degree scope mounted on an endoscope holder which allowed the freedom for bimanual excision. Subsequently, a 30° scope was introduced for visualization of the surrounding lesion in blind corners of the cavity using minimal retraction. There was no need for the use of other angled scopes. Tumor excision followed the same principles of cautery and suction (CUSA) evacuation using navigation guidance. In the initial 2 cases, the microscope was brought in at the end of surgery to confirm the definition of the tumor-brain interface, which reaffirmed good tumor clearance. In initial cortisectomies, the margins were not supported leading to subpial hemorrhages and cortical changes. Subsequent use of gloves strips circumvented the issue. Hemostasis was achieved in the usual manner followed by complete dural closure in every case.

Results

A total of eight patients of intraparenchymal lesions were operated in the present series, out of which seven were supratentorial and one was in infratentorial location. The age group ranged between 27 and 74 years old. Near to gross total resection was achievable in all of the cases, except in two (►**Fig. 1**, **2** and **3**). One patient with a dominant frontotemporal lobe tumor developed hemiparesis and motor aphasia in the postoperative period, which recovered gradually. The remaining patients had no neurological deficit (►**Table 2**). Considering

Table 1 Details of the patients including types of tumors and postoperative complications

Case No	Age/Sex	Location	Resection	Histopathology	Complication
1.	27 yrs/F	Left temporal (►**Fig. 1**)	Near total	Diffuse infiltrating astrocytoma Grade II	Nil
2.	34 yrs/F	Left posterior frontal (►**Fig. 2**)	Gross total	Oligodendroglioma Grade II	Right hemiparesis with aphasia
3.	57 yrs/M	Left cerebellar	Gross total	Hemangioblastoma Grade I	Nil
4.	74 yrs/M	Right parieto occipital (►**Fig. 3**)	Gross total	Glioblastoma multiforme Grade IV	Nil
5.	36 yrs/F	Left perisylvian	Gross total	Astrocytoma grade III	Nil
6.	64 yrs/M	Right parieto occipital	Subtotal	Glioblastoma Multiforme Grade IV	Nil
7.	33 yrs/M	Right Frontal	Near total	Oligodendroglioma grade II	Nil
8.	59 yrs/M	Left Fronto-Parietal	Gross total	Glioblastoma Multiforme Grade IV	Nil

Abbreviations: F, female; M, male.

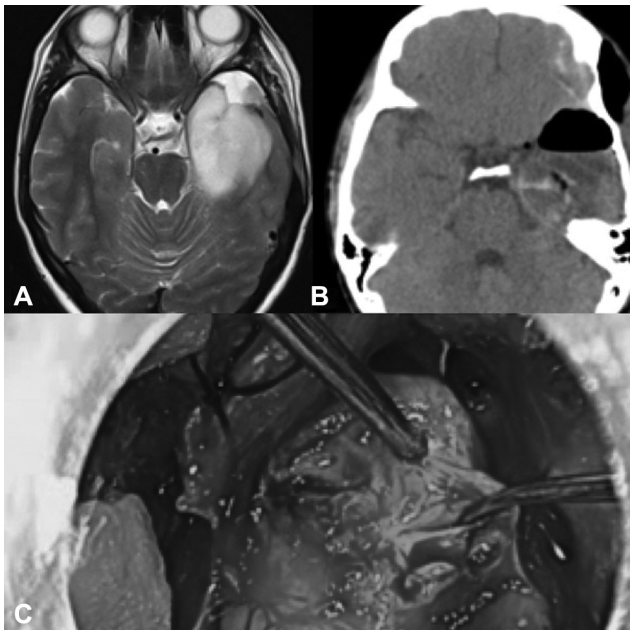

Fig. 1 (A) Axial T2 weighted magnetic resonance imaging showing the heterogenous hyperintense lesion in the anterior temporal lobe showing ill-defined margins. (B) Axial computed tomography image showing postoperative changes in the left temporal lobe and foci of air in the operative bed. (C) Intra operative endoscopic view during tumor excision showing partly fibrous tumor.

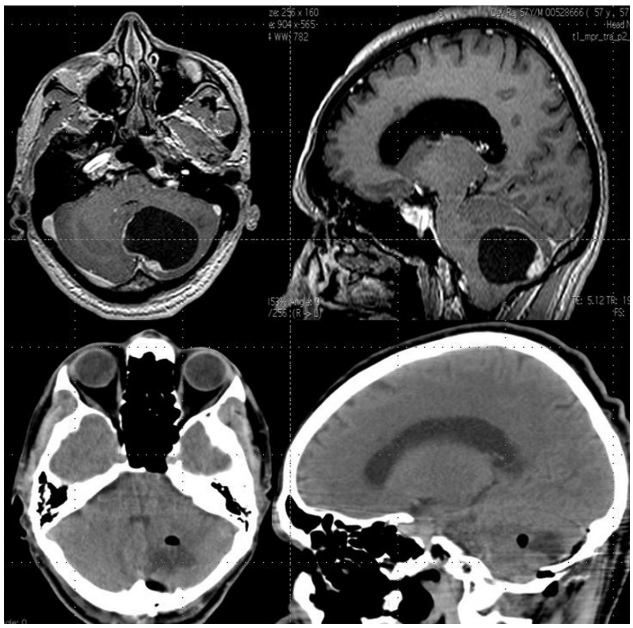

Fig. 3 (A and B) Preoperative axial and sagittal T1 contrast magnetic resonance imaging showing large cystic tumor with enhancing nodule in the left cerebellum. (C and D) Postoperative axial and sagittal plain computed tomography images showing complete excision with no tumor bed hematoma.

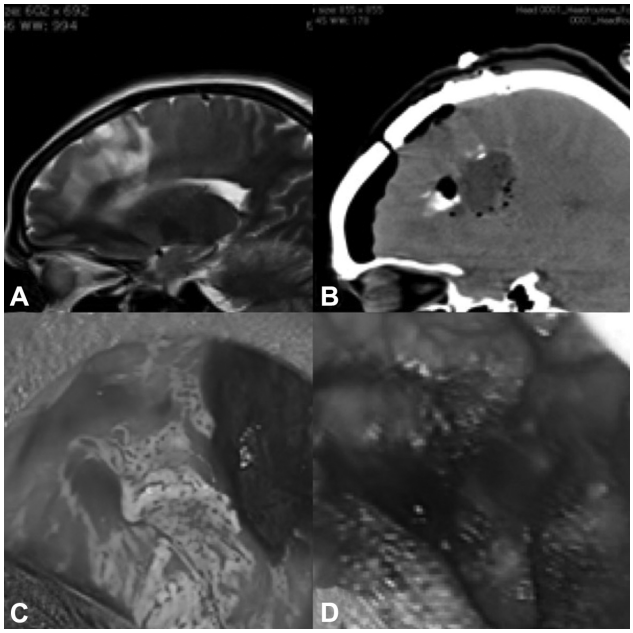

Fig. 2 (A) T2 weighted sagittal image of the brain showing lesion in the left frontal lobe. (B) Sagittal computed tomography image showing postoperative changes in the left frontal lobe with small foci of air at the postoperative site and extra axial nondependent air in the frontal region. (C) Intraoperative endoscopic image showing tumor tissue. (D) Endoscopic view after tumor excision showing the surgicel lining at the margins.

the evaluation of the endoscopic technique with microscopic procedure, the parameters compared were: operating time, illumination, clarity, magnification, blood loss, size of craniotomy, postoperative imaging. The surgical time was slightly longer than the microsurgical technique, most likely due to our learning curve, but blood loss was comparable to that of the microscopic technique. The illumination, clarity and magnification were at par with the microscope, but the blind corners were much better visualized with good clarity (►**Table 2**; ►**Fig. 1**, **2**). We saw a significant reduction in craniotomy size (►**Fig. 3**). The extent of excision was $>$ 95% in all cases except one; although the number of patients was not adequate to reach any conclusion, adequate visualization of blind corners definitely helped in excising the tumors with a good limit of confidence and safety with minimal damage to the normal tissue due to small cortisectomies. The patients recovered well and were discharged home on average 1 day earlier than those who were submitted to the routine microscopic approach with large craniotomy (►**Table 2** and **3**). A concise comparison between the standard microscopic approach and the pure endoscopic approach, with emphasis on selected important points, is shown in ►**Table 4**.

Discussion

Pure endoscopic resection of intraparenchymal brain tumors is a minimally invasive approach that is not routinely practiced by neurosurgeons. To the best of our knowledge, until now, there are two major series with 21 and 48 cases, respectively, by Kasam et al[1] and Plaha et al[2] with few other sporadic reports (►**Table 5**). The reason for the lower popularity of this technique is due to the unfamiliarity with the procedure, the long learning curve and apprehension about inadequate exposure and inadequate visibility through the endoscope.

Table 2 Evaluation of Parameters in pure endoscopic method

S No	Parameters	Case I (►Fig. 1)	Case II (►Fig. 2)	Case III	Case IV (►Fig. 3)	Case V	Case VI	Case VII	Case VIII
1	Surgical Time	2 hrs 15 mins	3 hrs 25 mins	2 hr 45 mins	2 hr 50 mins	2 hrs 30 mins	2 hrs 10 mins	1 hr 50 mins	2 hrs 10 mins
2	Illumination & Clarity	Very good specially at corners	Very good specially at corners	Very good specially at corners	Very good specially at corners	Very good specially at corners	Very good specially at corners	Very good specially at corners	Very good specially at corners
3	Magnification	Tumor brain interface well differentiated	Tumor brain interface well differentiated	Tumor brain interface well differentiated	At par with microscope with little difficulty in hemostasis at depth	At par with microscope with little difficulty in hemostasis at depth	Tumor brain interface well differentiated	At par with microscope with little difficulty in hemostasis at depth	Tumor brain interface well differentiated
4	Blood Loss	150–200 ml	200 ml	200 ml	250–300 ml	400 ml	150–200 ml	100–150 ml	150–180 ml
5	Craniotomy Size	70% of microscopic	Standard	50% of microscopic	40% of microscopic	60–70% of microscopic	Standard (extensive edema)	60% of microscopic	60–70% of microscopic
6	Tumor bed hematoma	No	Small	No	Significant but without mass effect	Significant but no mass effect	Small	Nil	Small

Table 3 Evaluation of parameters in randomly selected cases of pure microscopic excision of parenchymal tumors

S No	Parameters	Case I	Case II	Case III	Case IV	Case V	Case VI	Case VII	Case VIII
1	Surgical Time	1 hrs 50 mins	1 hrs 45 mins	2 hr 30 mins	2 hr 15 mins	2 hrs	2 hrs 10 mins	1 hr 50 mins	2 hrs 25 mins
2	Illumination & Clarity	Poor at corners no visualization of undermining edges	Poor at corners no visualization of undermining edges	Poor at corners no visualization of undermining edges	Poor at corners no visualization of undermining edges	Poor at corners no visualization of undermining edges	Poor at corners no visualization of undermining edges	Poor at corners no visualization of undermining edges	Poor at corners no visualization of undermining edges
3	Magnification	Good	Good	Good	Good	Good	Good	Good	Good
4	Blood Loss	100–120 ml	100–120 ml	100–150 ml	300 ml	100 ml	150–200 ml	100–120 ml	150 ml
5	Craniotomy Size	Large	Decompressive	Standard according to tumor size	Standard according to tumor size	Standard according to tumor size	Standard according to tumor size	Standard according to tumor size	Standard according to tumor size
6	Tumor bed hematoma	No	No	Small	No	Small	No	No	No

Table 4 Comparison of pure endoscopic with pure microscopic excision in parenchymal brain tumors

S No	Parameters	Pure Microscopic	Pure Endoscopic
1.	Surgical Time	Less time consuming	Comparatively more due to learning curve initially
2.	Illumination and clarity	Poor at Blind Corners	Neatly visualized and especially undermined edges
3.	Magnification	Good with 3D vision	At par with microscope but with comparatively difficult depth perception
4.	Blood Loss	Better controlled	Sometimes difficult to control due to difficult depth perception Microscope can aid at the end of surgery in case of difficulty
5.	Craniotomy Size	Large craniotomy	Mini craniotomy size reduction by minimum of 20–30%
6.	Tumor bed hematoma	Lower incidence	Incidence may be higher due to learning curve initially.

Table 5 Summary of major studies of pure endoscopic approach for excision of parenchymal brain tumors

Author	Method	Type of endoscope	Extent of resection	Limitations
Kassam et al, 2009[1]	Neuroendoport Conduit 11.5 mm	0-degree endoscope	Total resection 38%, near total 28.6%, subtotal 33.3% multiple	Manipulations of conduit required to achieve maximal resection. Conduit cannot be used for tumors reaching pial surface
Jo et al, 2011[4]	Transparent tubular conduit 11 mm	0-degree endoscope	Gross total resection in all cases	Small lesions (3 cm) limited
Otsuki et al., 1990[3]	Tubular conduit on stereotactic frame	0-degree endoscope	Total resection in 8 lesions; biopsy or aspiration in 7	Small lesions limited by size of conduit
Plaha et al, 2014[2]	Nontubular access corridor 10 mm	30-degree endoscope	Total resection 48%, > 95% resection 70%	Needs further development of microsurgical instruments and access corridor
Present study	Nontubular access corridor 10 - 15 mm	0 and 30-degree endoscope	Near total to gross total resection	Limited number of patients & variability in types of lesions

Although it is perceived that endoscopic brain tumor resection requires a long learning curve, neurosurgeons familiar with endoscopic transphenoidal procedures would already have a hang of working in a narrow, rigid corridor within the bounds of limited space. Selected entry through cortisectomy using a safe surgical corridor under neuronavigation guidance gives an easy access to the lesions. However, the maneuvering of the endoscope and the instruments need to be more gentle because of the risk of retraction injury to the normal parenchyma around the port of entry. Although the use of rigid conduits has been claimed to be less harmful as compared with normal brain retractors,[9] we agree with the proposed argument that a constant pressure on the brain would add to ischemic insults apart from compression effect on the surrounding normal parenchyma.[2,10] According to our experience, the use of a pulsatile retractor combined with latex glove lining provides the advantage of minimizing traction effect and allowing the desired exposure needed for resection. As a beginner, it is suggested to perform the initial cases with slightly larger exposure so as to have a leeway to revert to microscopic excision if the surgeon is inconvenienced at any stage.

Comparing the illumination and visibility between microscopic versus endoscopic excision, undoubtedly the microscope gives better resolution. However, it is also true that for deeper entry corridors there is considerable loss of light leading to poor visibility and resolution in microscopic techniques in deeper areas. This problem is compounded by manipulation of instruments at the depth. Contrarily, the endoscope has the advantage of better optical resolution as the light source is nearer to the target. This enhances the visibility and adds advantage to better differentiation of the brain-tumor interface without compromising the magnification of the image.

Resection of a lesion without fresh neurological deficit remains a major challenge in all intraparenchymal lesions. The microscopic vision is limited by straight projection of light rays at the depth of the surgical field, which is different from endoscopic visualization as it provides a wide-angled panoramic view, giving better clarity at the depth. Moreover, the use of an angled endoscope can help in viewing the blind corners without much manipulation or retraction.

Our Learning Experience

Usually a single surgeon will suffice in the microscopic approach, but in the endoscopic approach there may be the need of an assistant to hold the scope and navigate. In the present series, the need for two persons was obviated by mounting the endoscope on a holder which gave an unhindered opportunity for bimanual excision by a single surgeon. However, it may take a while to switch over and get oriented from the resolution of a microscope to endoscope. As a beginner, it is always safe to begin with a bigger exposure and have a fall back option to bring in the microscope, if the situation demands. As it happened in one of our cases, it was decided to use the microscope for a brief period since there was difficulty in manipulating between the vessels of the sylvian fissure in a peri-sylvian lesion (case no 5, ►**Table 1**). Hence, there should not be any dogma to use technology interchangeably in situations on demand.

Cortisectomy length of 1.5 to 2 cm, which was initially supported by cotton patties, led to widening of the cortisectomy margins and damage to the edges. Subsequently, it was planned to insulate the edges with surgicel superimposed with glove patties with overlying cotton patties to hold them in place. Using this technique, the damage to the surrounding brain and to the extension of the cortisectomy margins was reduced to minimum, thus achieving near total resection in most of the cases avoiding unwanted cortical injury.

The resection of a lesion is facilitated by the initial use of a zero degree scope. Subsequent to reasonable debulking/excision of the tumor, the use of a 30° scope with minimal sector wise retraction of the corticectomy margins helps in achieving a total excision of the lesion, even at blind corners, through good resolution and visibility. The use of more obtuse angled scopes, in our experience, is not necessary.

Outcome and Complications

The level of resection achieved in previous studies varies from 29% to $>$ 95%.[1–4] We achieved near to gross total resection in all cases and the illumination, magnification and clarity was excellent. However, this is a small series to comment upon the exact extent of the excision of the lesions in a wide variety of cases. The blood loss in all cases was comparable to that of microscopic excision, with no postoperative tumor bed hematoma in any case. One patient with oligodendroglioma (case no 2, ►**Table 1**) situated in a strategic location in the dominant hemisphere, developed aphasia and right side weakness which improved gradually over a period of time. Although there was the issue of depth perception initially, that was overcome with subsequent experience. It is most important that the surgeon conducts a critical evaluation of clinical and radiological findings before embarking upon endoscopic excision, and also weighs the plausibility of conversion to microscopic excision to avoid any adventurous complications. The issue of falling brain and managing brisk bleeding in a vascular tumor bed may at times blind the vision through a scope. Hence a steady and slow resection of vascular lesions in a controlled way is likely to achieve the goal of satisfactory resection. As mentioned earlier, there should not be any hesitation to resort to the help of a microscope in situations of brisk bleeding. The resection of surface tumors, in our experience, turned out to be an easier option with hardly any need for retraction. This technique was demonstrated to be accurate and safe, and possibly will be expanded to remove other intraparenchymal lesions in the future.[11]

Conclusion

In spite of its innovative and beneficial aspects, neuroendoscopy, like any other diagnostic and treatment technique, has some risks. The most significant is perhaps the risk of local injury to the surrounding structures and normal brain. Other risks of neuroendoscopy include hemorrhage (with an associated difficulty in hemostasis) leading to raised intracranial

pressure. However, this procedure has high future potentials to establish itself as a minimally invasive technique, although it still remains in its nascent phase. With ongoing development of endoscopic instruments and advanced surgical techniques including multiport approaches, endoscopic surgery will be expanded beyond intraventricular and skull base lesions to intraparenchymal brain lesions. These advances will be important for the future of endoscope-assisted microsurgery. In the future, neuroendoscopy is expected to become routine in modern neurosurgical practice. Institutions should develop training programs for young neurosurgeons.[12]

Conflict of Interests

The authors have no conflict of interests to declare.

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5-aminolevulinic Acid and Surgical Margin Analysis in Calvarial Metastasis with Pericranium or Dural Extension: Technical Note

Ácido 5-aminolevulínico e análise da margem cirúrgica nas metástases da calvária com extensão de pericrânio ou dural: Nota Técnica

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Arq Bras Neurocir 2020;39(3):207–212.

Abstract

Metastasis to the calvarium with direct pericranium or dural infiltration may be treated with radical surgical removal in selected cases. We describe microsurgical resection of calvarial metastases with fluorescence-guided technique using 5-aminolevulinic acid (5-ALA) in two female patients with breast cancer. Fluorescence findings were positive in both cases. Margins in the scalp and dural layer were 5-ALA negative at the end of surgical removal. Intraoperative pathology was performed in all cases to confirm if oncological limits were free of disease. One case was 5-ALA positive in the outer layer of the dura-mater and another in the pericranium. At the end of the removal in both cases, the surgical margins were 5-ALA fluorescence-free. Intraoperative pathology confirmed oncological limits of the resection. 5-aminolevulinic acid fluorescence-guided surgery for calvarial metastases with pericranium and/or dural extension seems to be a safe and reliable method to aid the surgical margins for complete removal, possibly delaying or avoiding adjuvant irradiation for progression control.

Keywords
- 5-aminolevulinic acid
- calvarial metastases
- fluorescence surgery
- metastases
- skull metastases
- surgical margins

Resumo

Metástases da calvária com infiltração dural ou do pericrânio podem ser tratadas com remoção cirúrgica radical em casos selecionados. Descrevemos a ressecção microcirúrgica de metástases da calvária guiada por fluorescência usando ácido 5-aminolevulínico (5-ALA) em duas pacientes do sexo feminino com câncer de mama. Os achados da fluorescência foram positivos em ambos os casos. As margens nas camadas do couro cabeludo e dural foram negativas para 5-ALA ao final da remoção cirurgica. Patologia

received
January 3, 2020
accepted
March 24, 2020

DOI https://doi.org/10.1055/s-0040-1710312.
ISSN 0103-5355.

Palavras-chave
- ácido 5-aminolevulinico
- metástases da calvária
- cirurgia por fluorescência
- metástases
- metástases cranianas
- margens cirúrgicas

intraoperatória foi realizada em ambos os casos para confirmar os limites oncológicos. Um caso foi positivo para 5-ALA na camada externa da dura-máter e outra no pericrânio. No final da remoção, nos dois casos, as margens cirúrgicas foram 5-ALA negativas. A patologia intraoperatória confirmou as margens cirúrgicas livres. Cirurgia guiada por fluorescência com ácido 5-ALA para metástases da calvária com extensão para pericrânio e / ou dural parece ser um método seguro e confiável para auxiliar as margens cirúrgicas na remoção completa, possivelmente evitando ou retardando a irradiação adjuvante no controle da progressão.

Introduction

Skull metastases are a common condition in patients with disseminated bone metastatic disease. It may disseminate through blood, lymphatic transport or retrograde transport through the midline venous system.[1] Metastases to the calvarium are the commonest cranial tumors in adults and have less impact in the cancer evolution than intraparenchymal metastatic lesions.[2] They are often asymptomatic.

Early diagnosis of calvarial metastases is crucial for treatment success. The clinical presentation can be local pain or a palpable mass under the scalp. The disease was frequently underdiagnosed, often described in autopsies until the advances in imaging techniques increased the identification of previously asymptomatic lesions.[2,3]

Dural infiltration due to direct extension from calvarial metastasis is commonly observed, especially in patients with bone disease, and may account for $>$ 60% of pachymeningeal metastasis cases. The disease may also extent to the scalp, the subdural space and the brain parenchyma in $\sim$ 34% of cases in some series.[4] Proximity to dural sinuses, cranial nerves or eloquent cortex can cause severe neurological impairment, compromising treatment efficacy and survival prognosis.[5,6]

In patients with controlled systemic disease and Karnofsky performance status (KPS) $\geq$ 70%, surgical management can be a safe treatment modality aiming total removal with oncological margins,[4,6] possibly avoiding the necessity of local adjuvant irradiation.

5-aminolevulinic acid (5-ALA) fluorescence-guided surgery was first introduced in glioblastoma[7] and has been a reliable standard for complete tumor removal and better progression free survival. The 5-ALA accumulated in the malignant lesion is converted to protoporphyrin IX (PpIX) and, under a blue filter illumination, shows a selective fluorescence, differing normal from infiltrated tissue with high sensitivity and specificity.[8]

About 40 to 62% of brain metastasis[9–11] and 77 to 96% of intracranial meningiomas[12] can also exhibit 5-ALA fluorescence, so its use may improve the extent of surgical resection. In these cases, there is a special focus in avoiding missed residual tumors, which can compromise local-recurrence rate and progression free survival. Although the benefits of 5-ALA fluorescence in meningioma surgery for the identification and removal of bone infiltration or hyperostosis has been described,[13] there is few current data about its application for calvarial metastases with or without contiguous tissues (scalp and dura-mater) involvement.[3]

The present article aims to analyze the use of 5-ALA guided surgery in calvarial metastases with dural infiltration correlated with intraoperative pathology to improve the oncological safe margins to possibly reduce the risk of recurrence or the necessity of adjunct local treatment.

Materials and Methods

Between November 2015 and August 2019, 200 consecutive patients underwent 5-ALA fluorescence surgery in the Instituto de Neurologia de Curitiba, Curitiba, PR, Brazil. There were 25 patients with brain metastases and 2 patients with solitary metastatic tumor located in the calvarium without intraparenchymal disease. We retrospectively reviewed these two 5-ALA positive cases eligible for the study. Both cases were studied with magnetic resonance imaging (MRI) with aid of computed tomography (CT) scans to evaluate the extent of bone disease.

5-aminolevulinic acid is provided by Carbolution Chemicals (St. Ingbert, Germany). All of the patients signed an informed consent form, and the study was approved by the Institutional Ethical Review Board. The 5-ALA solution was orally administered at a dose of 20 mg/kg 3 hours prior to the surgery. Patients care (anesthesia induction, positioning, etc.) were all performed as routine, including image-guidance with neuronavigation, although both cases showed a palpable mass below the scalp.

The Zeiss OPMI PENTERO 800 (Carl Zeiss, Oberkochen, Germany) with a special blue-light filter was used to identify 5-ALA-induced PpIX fluorescence and was graduated in strong, poor or negative. A curvilinear C-shape incision in the scalp was made around the mass, respecting the arterial pedicle, preserving the pericranium and incised circumferentially with a margin around the lesion. A single burr hole was performed, followed by the craniotomy. The specimen was removed with the galea and the inner table of the bone flap was inspected with the surgical microscope, first with the white and then with the blue light (►**Fig. 1**). The outer layer of the dura-mater in direct contact with the lesion was

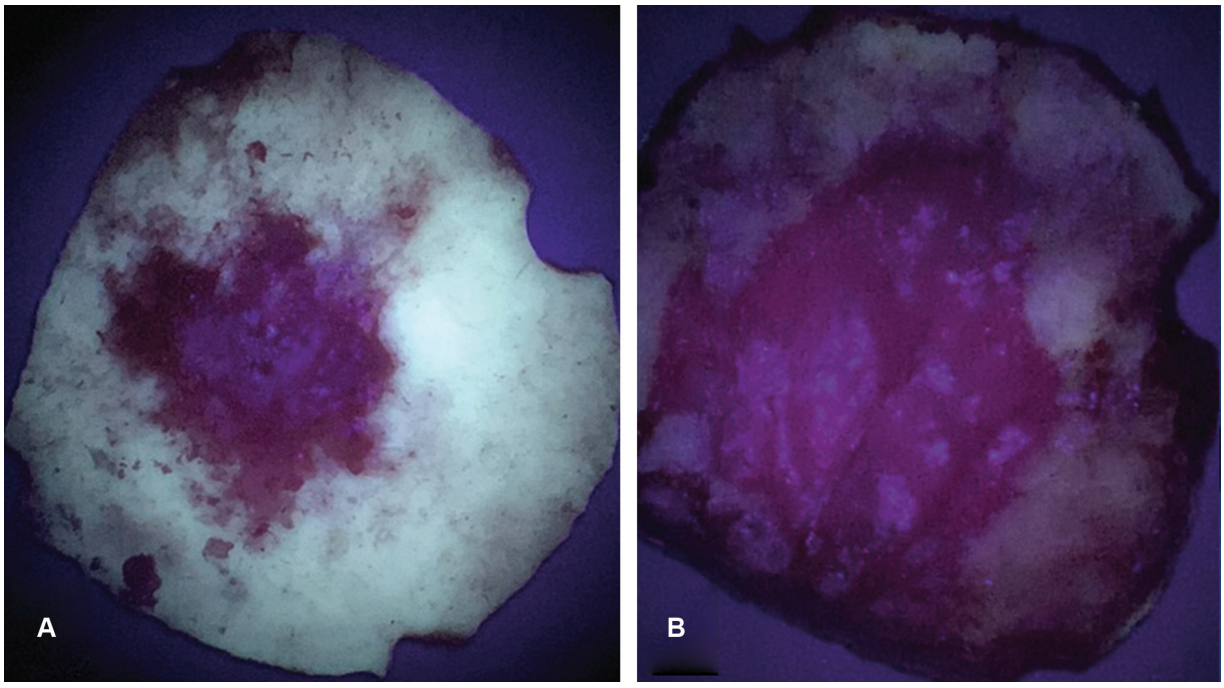

Fig. 1 Outer (a) and inner (b) table of calvarium inspected under blue light filter, showing lesion with a 5-ALA strong positiveness.

also inspected for 5-ALA graduation and was removed, avoiding entering the subdural space (►**Fig. 2**). Frozen section procedure was performed in the pericranium and dural margins to determine if tumoral tissue was present (►**Fig. 3**). After the resection, cranioplasty was performed and the skin was closed primarily. The entire specimen was inspected again under the microscope, to visualize the infiltration to the pericranium and the dura-mater.

Both patients studied retrospectively had diagnosis of solitaire metastatic calvarial lesion from breast cancer, age $<$ 70 years old, KPS of 90-100% and controlled systemic disease with first line treatment. ►**Table 1** shows the characteristics and findings of each case.

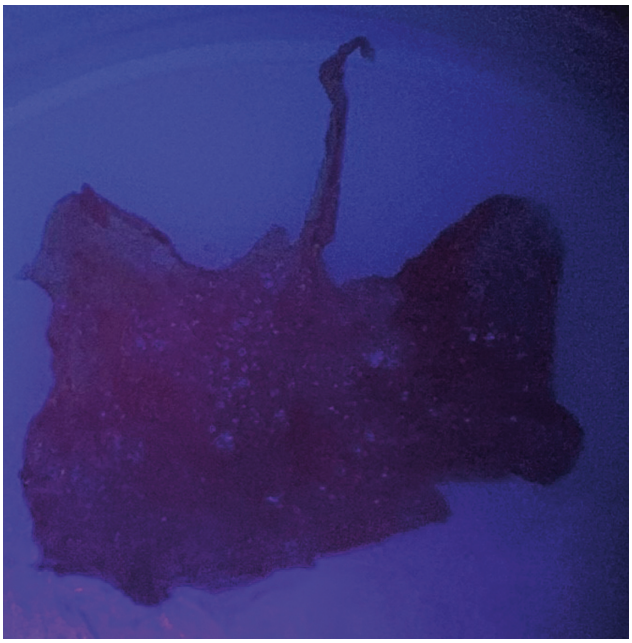

Fig. 2 Outer layer of dura-mater in direct contact with the mass inspected with the blue light filter, showing 5-ALA poor positiveness (a).

Results

Pericranium Findings

In one case, the inner layer, in direct contact with the bone mass, was 5-ALA strong positive. The intraoperative pathology confirmed tumor infiltration. The other case was 5-ALA negative, also corroborated with the histopathological analysis.

Bone Flap Findings

Both specimens showed an intraosseous mass, removed *en bloc*. The outer and the inner table were 5-ALA strong in the tumor and the margins were visible even with white microscope light.

Dural Findings

In one case, the outer dural layer was 5-ALA poor positive. It was removed preserving the inner layer to avoid the subdural space. In the other case, the 5-ALA finding was negative. Both diagnoses were corroborated with intraoperative pathology.

There were no postoperative complications. Both patients had MRI scan 24 hours, 1 month, 3 month and 6 months after the surgery, without signs of local disease progression or KPS worsening until the end of the writing of the present article. No local adjuvant treatment was realized.

Discussion

Bone metastasis is a frequent complication of cancer and is especially higher among patients with more advanced disease, but the exact incidence of calvarial metastases remains

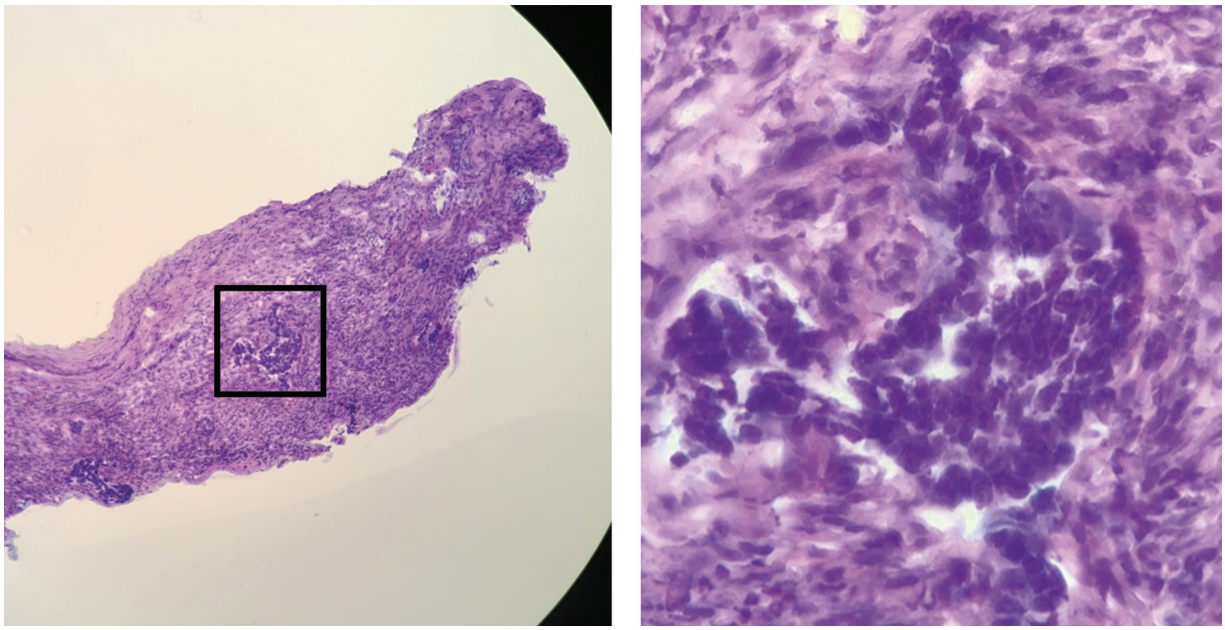

Fig. 3 Intraoperative pathology findings in 5-ALA positive outer dural margins, confirming tumor infiltration.

unknown. Dissemination may occur due to direct extension or by hematogenic pathway, with cancer cells adhering to the endosteal surface and invading the bone marrow.[2,3,6]

Breast, lung and prostate adenocarcinoma are the commonest primary lesions to metastasize to the skull due to a distinct bone tropism, but various other histologies have been reported.[14,15] Mitsuya et al reported 55% of skull metastases from breast cancer in a series of 175 patients, with a preponderance female versus male of 7:3 patients.[16] Once dissemination to the skull is diagnosed, the expected median survival rate is 20 months. In a retrospective study by Stark et al,[2] there was an average period of 4 years between the initial primary cancer diagnosis and the detection of intraosseous metastasis.

While cranial nerves impairment is the commonest clinical presentation of skull base cancer, patients with calvarial circumscribed intraosseous metastasis can be completely asymptomatic. In cases of circumscribed invasive dural extension, $\sim$ 18% of the patients can present pain and brain swelling. Cranial metastases overlying or invading the dural venous sinuses can turn into symptomatic and predict worst outcomes. Frontal and parietal bones are the most common sites of calvarial metastases, often presenting a well-circumscribed asymptomatic mass under the scalp.[4,5,16]

In the diagnostic evaluation, the following aspects are particularly useful to be considered in the diagnosis: localization of the lesion in the calvary or in the skull base; local, multiple or diffuse bone distribution; and intraosseous invasion to the scalp or dura-mater. Computed tomography scanning may help the identification of calvarial metastases as lytic or sclerotic. Magnetic resonance imaging findings present hypointense signal in T1-weighted noncontrast sequence and often homogeneous gadolinium enhancement. Fat subtraction is important to determine tumor margins.[4,6]

Management of calvarial metastases may depend on symptomatology, patient KPS, relationship with dural sinuses and eloquent cortex, histopathology, extent of spread and scalp infiltration.[3,5,6,16] Surgical treatment can be a safe palliative option for symptomatic patients, even when indicated after failed attempt with irradiation and/or chemotherapy.

In patients with a solitary metastatic mass, aggressive local treatment can sometimes result in prolonged survival.[3,4]

Table 1 5-aminolevulinic acid fluorescence and intraoperative pathology findings

Patient	Age (years old)/ Gender	Pathology	Tumor fluorescence	Pericranium fluorescence	Dura-mater fluorescence	Intraoperative pathology
1	33F	HER-2 negative, ER and PR positive	Strong	Negative	Outer layer: poor; Internal layer: negative	Pericranium negative; Bone tumor and outer dural layer positive; internal dural layer negative
2	40F	HER-2 negative, ER positive PR negative	Strong	Strong	Outer layer: negative; Internal layer: negative	Pericranium positive; Bone tumor positive; Dura-mater negative

Abbreviations: Her-2, human epidermal growth receptor 2; ER, estrogen receptor; PR, progesterone receptor.

Although surgical resection may quickly relieve symptoms, it can be challenging and increase surgery morbidity, especially in patients with delayed diagnosis or uncontrolled systemic disease. The pericranium can also be directly infiltrated, and, in these cases, *en bloc* removal can be performed with scalp resection with the bone mass.[6] Direct dural infiltration is related to higher local recurrence rates in cases of underlying sinus involvement due to the difficulties for complete resection.[5] These cases also predict a more aggressive disease with worst neurological impairment and shorter survival. Irradiation is a treatment option alone, when surgery is contraindicated, or adjuvant to control tumor growth.

5-aminolevulinic acid is the metabolic precursor of hemoglobin that induces the synthesis of protoporphyrin IX (PpIX), a fluorescent compound in appropriately violet-blue filtered light. The PpIX stored in malignant lesions aids the differentiation between normal brain and tumor tissue with high sensitivity and specificity. 5-aminolevulinic acid-guided fluorescence was first introduced in malignant glioma surgery as an adjuvant tool for optimizing the removal of these tumors,[7,16,17] leading to increased progression free survival.[7,8,17] Over the years, its vibrant application has been introduced and studied in other intracranial neoplasms, such as brain[9–11] and spinal cord metastases[18–20] and meningiomas.[12,13,21]

There is a 5-ALA positive fluorescence ranging from 77 to 96% of the intracranial meningiomas. The graduation in poor or strong may vary in the literature, but in an intratumoral homogenous fluorescence, it is observed in $>75\%$ of the cases. There is no apparent correlation between histopathological findings and 5-ALA intraoperative fluorescence.[13] The method can detect bone infiltration with 100% specificity and 89% sensitivity,[21] confirming suspected invasion on preoperative evaluation.[12]

More than 60% of intracranial metastases demonstrate a 5-ALA positive fluorescence, but it may range between 28 and 81.8% in large series.[10] Adjacent brain tissue may be 5-ALA positive without necessarily containing metastatic infiltration.[8] Furthermore, a heterogeneous positivity may be expected and even the previous administration of neoadjuvant chemotherapy can be a potential bias for fluorescence response.[9,10]

PpIV positive fluorescence is also related with a more benign behavior of brain metastases, while a negative fluorescence can be a more aggressive tumor with worse prognosis.[9] Yang et al[22] described the use of ALA for imaging and photodynamic targeting human epidermal growth receptor 2 (HER-2) positive tumors. Human epidermal growth receptor 2 is a driver oncogene with special importance in breast cancer classification, with sensitive ALA-mediated photodynamic therapy.

Both cases presented in our article were HER-2 positive and 5-ALA strong positive. We are routinely using 5-ALA fluorescence for intracranial gliomas and metastases since 2015,[18,19] and a primary diagnosis of breast cancer HER-2-positive may support this method of intraoperative guidance. There is not any study about 5-ALA fluorescence surgery aiming complete removal of calvarial metastasis. The management of these lesions can be controversial in the postoperative due to the decision about irradiation. Whole-brain radiotherapy is often elected in cases of diffuse calvarial involvement, while solitaire/oligometastatic disease supports local treatment.[3,4,6] Modifications in the chemotherapy may also be needed at the time of diagnosis. With the free oncological margins in both cases, local adjuvant irradiation was not indicated. Patients continue to perform periodic MRI for evaluation.

Conclusion

5-aminolevulinic acid fluorescence surgery for calvarial metastases may provide a simple and reliable guide to determine the oncological limits with the pericranium and underlying dura-mater.

Ethical Approval and Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (*CEP - Comitê de Ética em Pesquisa – Instituto de Neurologia de Curitiba*) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from both individual participants included in the present study.

Conflict of Interests

The authors have no conflict of interests to declare.

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Prenatal Diagnosis of Vein of Galen Aneurysmal Malformation Allows Early Transumbilical Endovascular Treatment

Diagnóstico pré-natal de malformação aneurismática da veia de Galeno possibilita tratamento endovascular precoce por acesso transumbilical

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Arq Bras Neurocir 2020;39(3):213–216.

Abstract

Neonates with vein of Galen aneurysmal malformation (VGAM) presenting with severe cardiac failure and pulmonary hypertension represent a challenge for endovascular therapy. When early treatment is required, the small femoral arteries in this population are usually difficult to cannulate. Alternatively, the umbilical vessels offer a natural pathway to reach the lesion. Therefore, prenatal diagnosis of VGAM allows for delivery planning, perinatal management, and embolization through umbilical approach, thus leading to better outcomes.

Keywords

- vein of Galen malformations
- arteriovenous malformations
- prenatal diagnosis
- umbilical arteries
- newborn infant
- endovascular procedures.

Resumo

Neonatos com malformação aneurismática da veia de Galeno (MAVG) apresentando insuficiência cardíaca severa e hipertensão pulmonar representam um desafio terapêutico. Quando o tratamento precoce é necessário, o pequeno diâmetro dos vasos femorais nessa faixa etária dificulta a punção e canulação. Como alternativa, os vasos umbilicais oferecem um acesso natural para alcançar a lesão. Assim, o diagnóstico pré-natal da MAVG proporciona planejamento adequado do parto em local com a estrutura necessária e cateterização dos vasos umbilicais ao nascer, o que permite tratamento precoce e melhor evolução desses pacientes.

Palavras-chave

- malformações da veia de Galeno
- malformações-arteriovenosas
- diagnóstico pré-natal
- cordão umbilical
- recém-nascido
- embolização terapêutica

received
February 28, 2020
accepted
March 24, 2020

DOI https://doi.org/10.1055/s-0040-1710311.
ISSN 0103-5355.

Introduction

Neonates with vein of Galen aneurysmal malformation (VGAM) presenting with early congestive heart failure (CHF) have a relatively poor prognosis.[1] The femoral arteries in this population are small and difficult to cannulate; thus, the umbilical vessels are a natural pathway to approach the brain vessels. Nevertheless, the umbilical artery catheterization is best performed right after delivery; therefore, prenatal diagnosis becomes important to plan early treatment and improve outcomes.

Methods and Results

A 29-year-old healthy woman at 31 weeks of gestation underwent a routine fetal ultrasound scan. It identified a 24 × 15-mm midline, anechoic structure above the thalamus. Color doppler revealed a VGAM draining into an enlarged falcine sinus. Fetal echocardiography showed mild cardiomegaly, with enlarged right chambers due to high output. A prenatal magnetic resonance imaging (MRI) during apnea demonstrated a choroidal type of VGAM, with dilated lateral ventricles (►**Fig. 1**). The findings were discussed with the parents, a neonatologist, a pediatric cardiologist, and a neuroradiologist.

At 40 weeks of gestation, a planned Caesarean section was performed, after previous reservation of the hemodynamic suite. The newborn was a 3,250-g male, with normal head circumference; on physical examination, there were a 2/6 systolic murmur and a 3/6 cranial bruit. The Bicêtre neonatal evaluation (BNE) score[1] was 11, while the Apgar scores were 1 at 1 minute, 5 on the 5th minute, and 8 at 10 minutes, after intubation and ventilatory support with oxygen. The neonate developed CHF soon after delivery, which was treated with fentanyl, furosemide, and milrinone. The umbilical artery and vein were cannulated, and he was called for intervention with 23 hours of life. An Echelon 10 microcatheter (Medtronic, Irvine, CA, USA) over a SilverSpeed 10 guidewire (Medtronic) was directly inserted through the umbilical artery cannula, and a digital subtraction angiography (DSA) showed a large VGAM, with several afferences and high-flow arteriovenous fistulas (►**Fig. 2**). Embolization was performed using Axium 3D or Helix mechanical detachable coils (Medtronic) followed by injection of Onyx ethylene-vinyl-alcohol-copolymer (EVOH) (Medtronic) until complete obliteration; the three main afferences were completely occluded, with two being posterior choroidal arteries and one pericallosal. The procedure was interrupted due to contrast volume but reduction of bruit was achieved. In the postoperative period, the infant evolved with tachycardia, treated with esmolol, and pneumonia, treated with oxacillin and amykacin. The cardiopulmonary function progressively worsened, failed to respond to medical treatment using digoxin and sildenafil, and the patient died of intractable CHF on the 20th day of life.

Discussion

The VGAM occurs during the 6th to the 11th weeks of gestation, due to the persistence of the median prosencephalic vein (of Markowski).[2,3] That is the precursor of the cerebral magna vein, which remains connected to the choroidal vessels.[2,3] Disease expression may vary from several fistulas, inhibiting cardiac function, to complete asymptomatic patients, incidentally diagnosed at adult age.[4]

Prenatal diagnosis of VGAM is commonly made during the third trimester, through fetal ultrasound.[2] Doppler studies can further help to understand the hemodynamics of the lesion, while echocardiography is useful to identify cardiac abnormalities.[2] Fetal MRI in apnea shows large flow void in

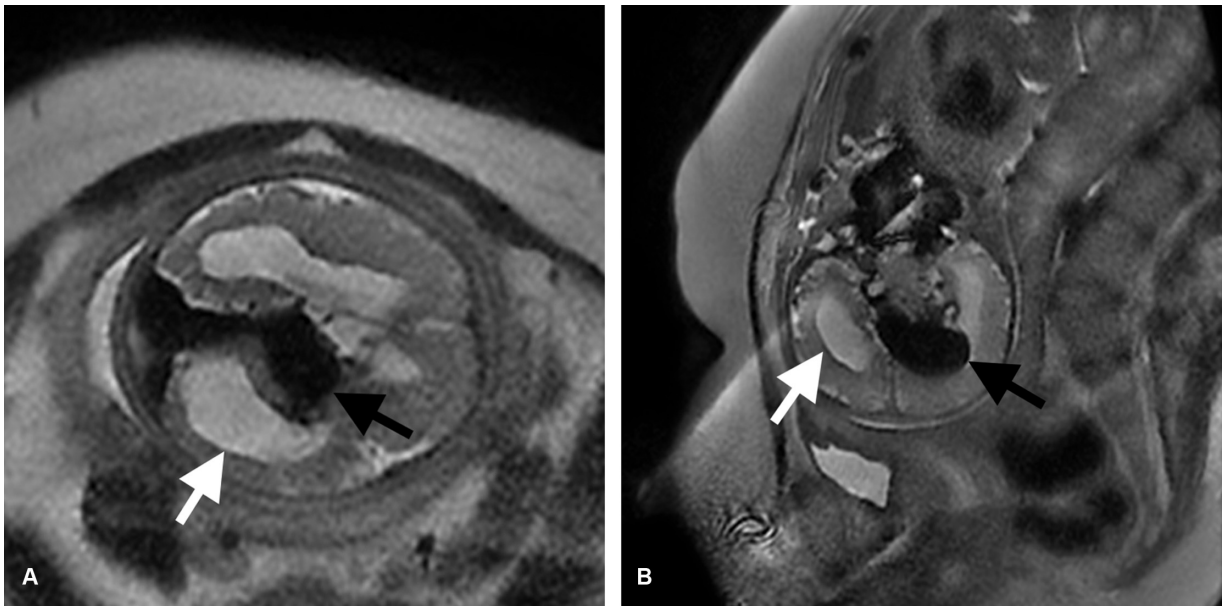

Fig. 1 (**a**) Axial and (**b**) coronal intrauterine T2-weighted magnetic resonance imaging in apnea shows median flow void (black arrows) and lateral ventricles dilatation (white arrows) due to vein of Galen aneurysmal malformation.

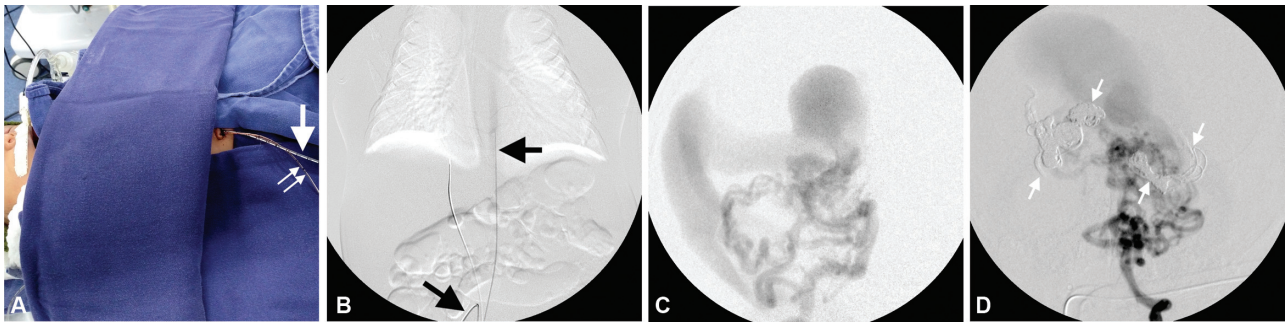

Fig. 2 (**a**) Cannulation of umbilical artery (arrow) and vein (double arrow); the umbilical artery provides easy access to the aorta (arrows) (**b**); vertebral angiogram evidences choroidal type of vein of Galen aneurysmal malformation fed by multiple afferences (**c**); embolization using coils and glue (arrows) occludes the main shunts (**d**).

the central region, enlarged falcine sinus and drainage to transverse sinuses. It also helps to identify hydrocephalus, as shown in our case. The diagnosis during the gestation allows planning of delivery in tertiary hospitals, with high-risk neonatal unit, neurosurgery, and neuroradiology support, favoring early intervention whenever necessary.

Treatment may avoid death and complications, such as hydrocephalus, CHF, or dural arteriovenous fistula. In a meta-analysis of 754 patients with VGAM, 76.7% of untreated patients died; and while microsurgery found an 84.6% mortality rate, endovascular therapy achieved favorable outcome in 72% of the patients, with a mortality rate of 15%.[5] Therefore, embolization is the treatment of choice.[6] It should be attempted as soon as possible for neonates with VGAM presenting CHF and pulmonary hypertension,[7] and a BNE score between 8 and 12 out of 21 requires urgent therapy (►**Table 1**).[1]

The transfemoral approach is commonly used for transarterial embolization; however, catheterization of the femoral artery can be difficult in neonates due to small vessels diameter.[8] Furthermore, it may cause thromboembolic complications or arterial occlusion, and maintenance of a vascular sheath several days for repeated interventional procedures is associated to leg ischemia.[8] Otherwise, the transumbilical arterial approach is technically easier and safer than other methods.[8] The umbilical cord has three vessels: one larger oval umbilical vein, with thin wall, running to the left portal vein; and two smaller, round umbilical arteries, with thick wall, originated from the internal iliac arteries and enabling direct access to aorta.[8] The umbilical arteries suffer prompt constriction after delivery; thus, its cannulation should be conducted immediately after birth; and although it can be performed later, it becomes almost impossible after the 4th postnatal day.[8] Transvenous embolization can be done through direct sinus puncture, jugular, femoral, or umbilical approaches.[8] Because the abrupt total occlusion of the venous side with coils was associated with hemorrhagic complication,[1] we attempted to occlude the high-flow arteriovenous shunts in a graded fashion. Arterial afferences can be obliterated using n-butyl cyanoacrylate (NBCA), EVOH, coils, or a combination of these.[6] Complications related to embolization of the VGAM include

Table 1 The Bicêtre neonatal evaluation score (0–21 points) indicates the management

Points	Cardiac function	Cerebral function	Respiratory function	Hepatic function	Renal function
5	Normal	Normal	Normal	–	–
4	Overload, no medical treatment	Subclinical, isolated EEG abnormalities	Tachypnea, finishes bottle	–	–
3	Failure; stable with medical treatment	Nonconvulsive intermittent neurological signs	Tachypnea, does not finish bottle	No hepatomegaly, normal hepatic function	Normal
2	Failure; not stable with medical treatment	Isolated convulsion	Assisted ventilation, normal saturation $FiO_2 < 25\%$	Hepatomegaly, normal hepatic function	Transient anuria
1	Ventilation necessary	Seizures	Assisted ventilation, normal saturation $FiO_2 > 25\%$	Moderate or transient hepatic insufficiency	Unstable diuresis with treatment
0	Resistant to medical therapy	Permanent neurological signs	Assisted ventilation, desaturation	Abnormal coagulation, elevated enzymes	Anuria

Abbreviations: EEG, electroencephalogram; FiO2, fraction of inspired oxygen.
Patient presenting with < 8 points: not to treat; 8–12 points: emergency endovascular intervention; > 12 points: medical management until the child is at least 5 months of age.[1]

neurological disability, death, hemorrhage, and sinus thrombosis.[1,3] Despite the unfavorable outcome of the described case, in a retrospective review, major brain lesions during prenatal evaluation were associated with poor outcome in all cases.[2]

Conclusion

Prenatal diagnosis of VGAM is important to allow for delivery planning and transumbilical cannulation. This offers a chance for early treatment and improved outcomes.

Conflict of Interests

The authors declare that there are no conflict of interests.

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A Diffuse Leptomeningeal Glioneural Tumor Case Producing Hydrocephalus and Polyradiculopathy

Relato de um caso de tumor glioneuronal leptomeníngeo difuso produzindo hidrocefalia e polirradiculopatia

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Arq Bras Neurocir 2020;39(3):217–221.

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Abstract

The present report describes the case of a male 17-year-old patient who progressively developed a hydrocephalus and polyradiculopathy due to involvement of central nervous system (CNS) by a diffuse leptomeningeal glioneuronal tumor (DLGNT). The tumor had partial remission in response to the treatment with radiotherapy plus procarbazine, lomustine, and vincristine (PCV) chemotherapy, and the patient had improvement in function and pain levels. The current knowledge about DLGNT, including its clinical manifestations, imaging findings, histological characteristics, and treatment are revised and discussed in the present paper.

Keywords
- leptomeningeal glioneuronal tumor
- polyradiculopathy
- hydrocephalus
- oligodendroglial-like leptomeningeal tumor of childhood
- PCV chemotherapy

Resumo

No presente relato de caso descrevemos um paciente do sexo masculino, com 17 anos de idade, que desenvolveu progressivamente hidrocefalia e polirradiculopatia, devido ao envolvimento do sistema nervoso central por um tumor glioneuronal leptomeníngeo difuso (TGNLD). Nesse caso peculiar obtivemos remissão parcial da neoplasia, melhora funcional e controle álgico do paciente após o tratamento com radioterapia e quimioterapia adjuvante com procarbazina, lomustina e vincristina (PCV). O conhecimento atual sobre TGNLD, incluindo suas manifestações clínicas, achados de imagem, características histológicas e tratamento são revisados e discutidos neste artigo.

Palavras-chave
- tumor glioneural leptomeníngeo difuso
- polirradiculopatia
- hidrocefalia
- oligodendroglial-like
- PCV

Introduction

The diffuse leptomeningeal glioneuronal tumor (DLGNT) is a rare primary central nervous system (CNS) neoplasm, which was recognized as a distinctive entity in 2016 by the World Health Organization (WHO) classification of CNS tumors.[1] Usually, its diagnosis, based on clinical-epidemiological aspects, is difficult and challenging because it has no pathognomonic signs, and its clinical presentation and imaging findings may vary widely. Despite this, in most descriptions,

received
February 17, 2020
accepted
May 12, 2020

DOI https://doi.org/10.1055/s-0040-1713918.
ISSN 0103-5355.

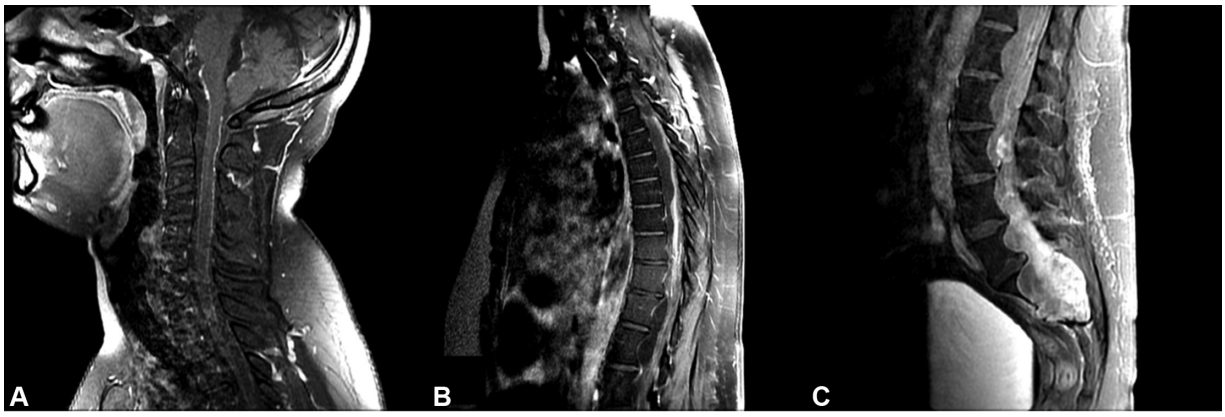

Fig. 1 T1-weighted magnetic resonance imaging with gadolinium. Diffuse leptomeningeal enhancement to the gadolinium injection in the (**A**) basal cisterns, 4th ventricle, and cervical spinal cord, (**B**) thoracic spinal cord, and (**C**) lumbar spinal cord, and cauda equina.

it was more prevalent at a young age, showed slow-growing rate, and imaging exams revealed communicating hydrocephalus with intense leptomeningeal enhancement on T1-weigheted images, more frequently in the basal cisterns. Nevertheless, its genetic and epigenetic changes and its exact biological behavior are not yet fully known.[2,3] We described a late diagnosis of DLGNT in a patient that progressively developed hydrocephalus and polyradiculopathy. Clinical manifestations, imaging and histological characteristics are reported and discussed in the present paper to add evidence and advance current knowledge about the DLGNT.

Case Report

A 17-year-old male patient sought medical attention at a hospital a few years ago complaining of low back pain, motor incoordination, dizziness, gait disturbance, urinary incontinence, blurred vision, headache, and episodic epileptic seizures, which all had gotten worse progressively in the last months. On his brain computed tomography (CT), a hydrocephalus was diagnosed, which required a ventriculoperitoneal shunt. Due to relief of most of the symptoms, the patient abandoned the follow-up and investigation workup, though the etiology of the hydrocephalus was not accomplished. The patient sought medical attention in our service due to back pain, weakness, and muscle atrophy in the lower limbs, urinary and fecal incontinence, paresthesia and hypoesthesia in different regions of the body. The brain and spine magnetic resonance imaging (MRI) showed a diffuse contrast enhancement on T1-weighted images in addition to multiple infiltrative nodular and cystic lesions in the cranial and spinal subarachnoid space, especially in the basal cisterns, brain ventricles, and in the cauda equina (►**Fig. 1**, **2**). A biopsy of a lesion in the cauda equina was performed, and the diagnosis of diffuse leptomeningeal glioneuronal tumor was confirmed (►**Figs. 3**, ►**Table 1**). At this time, a palliative treatment was proposed, and, a month later, he started to receive three-dimensional conformal radiotherapy to the craniospinal axis (36 Gy in 20 fractions over 4 weeks) with a boost to the sacral tumor (18 Gy in 10 fractions over 2 weeks), adding up to a total dose of 54 Gy. After that, he underwent 3 courses of conventional procarbazine, lomustine, and vincristine (PCV) chemotherapy over 14 weeks, without any complications. Despite partial response to the treatment (►**Fig. 4**), the patient had improvement in pain levels, function, and quality of life. Although he is still incontinent and unable to walk without assistance, we

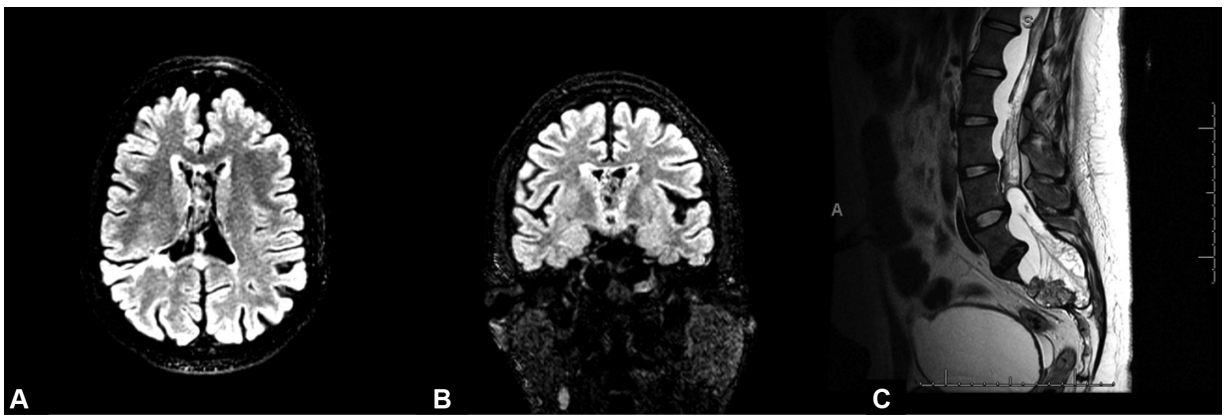

Fig. 2 T2-weighted and fluid attenuated inversion recovery magnetic resonance imaging. Hyperintense subpial nodules and cysts in the (**A**) septum pelucidum, lateral ventricles, and 3rd ventricle, (**B**) thoracic spinal cord, and (**C**) lumbar spinal cord, and cauda equina.

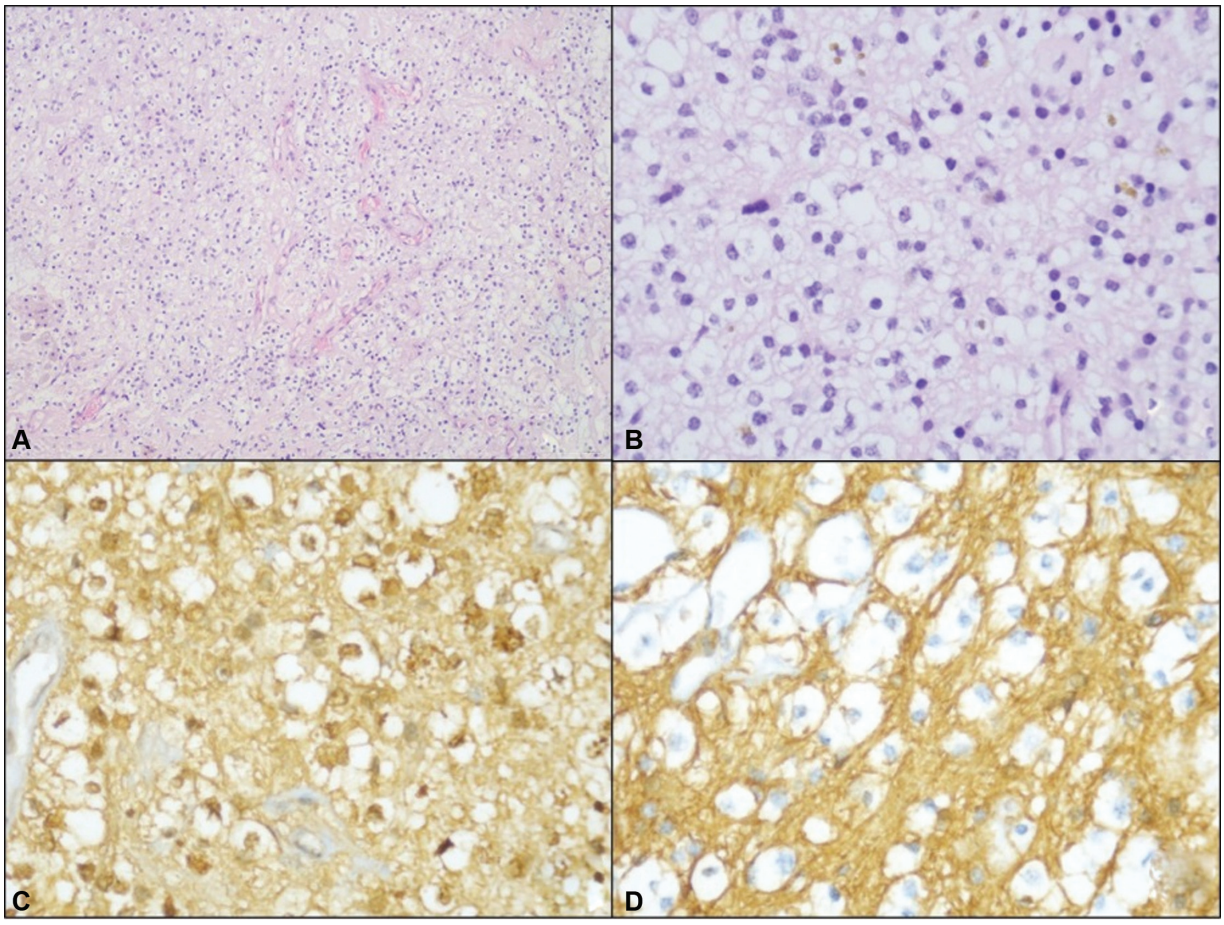

Fig. 3 Histopathological and immunohistochemical study. (**A**) low power examination reveals a diffuse leptomeningeal proliferation of tumor cells with clear cytoplasm; (**B**) at higher magnification, the nuclei are round and bland. No mitotic figures were seen; (**C, D**) tumor cells were diffusely positive for S100 and glial fibrillary acidic protein (GFAP).

Table 1 Immunohistochemistry staining results

Stain	Results	Characteristics
S100	Positive	
Neu-N	Positive	Weak
GFAP	Positive	Diffuse
Synaptophysin	Positive	
EMA	Positive	Focal
CD68	Positive	Macrophages
BRAF	Positive	Focal
Ki67	Positive	$< 5\%$
Mutant IDH1	Negative	

Abbreviations: **S100**, S100 protein; **BRAF**, BRAF mutation test; **CD68**, **GFAP**, glial fibrillary acid protein; **Ki67**, Ki-67 labeing index.

consider that his condition of total disability and full dependency (40% on KPS scale) has positively changed to a functional status, in which he is able to care for most of his needs (60% on KPS scale) and can be included in a rehabilitation program.

Discussion

The DLGNT, also known as disseminated oligodendroglial-like leptomeningeal tumor of childhood, is a primary CNS tumor characterized by diffuse leptomeningeal dissemination of neoplastic glioneuronal cells. Despite its indolent progression, it can rarely present itself as an isolated parenchymal lesion, and the morbidity and mortality rates are frequently high.[4,5] Sometimes, its behavior can be more aggressive, especially in adults or elderly people.[2] The clinical manifestations are directly related to the development of hydrocephalus and infiltration of spinal and cranial nerves.

On MRI, the DLGNT is characteristically described as thick, nodular leptomeningeal enhancement particularly around the basal cisterns, which may extend over the surface of the brain and spinal cord. Further findings are the presence of small subpial cysts or nodular T2 hyperintense lesions. Usually, it is isointense on T1-weighted images and exhibits remarkable contrast enhancement, typically located in the posterior fossa, brainstem, spinal cord, and cauda equine.[3,4,6] One of the most important characteristics of the DLGNT is that, often, there is no definitely dominant primary parenchymal mass, even though, in the descriptions of some cases,

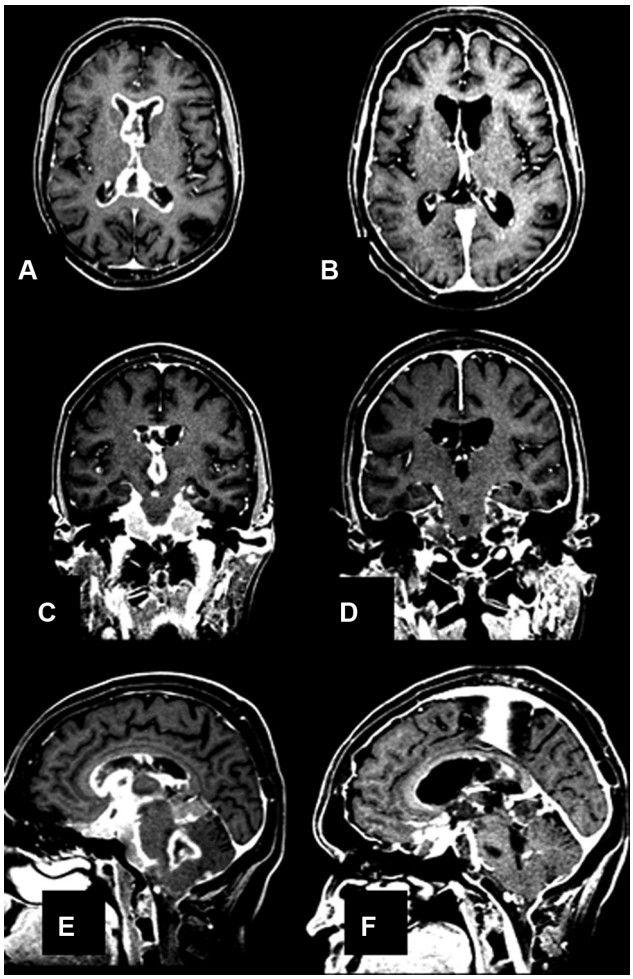

Fig. 4 T1-weighted magnetic resonance imaging with gadolinium pre and posttreatment. Partial remission of the tumor in response to radiotherapy plus procarbazine, lomustine, and vincristine (PCV) chemotherapy. The nodular and thick gadolinium enhancement observed on pretreatment T1-weighted magnetic resonance imaging (**A**, **C** and **E**) became thinner and less intense 3 months after the treatment (**B**, **D** and **F**).

intraparenchymal lesions were detected, more frequently in the spinal cords.[3,4] In the initial stages, the radiographic diagnosis might be challenging, since an idiopathic communicating hydrocephalus and an unspecific diffuse leptomeningeal contrast enhancement of the basal cisterns and spinal cord might represent several diseases. The main differential diagnoses to DLGNT are tuberculous meningitis, meningeal carcinomatosis from primary or secondary neoplasms, and fungal meningitis.[5]

The histogenesis of DLGNT is unknown, but it is postulated that they originate from multipotent cells, positive for glial and neuronal markers, which are capable of divergent differentiation.[4] In the histological aspect, these tumors have a low to moderate cellularity with a biphasic astrocytic population (positive for glial fibrillary acidic protein [GFAP]) and neurocytes (positive for synaptophysin). The monomorphic aspect is predominant and consists of oligodendroglial-like cells with clear cytoplasm and rounded nuclei. The DLGNT usually has low mitotic rate. The presence of anaplasia or Ki67 $>$ 4% might predict a worse prognosis. The main immunohistochemical findings are: high reactivity to oligodendrocyte transcription factor 2 (OLG-2), microtubule-associated protein 2 (MAP-2) and S-100. Typically, the NeuN, EMA, and mutant IDH1 (R132H) are negative.[4]

All DLGNT carry chromosomal arm 1p deletion, as others genetic and epigenetics aberrations that are believed to activate the mitogen-activated protein kinase/ extracellular-signal-regulated kinase (MAPK/ERK) pathway, mostly because of the KIAA1549: BRAF fusion. Such changes have been proposed as tumors biomarkers and therapeutic targets, but there is currently a lack of evidence that mitogen-activated protein kinase (MEK) inhibitors may improve the clinical outcome of patients with DLGNT.[3]

Diffuse leptomeningeal glioneuronal tumor can be subdivided in two molecular classes, based on DNA methylation profiling, namely, DLGNT-MC-1 and DLGNT-MC-2.[3] It is supposed that codeletion 1p19q is much more frequent in the DLGNT-MC-1 group, which is associated to a lower age of diagnosis (median 5 *vs* 14 years) and a less aggressive clinical course. Furthermore, all patients in the DLGNT-MC-2 group display a gain of chromosome 1p arm.

There is no guideline to treat DLGNT, and the current approaches are based on low-grade glioma's treatment of children and young adults. It is not clear if different combinations of surgery, radiotherapy, and chemotherapy can improve the clinical outcomes and survival; therefore, a conservative or palliative approach must not be ruled out. Promising outcomes have been described with temozolomide, bevacizumab, and vincristine associated with carboplatin, and the E-HIT 2000–4 and SIOP-LGG 2004 chemotherapy protocols.[4,5]

In conclusion, our case report suggests that radiotherapy plus PCV chemotherapy can have positive effects on DLGNT treatment and should be considered as a good approach to treat this particular tumor.

Compliance with Ethical Standards

The present case report has not been previously presented or published in part or in full.

The present case report has been written in accordance with Committee on Publication Ethics (COPE) guidelines and complies with the Case Report (CARE) guidelines.

Patient Consent

The patient has agreed with the present case report article and has consented to its submission to the journal.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Intra-Axial Metastatic Angiosarcoma of the Central Nervous System Associated with Anemia, Pulmonary Tuberculosis and Short Survival

Angiossarcoma metastático intra-axial do sistema nervoso central associado a anemia, tuberculose pulmonar e sobrevivência curta

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Arq Bras Neurocir 2020;39(3):222–227.

Abstract

Introduction Angiosarcoma (AG) is a malignant mesenchymal neoplasm that predominantly affects the soft tissues and, to variable degrees, expresses the morphological and functional characteristics of the endothelium. The incidence of sarcomas of the central nervous system (CNS) is low (0.5% to 2.7%), and AGs involving the brain are even rarer.

Case Description A 45-year-old male patient presented with complaints of headache, nausea, and vomiting. An examination showed bilateral papilledema and a right lung pleurotomy. The patient's previous history included drug addiction, pulmonary tuberculosis, lung abscess, pleural empyema, and pulmonary artery embolization for severe hemoptysis. Computed tomography/magnetic resonance imaging scans revealed a large intra-axial lesion extending into the right parietal and temporal lobes, with hemorrhagic zones. The patient underwent surgical resection of the lesion. Microscopy showed a poorly-differentiated, high-grade malignant tumor composed of plump/epithelioid cells forming small vascular spaces and solid nests, compatible with AG.In the postoperative period, the patient developed recurrent hemoptysis. A biopsy of the tissues adjacent to the pleurotomy determined the diagnosis of pulmonary AG. At 30 days after the resection, the patient died from hemoptysis, hemothorax, lung atelectasis, and intracranial hypertension related to the recurrence of the brain tumor.

Keywords
- angiosarcoma
- brain sarcoma
- central nervous system
- pathology
- immunohistochemistry
- prognosis

received
February 9, 2020
accepted
March 24, 2020

DOI https://doi.org/10.1055/s-0040-1712108.
ISSN 0103-5355.

Conclusion Angiosarcoma is a rare neoplasia related to short survival due to the high proliferative index, which must be considered in patients presenting hemorrhagic tumors. No specific genetic abnormalities have been described for this neoplasia.

Resumo

Introdução O angiossarcoma (AG) é uma neoplasia mesenquimal maligna que afeta predominantemente os tecidos moles e, em graus variáveis, recapitula as características morfológicas e funcionais do endotélio. A incidência de sarcomas do sistema nervoso central (SNC) é baixa (0,5% a 2,7%), e os AGs envolvendo o cérebro são ainda mais raros.

Descrição do Caso Paciente masculino, 45 anos, apresentou queixa de dor de cabeça, náusea e vômitos. O exame físico mostrou papiledema bilateral e pleurostomia à direita. A história prévia incluía drogadição, tuberculose pulmonar, abscesso pulmonar, empiema pleural e embolização da artéria pulmonar por hemoptise grave. A tomografia computadorizada / ressonância magnética revelou uma grande lesão intra-axial com zonas hemorrágicas que se estendia para os lobos parietal e temporal direitos. O paciente foi submetido à ressecção cirúrgica da lesão. A microscopia mostrou um tumor maligno de alto grau, pouco diferenciado, composto por células fusiformes / epitelioides, formando pequenos espaços vasculares e ninhos sólidos, compatíveis com AG. No pós-operatório, o paciente desenvolveu hemoptise recorrente. A biópsia dos tecidos adjacentes à pleurostomia determinou o diagnóstico de AG pulmonar. Após 30 dias da ressecção, o paciente faleceu por hemoptise, hemotórax, atelectasia pulmonar e hipertensão intracraniana relacionada à recorrência do tumor cerebral.

Conclusão A AG é uma neoplasia rara relacionada à curta sobrevida devido ao alto índice proliferativo, que deve ser considerada em pacientes com tumores hemorrágicos. Nenhuma anormalidade genética específica foi descrita para esta neoplasia.

Palavras-chave
- angiossarcoma
- sarcoma cerebral
- sistema nervoso central
- patologia
- imuno-histoquímica
- prognóstico

Introduction

Malignant mesenchymal neoplasms of the central nervous system (CNS) are uncommon lesions that typically affect adults and occur as secondary tumors. Angiosarcomas (AGs) are aggressive supratentorial tumors that rarely affect CNS tissues.[1–3] The primary tumor site can be difficult to determine when CNS AG is diagnosed with involvement of other organ systems. Brain AGs are intra-axial enhancing lesions associated with edema and mass effect.[1,3–6] Upon gross examination, the tumor is typically soft and reddish, with extensive hemorrhagic areas. Microscopically, it is described as a high-grade tumor with elongated to plump cells and distinct vascular channels. Undifferentiated tumors, however, are not uncommon.[1–3,6] The present study reports a case of a male patient with metastatic CNS AG and concomitant iron-deficiency anemia, tuberculosis, and pulmonary AG. We then discuss the morphological and clinical findings of this unusual neoplasm.

Case Report

A 45-year-old male patient was referred to the hospital with complaints of headache, nausea, and vomiting for 6 days. He had a previous history of drug addiction and pulmonary tuberculosis, which had been treated in the previous eight months. The pulmonary tuberculosis was complicated by a pulmonary abscess, severe hemoptysis, pleural empyema, and pulmonary hypertension. The patient underwent pulmonary artery embolization for the management of the hemoptysis in the previous two months. Upon physical examination, the patient had a regular general condition, bilateral papilledema, and a right lung pleurotomy. Iron-deficiency anemia was detected in a laboratory test and was associated with the multiple episodes of moderate to severe hemoptysis. *Mycobacterium tuberculosis* was previously identified in lung-biopsy material by Ziehl–Neelsen staining. Computed tomography (CT) and magnetic resonance imaging (MRI) scans revealed an intra-axial expansive lesion measuring 4.8 cm in largest diameter in the right parietal and temporal lobes (►**Fig. 1**) associated with a large hematoma, perilesional edema, and midline shift. The patient underwent surgical resection of the lesion and drainage of the hematoma that was responsible for intracranial hypertension. The surgical specimen was composed of irregular, soft, and reddish tissue fragments, the largest measuring 2.2 cm in diameter. The microscopic examination revealed a poorly-differentiated, high-grade malignant tumor composed of plump epithelioid cells forming small vascular spaces and solid nests (►**Fig. 2**). The lesion had positive immunostaining for CD34 (►**Fig. 3**), CD31 (►**Fig. 4**), Fli-1, factor VIII, and VEGFR and negative immunostaining for glial fibrillary acidic protein (GFAP), synaptophysin, neurofilament protein, CKM, actin 1A4, desmin, HHV-8, SOX-10, Anti Melan A antibody (melan-A). The diagnosis of CNS AG was thus established. In the postoperative period, the patient had new

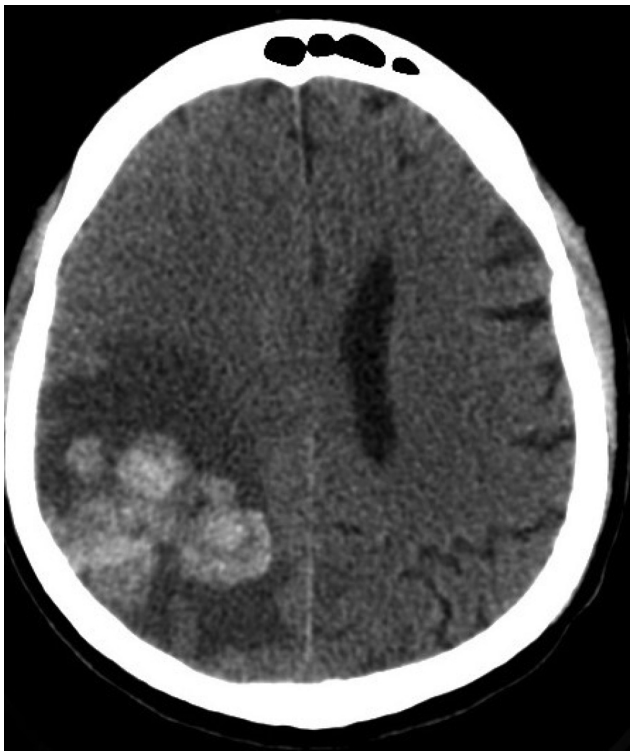

Fig. 1 Computed tomography scan showing a lesion extending into the right parietal and temporal lobes.

episodes of hemoptysis, and CT scans showed a large lesion compromising the lower lobe of the right lung(►**Fig. 5**), associated with hemothorax. A lung biopsy of the site of pleurotomy determined the diagnosis of AG. The patient died 30 days after brain resection from massive hemoptysis, hemothorax, right lung atelectasis, and intracranial hypertension caused by tumor relapse (►**Fig. 6**).

Discussion

Angiosarcoma is a malignant mesenchymal neoplasm that, to variable degrees, expresses the morphological and functional characteristics of the endothelium. The incidence of brain sarcomas varies from 0.5% to 2.7%, and AG accounts for less than 1% of all sarcomas. The malignancy has a significant predilection for the skin (~50% of cases) and superficial soft tissues, affecting predominantly the lower limbs.[1,3,7–9] About 10% of AGs are located in deep soft tissues, whereas the remainder are found mainly in the heart, spleen, breast, kidney, and bones. Metastatic and primary CNS AGs are very rare, but can occur in children and adults. Congenital cases have also been reported.[1–3,10–12] Metastatic CNS AGs are associated with intra-axial hemorrhage, and disseminate to cerebral tissues via a hematogenous route, although direct invasion of adjacent tissues can also occur. The heart is reported as the most common primary site for AG tumors metastasizing to the brain (~75% of cases, usually originating in the atrium).[1–3,10–12] Less commonprimary sites include the skin, the legs, the lungs, the pleura, the kidneys, the soft tissues, the gastrointestinal tract, the bones, and the spleen.

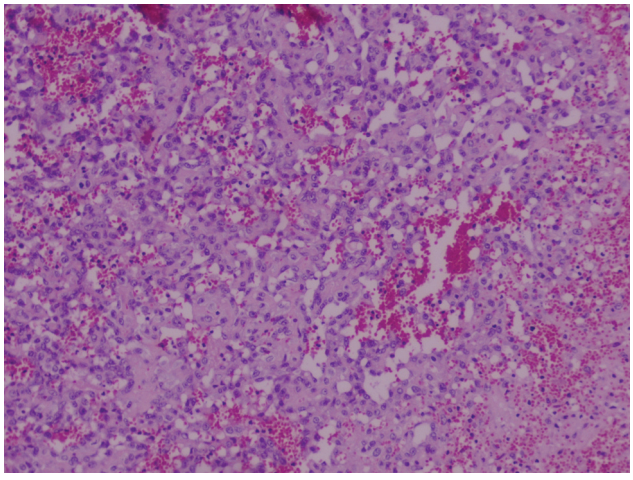

Fig. 2 Microscopy image of a poorly-differentiated, high-grade malignant tumor composed of plump epithelioid cells forming small vascular spaces. Hematoxylin-eosin, ×200.

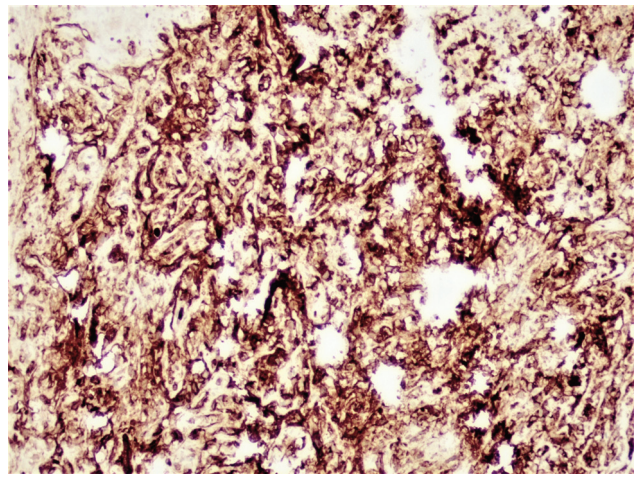

Fig. 3 Neoplastic cells showing marked immunostaining for Cluster of Differentiation 34 (CD34) (Ventana Systems), ×200.

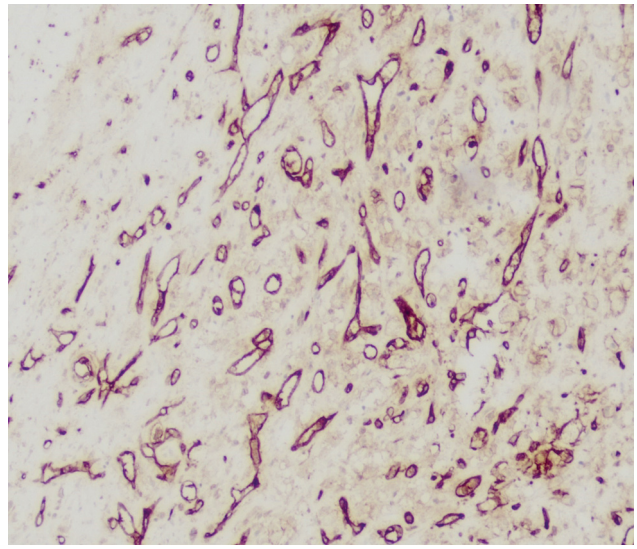

Fig. 4 Neoplastic cells showing positive immunostaining for Cluster of differentiation 31 (CD31) (Ventana Systems), ×200.

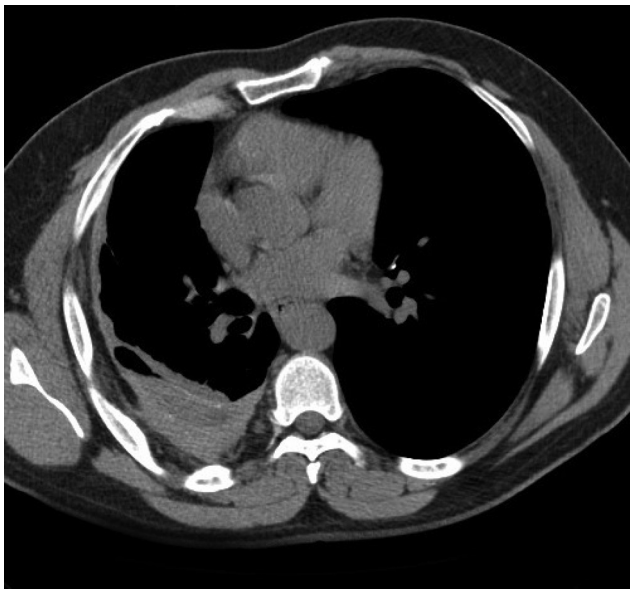

Fig. 5 Computed tomography scan showing a right hemothorax and an expansive lesion affecting the lower lobe of the right lung.

Exposure to industrial solvents, radiation, neurofibromatosis, Maffucci syndrome, Klippel–Trenaunay syndrome, and old surgical scars have been suggested as etiological factors.[12–16]

The most common findings of CNS AG are related to the mass effect and hemorrhagic episodes, including headache, nausea, vomiting, dizziness, seizures, hemiparesis, hemianopsia, lethargy, aphasia, and increased intracranial pressure.[1,3,10,12–14] The frontal, temporal, and parietal lobes are predominantly compromised (~70% to 80% of the cases).[1,3,10,12–14] The CT/MRI scans usually reveal a heterogeneous hemorrhagic lesion with variable signal intensities on T1- and T2-weighted images and adjacent areas of edema. Hydrocephalus, cystic dilation, and calcifications may be identified in large tumors by radiological examination.[1,3,10,12–14] Extensive hemorrhagic lesions are frequently misdiagnosed as hematomas on CT scans. The radiological differential diagnosis of CNS AG includes other tumors with hemorrhagic foci, such as choriocarcinoma, thyroid cancer, melanoma, renal-cell carcinoma, lung carcinoma, and glioblastoma.[1,12,14–19]

Upon gross examination, AGs are typically multinodular hemorrhagic masses with cystic degeneration and necrosis.[1–3,6,12,16] Microscopically, AGs show a wide range of morphological traits, ranging from anaplastic tumors to well-differentiated, anastomosing vessels. Different characteristics can be observed in a single neoplasm. Solid areas are composed of high-grade epithelioid plump cells with abundant cytoplasm and large nuclei.[1–3,6,12,16,20] Well-differentiated areas are characterized by distinct branched vascular channels covered by endothelial cells with mild to moderate atypia. The nuclei are usually vesicular and contain one or several small nucleoli or a prominent macronucleolus. The cytoplasm is commonly eosinophilic and often contain one or more vacuoles, which may be clear or empty, or hold intact or fragmented erythrocytes.[1–3,6,12,20] The architectural patterns include sinusoidal, ectatic, cavernous, solid, fascicular, epithelioid, and, rarely, foamy cells. The majority of AGs show a high mitotic index, marked nuclear atypia, and coagulative necrosis. In some areas, the tumor may contain a considerable amount of connective tissue interspersed between the vascular spaces.[1–3,6,12,16,20] The immunohistochemical profile of neoplastic cells includes positive staining for CD34, CD31, factor VIII, The transcription factor

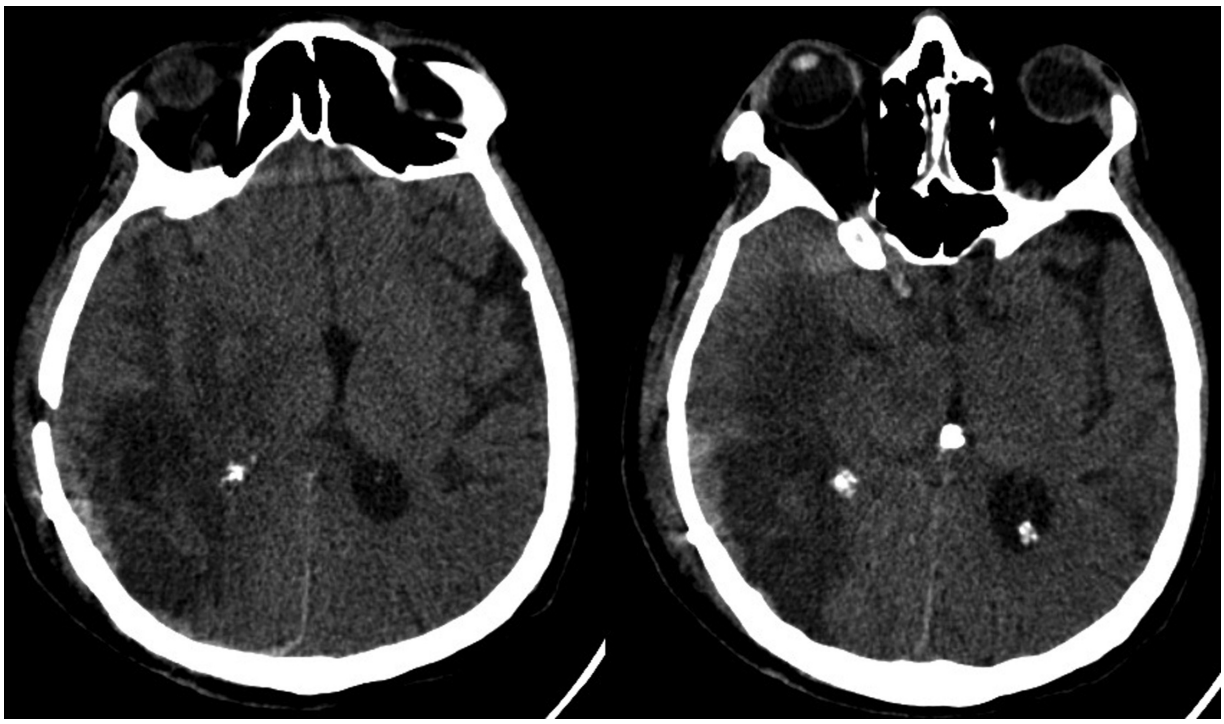

Fig. 6 Postoperative computed tomography scan showing a tumoral lesion compromising the right parietal and temporal lobes.

Table 1 Similar cases of metastatic angiosarcoma of the central nervous system reported in the literature

Authors	Age/ Gender	Clinicalfindings	Topography	Primary site	Treatmentmodality	Outcome
Lin et al[23]	63 years/ male	Weakness in the rightarm	Left frontal lobe	Heart	Tumor resection	Alive 12 months aftersurgery
Zakaria et al[10]	45 years/ female	Two-week history of confusion, left hemiparesis and upper motor neuron facial palsy	Multiple cerebral lesions	Heart	Radiotherapy	Died after three weeks in the hospital
Zakaria et al[10]	68 years/ female	Three-week history of occipital headache, ataxia and weakness in the left arm	Left cerebellar, right occipital and parietal periventricular regions.	Heart	Excision of the left cerebellar lesion	Died six weeks after brain surgery
Kuratsu et al[5]	17 years/ male	Severe headache and progressively worsening visual complaint	Pineal region	Liver	Radiationtherapy	Died twelve months after brain surgery
Kuratsu et al[5]	31 years/ female	Severe headache and a mild right hemiparesis	Left posterior temporal lobe, left thalamus, and cerebellar vermis	Femur	Surgical resection	Died sixteen months after brain surgery
Akutsu et al[15]	53 years/ male	Sudden onset of left-sided hemifacial convulsion and dysarthric speech	Right frontal lobe	Aorta artery	Surgical resection	Died after surgery
Vaquero et al[17]	30 years/ male	Headacheandvomiting	Right frontal lobe	Heart	Surgical resection	Died sixteen months after brain surgery
Kardes et al[24]	35 years/ male	Decline in the level of consciousness and quadriparesia	Both parieto-occipitalareas	Penis	Surgical resection	Died one month after brain surgery
Plotnik et al[25]	61 years/ female	Blurringof visual acuity	Right occipital lobe	Spleen	Surgical resection	Lived five years after splenectomy

erythroblastosis virus E26 transforming sequence related gene (ERG), Fli-1, and, less frequently, D2–40 and Anti-alpha smooth muscle Actin antibody (SMA). Epithelioid AG frequently exhibits positive immunostaining for CKM and EMA. Expression for HHV-8 and latency-associated nuclear antige (LANA-1) antibodies are characteristic of Kaposi sarcoma, whereas gliosarcoma with angiosarcomatous features may show positive staining for GFAP.[6–9,11–13,21] The ultrastructural findings include epithelioid/plump neoplastic endothelial cells disposed in a basal lamina and showing tight junctions and surface-oriented pinocytotic vesicles. An incomplete layer of pericytes is a common ultrastructural finding of CNS AGs.[1,2,6–8,12,13,16] No specific genetic abnormalities have been described for primary CNS AGs, which frequently exhibit upregulation of vascular-specific receptor tyrosine kinases, such as TIE1, KDR, FLT1, and TEK. Upregulation of VEFGR3 (FLT4) in 5q35 is found in 25% of metastatic AG cases, and upregulation of MYC in 8q24 is a hallmark of radiation-induced AG. Mutations in vascular endothelial growth factor (VEFGR) (KDR) are observed in 10% of AG cases. Histological differential diagnoses include epithelioid hemangioendothelioma, Kaposi sarcoma, gliosarcoma with angiosarcomatous features, metastatic carcinomas, and choriocarcinoma.[1,7,11,16,20–25] ►**Table 1** shows a short narrative review of metastatic CNS AG cases found in the PubMeddatabase that are comparable to the case herein reported.

Surgical resection of both primary and secondary CNS AGs with adjuvant chemotherapy is the treatment of choice. There is no significant evidence for radiotherapy.[2,3,8,10,12,13,16,18,22] The prognosis is poor, with most patients dying within six months after surgery/histological diagnosis. The factors associated with a worse prognosis include older age, large tumors, and high Cell proliferation marker (K_i-67) expression.[2,3,10,12,16,18,22]

Angiosarcoma is a rare neoplasia related to short survival due to the high proliferative index, and it must be considered in patients presenting hemorrhagic tumors. In the present article, the authors reported a case of lung AG determining CNS metastasis and severe anemia due to frequent episodes of intractable hemoptysis. At this time, no immunohistochemical findings are able to predict the prognosis or clinical course, and no specific genetic abnormalities have been described for this neoplasia.

Abbreviations and Acronyms

CNS	central nervous system
AG	angiosarcoma
CT	computed tomography
MRI	magnetic resonance imaging
CD34	cluster of Differentiation 34
CD31	cluster of differentiation 31
Fli-1	nuclear marker of endothelial differentiation
VEGFR	vascular endothelial growth factor.
GFAP	glial fibrillary acidic protein
CKM	anti-cytokeratins
actin	1A4 anti-α-Actin antibody
HHV-8	anti-hyman herpesvirus type 8
SOX-10	SRY-related HMG-box 10 protein
melan-A	anti Melan A antibody
ERG	the transcription factor erythroblastosis virus E26 transforming sequence related gene
D2–40	podoplanin
SMA	anti-alpha smooth muscle actin antibody
EMA	epithelial membrane antigen antibody
LANA-1	latency-associated nuclear antigen

TIE1	tyrosine kinase with immunoglobulin like and EGF like domains 1
KDR	anti-KDR (Ab-1214) antibody
FLT1	fms related tyrosine kinase 1 protein
TEK	anti-tyrosine-protein kinase receptor
VEFGR3	vascular endothelial growth factor receptor 3
FLT4	fms related receptor tyrosine kinase 4
MYC	recombinant Anti-c-Myc antibody
Ki-67	cell proliferation marker

Conflict of Interests

The authors have none conflict of interests to declare.

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Spinal Cord Stimulation as a Treatment Option for Refractory Chemotherapy-Induced Peripheral Neuropathy: Case Report

Estimulação medular para tratamento da polineuropatia dolorosa induzida por quimioterapia: Relato de caso

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Arq Bras Neurocir 2020;39(3):228–231.

Abstract

Colorectal cancer is one of the most common oncological diseases. Chemotherapy is usually recommended as an adjuvant treatment for stage-II, -III, and -IV tumors. Approximately 10% of the patients develop neuropathic pain after chemotherapy, and they may remain refractory despite the administration of drugs that are commonly used to treat neuropathic pain. Spinal cord stimulation is a good treatment option for neuropathic pain of the lower limbs, and it should be trialed in patients with chemotherapy-induced peripheral neuropathy. We report the case of a patient with oxaliplatin-induced neuropathy and neuropathic pain refractory to oral medication who was successfully treated by spinal cord stimulation.

Keywords
- spinal cord stimulation
- chemotherapy-induced peripheral neuropathy
- colorectal cancer

Resumo

O câncer colorretal é uma das neoplasias mais comuns na população em geral. A quimioterapia é habitualmente recomendada como tratamento adjuvante para tumores em estágios II, III e IV. Aproximadamente 10% dos pacientes irão desenvolver dor neuropática após a quimioterapia e eles podem se tornar refratários apesar da utilização de medicamentos para tratamento de dor neuropática. A estimulação medular espinhal é uma intervenção usualmente efetiva para alívio da dor neuropática em membros inferiores e deve ser testada em pacientes com neuropatia dolorosa induzida por quimioterapia. Nós descrevemos o caso de uma paciente portadora de neuropatia induzida por quimioterapia e dor neuropática refratária a medicações orais, a qual foi tratada de maneira bem-sucedida pela estimulação medular espinhal

Palavras-chave
- estimulação medular espinhal
- neuropatia periférica induzida por quimioterapia
- câncer colorretal

received
August 19, 2019
accepted
March 10, 2020

DOI https://doi.org/10.1055/s-0040-1709985.
ISSN 0103-5355.

Introduction

Colorectal cancer (CRC) will affect 6% of the Western population.[1] Similar to other cancers, chemotherapy-based treatments are the mainstay of CRC control. Neuropathy is a common chemotherapy complication, and ~70% of the patients present with some degree of neuropathic symptoms during treatment. Moreover, up to 10% of the patients develop long-term neuropathic pain after cancer, adding another layer of burden to the lives of cancer survivors.[2] Colorectal cancer is the third most common type of cancer. In Brazil, its incidence is estimated to be ~36,000 new cases per year. The overall survival rate is 65% at 5 years, and 58% at 10 years. Adjuvant chemotherapy is usually recommended for stages II, III, and IV, and oxaliplatin is a part of almost all of the chemotherapy regimens. If we consider that at least 10% of the patients receiving oxaliplatin will develop chronic neuropathy, then there will be ~3,300 new cases of chemotherapy-induced peripheral neuropathy (CIPN) associated with the oxaliplatin treatment in Brazil annually. In randomized controlled trials, very few drugs have shown efficacy in controlling chemotherapy-related neuropathic pain, and patients may remain refractory despite the administration of drugs commonly used to treat neuropathic pain, such as anticonvulsants (gabapentinoids), tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and opioids. After getting the approval of the institutional review board, we report the case of a patient with oxaliplatin-induced neuropathy and neuropathic pain refractory to oral medication who was successfully treated by spinal cord stimulation (SCS).

Case Report

A 51-year-old woman diagnosed with CRC underwent right hemicolectomy and tumor resection (the pathological examination revealed an adenocarcinoma) and received a systemic fluorouracil, leucovorin and oxaliplatin (FLOX) regimen as adjuvant therapy. After the second cycle of chemotherapy, she developed grade-3 neuropathy, and the chemotherapy was discontinued. She then developed severe cold allodynia and painful dysesthesia of the hands and pharyngolaryngeal dysesthesia occasionally when drinking cold water. Her cancer was controlled; however, six months later, she developed severe burning and tingling pain in the lower limbs. Upon neurological examination, she had glove- and stocking-like distribution of cold and pain hypoesthesia associated with intense dynamic mechanical allodynia in both feet. Axonal sensory-predominant length-dependent polyneuropathy was confirmed by nerve conduction tests, and oxaliplatin-induced neuropathic pain was diagnosed. The patient received first-line (pregabalin, gabapentin, amitriptyline, venlafaxine, duloxetine), second-line (subcutaneous botulinum toxin injection, tramadol) and third-line (oxycodone and methadone) treatments at the maximal tolerated dosage with no significant clinical improvement. She was eventually discharged from regular oncological follow-up after being considered cured of her CRC, but the refractory pain persisted. AnSCS trial was then proposed. The paddle was implanted at level T10–T12 (tripolar electrode – Specify, Medtronic, Minneapolis, MN, EUA. 5-6-5; PrimeAdvanceSureScan MRI neurostimulator – Medtronic, Dublin, Ireland) with a stimulation trial lasting seven days. During this trial period, she had significant improvement in her pain in both lower limbs – the 11-point numeric rating scale (NRS, in which 0 means no pain and 10 means the maximum tolerable pain) decreased ~50% (the presurgical NRS was 9, and the postoperative NRS was 4), and the pulse generator was then durably implanted.

After surgery, she was kept on continuous stimulation at a frequency of 40 Hz, a pulse width of 350 ms, and a voltage of 1 V (►**Fig. 1**), and the improvement was maintained with the pain well-controlled at the last outpatient follow-up at one year. At this visit, the neuropathic pain symptom inventory (NPSI) score was reduced from 55/100 (baseline) to 25/100, with a greater reduction in the superficial-spontaneous and evoked pain and dysesthesia subscores (►**Table 1**). The pain medications were progressively reduced (►**Table 2**).

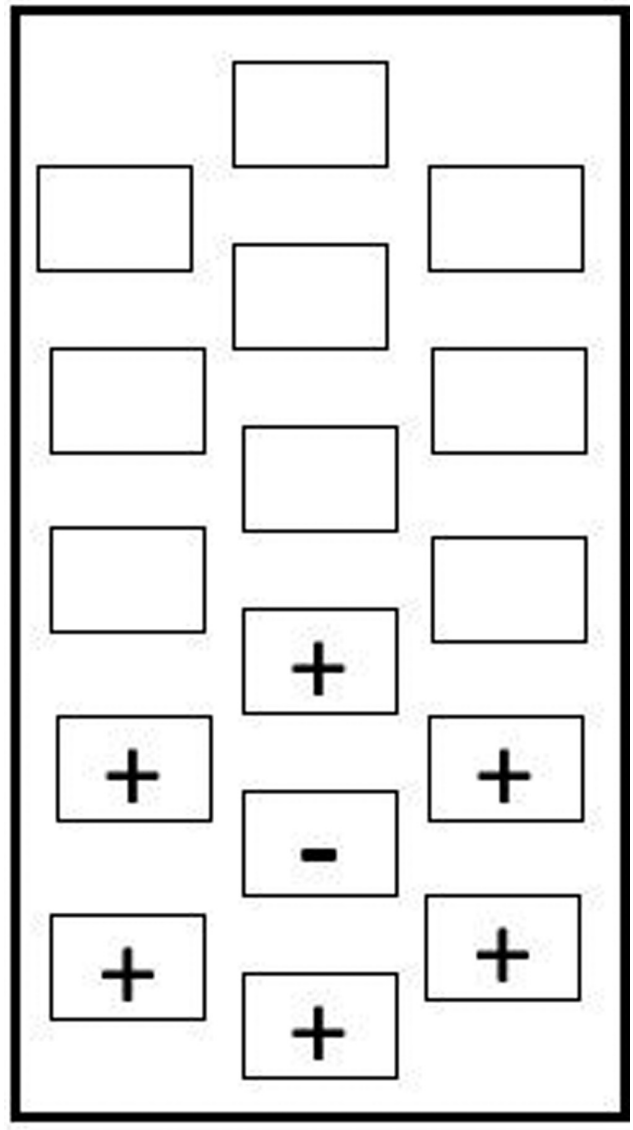

Fig. 1 5-6-5 electrode configuration.

Table 1 Pre- and postoperative Neuropathic Pain Symptom Inventory subscores

Neuropathic Pain Symptom Inventory subscores	Preoperative	Postoperative
Superficial spontaneous pain	9/10	0/10
Deep spontaneous pain	17/20	16/20
Paroxysmal pain	1/20	1/20
Evoked pain	14/30	2/30
Paresthesia/dysesthesia	14/20	6/20

Table 2 Medications taken by the patient before and after the implantation of spinal cord stimulation

Drug	Preoperative	Last follow-up
Pregabalin	600 mg	none
Venlafaxine	225 mg	150 mg
Lamotrigine	400 mg	400 mg
Methadone	40 mg	15 mg
Chlorpromazine	40 mg	24 mg

Discussion

Neuropathic pain is a common finding in cancer patients, and it is present in up to 40% of the cases. There are many etiologies related to neuropathic pain, such as, nerve or plexus compression by the tumor, direct tumor invasion, central pain, paraneoplastic syndrome, radiation-induced neuritis, chemotherapy-induced neuropathy, and others.[3]

In oncological patients, CIPN is a common complication. Starabovaand Vetter[4] reported six main types of chemotherapy drugs associated with an increased risk of neuropathy: taxanes (paclitaxel and docetaxel), vinca alkaloids (vincristine and vinblastine), platinum-based antineoplastics (oxaliplatin and cisplatin), epothilones, proteasome inhibitors, and immunomodulatory drugs (thalidomide). The main risk factors associated with the development of CIPN are older age, concomitant diabetes mellitus, previous neuropathy, smoking, and abnormal creatinine clearance.[3–5]

Depending on the severity of the neuropathy, the antineoplastic drugs may need to be reduced in dose, and, in some instances, discontinued. Some patients may improve after these alterations in treatment regimens, but, in some instances, they do not revert the neuropathy. Tricyclic antidepressants (amitriptyline, nortriptyline, imipramine), gabapentinoids (gabapentin and pregabalin), SNRIs (venlafaxine and duloxetine), anticonvulsants (lamotrigine and carbamazepine), and opioids (tramadol, methadone) are the main therapeutic options to treat neuropathic pain in general, and are frequently prescribed in CIPN. Even with the best medical treatment, many patients will not achieve adequate relief of pain and sensory symptoms. In this population, another treatment option for neuropathic pain treatment should be considered.[4,6] Some studies have reported good results after treatment with topical lidocaine and capsaicin patches. Botulinum toxin has also been described as an effective treatment for neuropathic pain in some patients.[6,7]

Spinal cord stimulation is the most commonly recommended surgical treatment for patients with neuropathic pain in the lower limbs that has failed to respond to optimal analgesic drug treatment and physical therapy. It is mainly indicated for failed back surgery syndrome and complex regional pain syndrome.[8,9] Most patients will experience more than 50% of pain relief at the long-term follow-up.[8] Spinal cord stimulation provokes changes in the integration of autonomic, sensory and motor information in the spinal cord, and it also triggers top-down inhibitory modulation of nociceptive inputs.[9,10] While SCS is frequently indicated for non-cancer-related neuropathic pain, long-term cancer survivors may suffer from neuropathic pain similar to that experienced by chronic diabetic or postherpetic neuralgia patients.

Spinal cord stimulation has already been described as a successful treatment for CIPN. Braun Filho and Braun[11] reported one case of SCS following vincristine therapy, which provided pain relief above 50% after percutaneous SCS. Cata et al,[12] in 2004, also reported two cases of SCS implantation following CIPN. The first patient had more than 90% of pain relief 4 months after surgery, and the second had more than 50% of pain relief at the 3-month follow-up. Abd-Elsayed et al[13] described a patient who underwent lead placement and had 95% of pain relief, which was maintained 2 years after treatment initiation (►**Table 3**). In all of the reports, the patients underwent the SCS trial before permanent implantation.[11–13] There were no reports of failed SCS trials, despite the potential bias related to negative results.

Table 3 Previous reports of spinal cord stimulation after chemotherapy-induced peripheral neuropathy

	Chemotherapy regimen	Type of spinal cord stimulation	Follow-up	Pain relief
Abd-Elsayed et al[13]	Not described	Laminectomy	2 years	95%
Braun Filho and Braun[11]	Vincristine	Percutaneous	3 months	> 50%
Cata et al[12]	Not described	Laminectomy	4 months	> 90%
Cata et al[12]	Vincristine	Laminectomy	3 months	> 50%

Conclusion

The present paper describes a long-term follow-up successful SCS for CIPN. The improvement was mainly observed in the evoked component of neuropathic pain. While this strategy warrants a cost-effectiveness assessment, the existing case-reports suggest that SCS could be a valid option to treat neuropathic patients refractory to the usual medical management. A clinical SCS trial in cancer survivors with CINP refractory to medical treatment would help better support this approach and better appraise its potential limitations, which, for the time being, are perhaps underreported.

Conflict of Interests

The authors have no conflict of interests to declare.

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Cerebellar Dysplastic Gangliocytoma: Case Report

Gangliocitoma Displásico Cerebelar: Relato de Caso

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Arq Bras Neurocir 2020;39(3):232–234.

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Abstract

Lhermitte-Duclos disease (LDD), or cerebellar dysplastic gangliocytoma, is a rare type of cerebellar tumor, from unknown origin. Patients can be asymptomatic for several years, but there are usually imprecise neurological signs for long periods.

Keywords
- gangliocitoma
- Lhermitte-Duclos
- cerebellar tumor
- benign tumor

Resumo

A doença de Lhermitte-Duclos (LDD), ou gangliocitoma displásico do cerebelo, é um tipo raro de tumor cerebelar, de origem desconhecida. Os pacientes podem ser assintomáticos por vários anos, mas geralmente há sinais neurológicos imprecisos por longos períodos.

Palavras-chave
- gangliocitoma
- Lhermitte-Duclos
- tumor cerebelar
- tumor benigno

Introduction

Lhermitte-Duclos disease (LDD), or cerebellar dysplastic gangliocytoma, is a rare type of cerebellar tumor of unknown origin.[1,2] The first report was documented in 1920.[2–4] Patients can be asymptomatic for several years, but there are usually imprecise neurological signs for long periods.[1,5] Diagnosis is made through magnetic resonance imaging (MRI) and confirmed by histopathological exam.[1–3] We report the case of a 74-year-old patient, with sudden onset of symptoms, presenting this uncommon cerebellar lesion.

Case Report

A 74-year-old female patient sought medical attention due to a sudden onset of gait disturbance associated with headache and vomiting 20 days earlier. The patient had a history of tobacco use, systemic arterial hypertension, type-2 diabetes mellitus, cardiac insufficiency, schizophrenia, and a sigmoid adenocarcinoma, treated several years earlier. On neurological examination, the patient presented mild consciousness disturbance (Glasgow 14), dysmetria, and dysdiadochokinesia. An MRI was performed, which evidenced a mass lesion in the right cerebellar hemisphere, hyperintense on T2-weighted imaging and hypo intense on gadolinium-enhanced T1-weighted imaging. The lesion measured 5.8×3.6 cm and was associated with peripheral vasogenic edema (►**Fig. 1**), which caused mass effect, sulci blurring among the cerebellar folia as well as compression of the cerebellar-pontine cistern and fourth ventricle.

Microsurgical treatment was performed through a suboccipital craniotomy, with a near total resection of the lesion. Control computed tomography (CT) scan confirmed the extent of the resection. In the postoperative period, the patient sustained the previous deficits. Anatomo-pathological examination evidenced proliferation of round cells in the cerebellum (►**Fig. 2**), and immunohistochemistry was suggestive of cerebellar dysplastic gangliocytoma (World Health Organization [WHO] grade I— Lhermitte-Duclos disease), positive for Neu-N, glial fibrillary acidic protein

received
August 26, 2019
accepted
March 24, 2020

DOI https://doi.org/10.1055/s-0040-1710313.
ISSN 0103-5355.

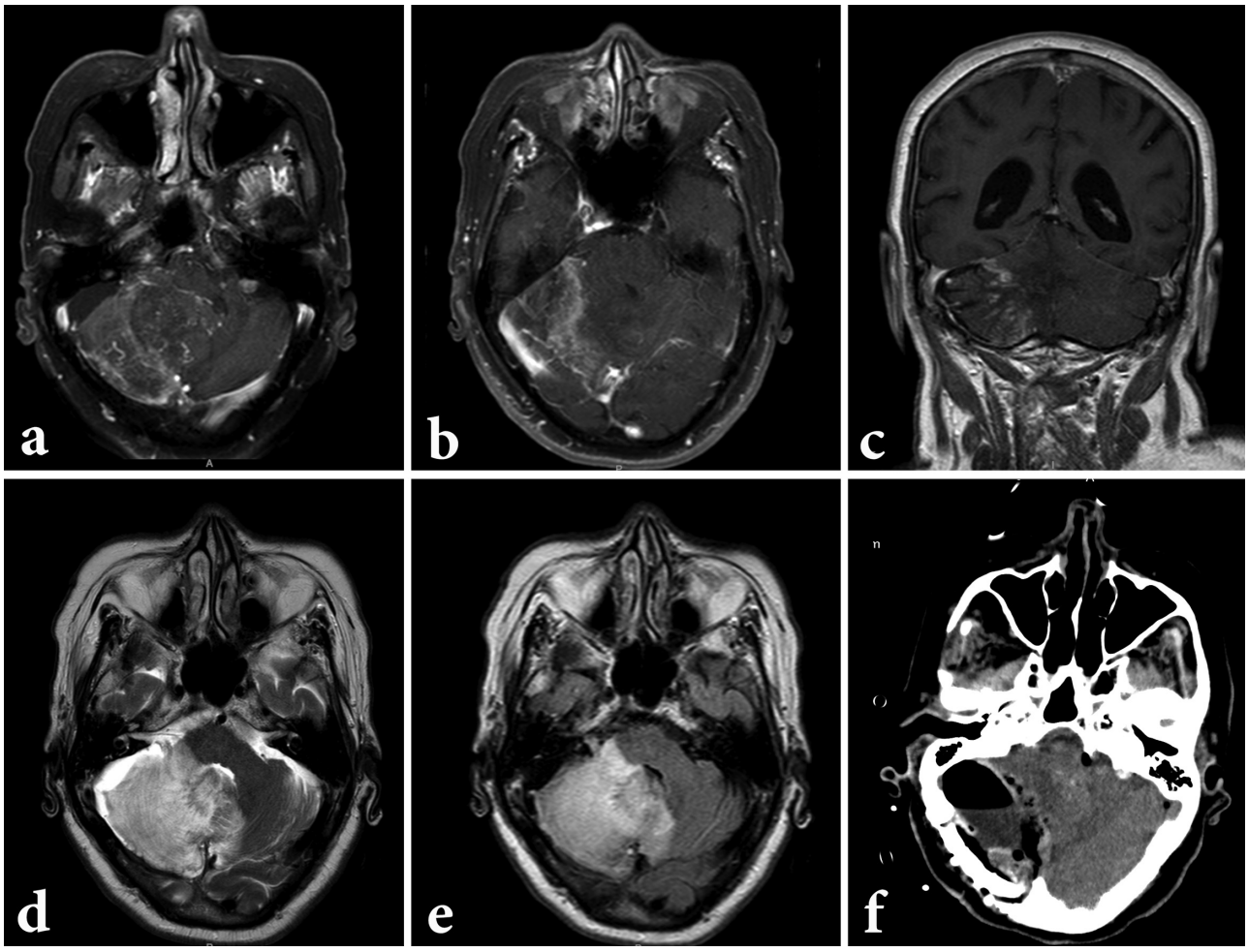

Fig. 1 (a,b) T1-weighed axial magnetic resonance imagining (MRI) with gadolinium, evidencing extensive lesion in the right cerebellar hemisphere, with imprecise limits, moderate enhancement by the contrast and mass effect, distorting the fourth ventricle. (c) T1-weighed coronal MRI. (d) T2-weighed axial MRI. (e) fluid-attenuated inversion recovery (FLAIR) axial MRI confirming the infiltrative pattern of the lesion. (f) Post-operative axial CT scan, evidencing extensive resection of the lesion.

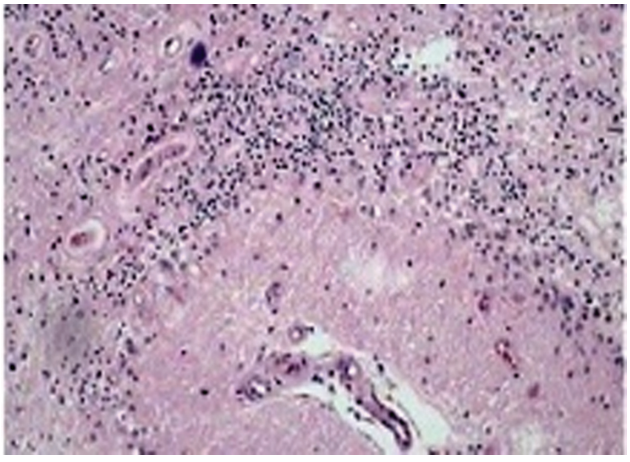

Fig. 2 Ganglionic cells with smooth atypia and single calcification focus. Hematoxylin & Eosin stain, 50x.

(GFAP), synaptophysin and phosphatase and tensin (PTEN) antibodies.

The patient presented increase in the clinical status, with improvement in the gait, and was able to walk without assistance. The patient also present transient neuropathy of the accessory nerve. She remains in rehabilitation program to this day.

Discussion

Lhermitte-Duclos disease (LDD) is an extremely rare type of benign cerebellar tumor of unknown ethiology.[1] It was initially documented in 1920.[3,4] It usually presents in young adults, with no predilection for gender or race,[2,4,6,7] with a prevalence of < 1 for 1,000,000 patients.[1] It is a lesion of the cerebellar cortex,[3] characterized by loss of the normal cortex architecture and focal widening of the cerebellar folia. It is still not clear if the cerebellar dysplastic gangliocytoma is a neoplastic or hamartomatous lesion of the cortex; if neoplastic, it corresponds to a grade I lesion of the WHO classification.[5]

Generally, it has an indolent and chronic course, with the possibility of acute onset of symptoms.[3] It manifests with headache, visual disturbance, cerebellar dysfunction, ataxia, cranial nerve palsies, and obstructive hydrocephalus,[2,6,7] mainly in the 3rd or 4th decade of life.[6,7] Acute onset of

neurological deficits, as in the case presented, is rarely reported.[5]

Lhermitte-Duclos disease can be familiar or sporadic.[8] The occurrence of associated hereditary syndromes, such as Cowden disease, has been reported.[2,5–7] Cowden disease is an autosomal dominant disturbance characterized by multiple hamartomas and associated with a wide range of malignancies of the thyroid, skin, breast, intestine, and kidney. The exact correlation, nevertheless, is still uncertain.[3] Molecular studies suggest a high frequency of abnormalities in the PTEN/AKT path, an important regulator of cellular growth.[6,8] It is recommended that every patient diagnosed with LDD should be investigated regarding Cowden disease and mutations in PTEN. Furthermore, individuals with LDD and Cowden disease or PTEN mutation should receive continuous attention in order to prevent the associated malignancies.[3,4,8]

Although the confirmatory diagnosis is made through histopathological findings, the MRI can give good markers of the usual characteristics of this specific condition. Lesions are usually hypointense on T1-weighted sequence and hyperintense in T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences.[1–3,6,8] Thus, widening of the cerebellar folia appears as parallel linear stria in the lesion surface. This pattern is called "tiger's stripe" or "striated cerebellum", which is characteristic of LDD.[5,6] The mass lesion is circumscribed, usually restricted to one cerebellar hemisphere and has different appearance compared to the adjacent tissue. In rare cases, there is contrast enhancement, which is a finding that can represent venous proliferation of the external layers of the cerebellar cortex and prominent venous drainage.[8] The computed tomography (CT) scan image characteristics consisting of hypodense areas and calcifications are unspecific to the diagnosis of LDD.[5,7]

The disease has classic histopathological characteristics[3]; the internal granular and molecular layer have diffuse enlargement, with dysplastic cells, replacing the internal molecular layer with hypermyelinization of the molecular layer.[1,2,6] There are no mitotic figures, nor necrosis.[3] The Purkinje cells, as well as the white matter, are reduced or absent.[2,5,6] In the immunohistochemistry studies, these cells are positive for synaptophysin.[3,6]

The definitive treatment for this condition involves microsurgical resection of the lesion.[1,6–8] Nevertheless, in asymptomatic patients, diagnosed incidentally through MRI, conservative management can be justified.[1] Patients that present acute onset of symptoms, or with significant cerebellar mass effect on CT scan should be submitted to microsurgical resection of the lesion, even when the diagnosis is unclear.[5] In elderly patients, partial resection can be recommended in order to reduce the mass effect and avoid surgical complications.[2,7]

Recurrence of the disease in the postoperative period is considered rare.[1,6] Due to its association with the Cowden disease in adults, one should always rule out concomitant malignancies (particularly breast and genitourinary cancers) and perform genetic tests to diagnose Cowden disease.[3,8]

Conclusion

Lhermitte-Duclos disease is an extremely rare lesion of unknown etiology that can be associated with Cowden disease and mutations in the PTEN path. For this reason, if the MRI is compatible, histopathological analysis should be performed. The definitive treatment is surgical, with resection of the lesion.

Conflict of Interests

The authors have no conflict of interests to declare.

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A Rare Case of Medulloblastoma with Supratentorial Metastasis Two Years after Treatment

Um caso raro de meduloblastoma com metástase supratentorial dois anos após o tratamento

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Arq Bras Neurocir 2020;39(3):235–238.

Abstract

One of the most invasive malignant tumors of the cerebellum is medulloblastoma, which is also the most common malignant tumor of the brain in children. Patients with a recurrent disease following initial treatment have the most unfavorable prognosis. The most common metastasis locations are the spine, the posterior fossa, the bones, and the supratentorium. Late medulloblastoma metastasis in the supratentorial intraventricular region is uncommon. We report here a case with supratentorial seeding.

Keywords
- medulloblastoma
- metastasis
- supratentorial
- recurrence

Resumo

Um dos tumores malignos mais invasivos do cerebelo é o meduloblastoma, que também é o tumor maligno mais comum do cérebro em crianças. Pacientes com a doença recorrente após o tratamento inicial têm o prognóstico mais desfavorável. Os locais mais comuns de metástase são a coluna vertebral, a fossa posterior, os ossos, e o supratentório. Metástase tardia de meduloblastoma na região intraventricular supratentorial é incomum. Relatamos aqui um caso com semeadura supratentorial.

Palavras-chave
- meduloblastoma
- metástase
- supratentorial
- reincidência

Introduction

One of the most invasive malignant tumors of the cerebellum is medulloblastoma, which is also the most common malignant tumor of the brain in children.[1] During the last thirty years, developments in imaging, surgery, pathologic stratification, radiotherapy, and chemotherapy have improved the rate of long-term survival or cure in children. The outcome for infants, adults, and high-risk patients is less favorable.[2] Patients with a recurrent disease after the initial treatment have the most unfavorable prognosis.[3] The most common metastasis locations are the spine, the posterior fossa, the bones, and the supratentorium.[3] It has been reported that supratentorial metastasis is more common within the subfrontal region,[3,4] while late medulloblastoma metastasis in the supratentorial intraventricular region is uncommon. We report here a case with supratentorial seeding.

Case Presentation

A 4-year-old girl was diagnosed with medulloblastoma, which was confirmed by histopathology and immunohistochemistry staining, causing headache, nausea, vomiting, and vertigo. Thirty sessions of radiation therapy and gross total tumor resection were included in the treatment. Furthermore, shunt placement was performed after the surgery because of the

received
March 18, 2020
accepted
April 22, 2020

DOI https://doi.org/10.1055/s-0040-1713093.
ISSN 0103-5355.

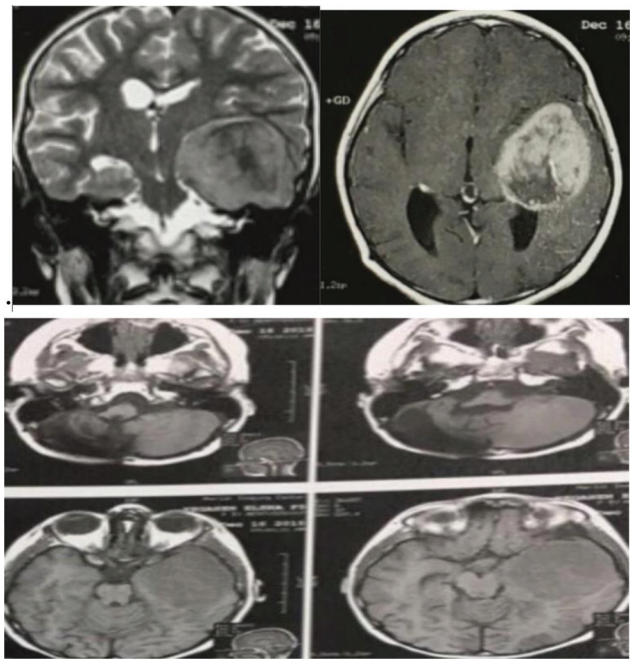

Fig. 1 Brain MRI showing postoperative changes and cavity within the right cerebellar hemisphere, as well as a new T1 low, T2 high signal intensity intracranial enhancing mass lesion within the left temporal lobe measuring $\sim 68 \times 58 \times 46$ mm.

hydrocephalus observed in the patient. No spinal metastatic dissemination was found in the postoperative staging. The patient had no complaints in the routine clinical follow-ups, showing normal physical and intellectual development. Local tumor recurrence or spinal drop metastasis were not found by surveillance magnetic resonance imaging (MRI) scans. The patient started a subtle history of restlessness and headache after two years. She was alert and had no focal neurological deficit on admission.

In the following brain MRI with and without contrast, a new well-defined intra-axial mass lesion was reported within the left temporal lobe, with mass effect and left to right midline shift, most likely a metastatic lesion or high-grade primary glioma (►**Fig. 1**). A brain computed tomography (CT) scan also showed a hyperdense mass within the left temporal lobe (►**Fig. 2**).

The patient underwent resection of the left temporal lobe lesion, which was diagnosed as medulloblastoma according to the pathology report (►**Fig. 3**).

With the history of cerebellar medulloblastoma two years before, the new developing lesion within the left temporal lobe is highly suggestive of intracranial supratentorial tumor metastasis.

Discussion

The prevalence of medulloblastoma is higher in males than in females, accounting for a higher percentage of brain tumors in children than in adults.[5] The top presenting attributes of medulloblastoma are usually relevant to hydrocephalus and cerebellar dysfunction, including nausea/vomiting, headache, unsteady gait, and truncal ataxia.[3] Almost 83% of tumors in children are observed in the midline, while, 49% of tumors in adults are lateral.[6] In case of metastasis, recurrence at just one location and further from the primary diagnosis time are known as more desirable prognostic indeces.[7] The posterior fossa, the spine, the supratentorium, and the bones respectively are the locations in which metastases most typically occurred.[3] Supratentorial diffusion is generally within the sub-frontal region and maybe consequently of overly great radiation guarding of the orbital roof to inhibit irradiation of the cribriform plate, enabling a nidus of relapse.[8] Ramaswamy et al[9] published the largest series of recurrent medulloblastoma in patients who were mostly younger than 16 years of age. They

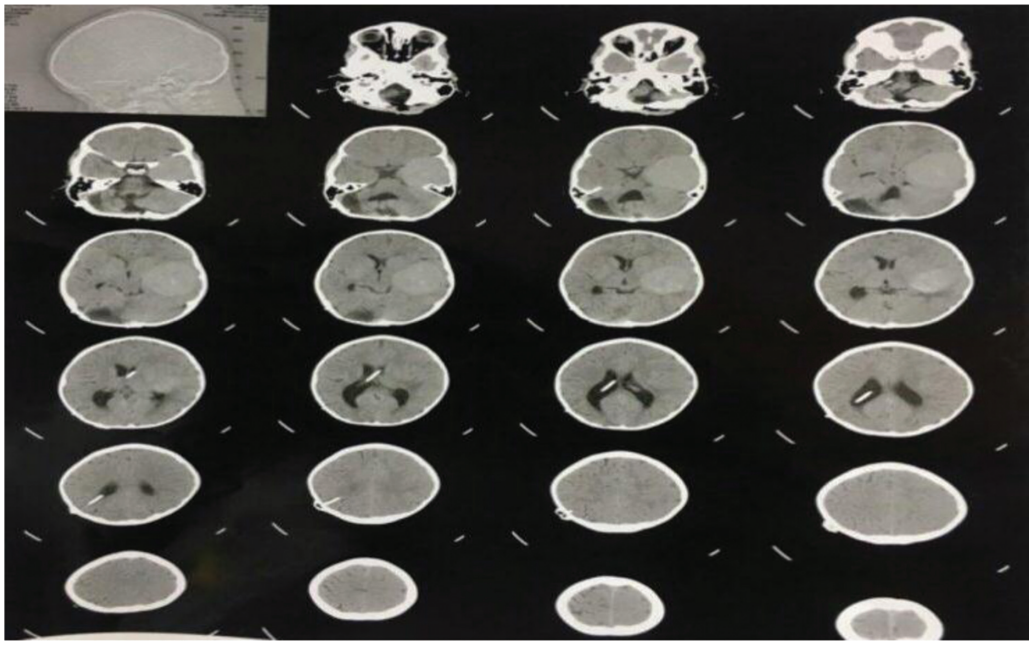

Fig. 2 Brain CT scan.

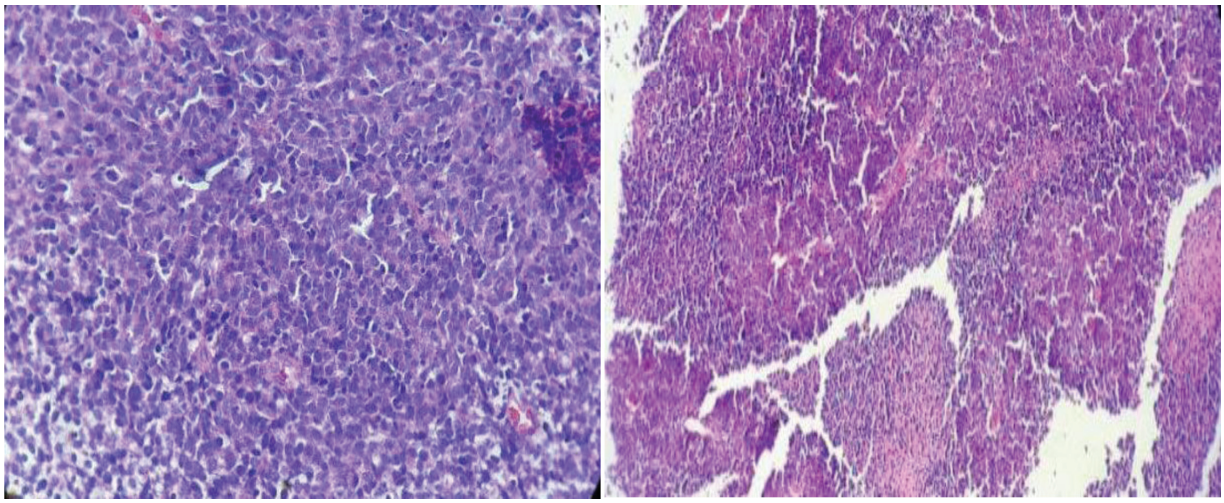

Fig. 3 The tumor cells stained positive for synaptophysin and neuron-specific enolase (NSE), and negative for LCA (Leukocyte common antigen), CD 99 (Cluster of differentiation), and glial fibrillary acidic protein (GFAP) on the immunohistochemistry staining (only hematoxylin and eosin [H&E] slides available).

found distant metastasis as the most common pattern of tumor relapse compared with local relapse. Kumar et al[10] reported 2 adults with the ages of 31 (case 1) and 20 (case 2) years, who had metastasis in the supratentorial region 3.5 years and 11 months respectively after total elimination of the medulloblastoma in the posterior fossa. The 31-year-old adult had spinal metastasis as well. Both patients had undergone cranio-spinal irradiation. Case 1 underwent laminectomy, and case 2 was submitted to craniotomy due to the presenting signs.[10] Abode-Iyamah et al[5] reported the case of a 22-year-old male presenting with isolated, separated pellucidum relapse of the medulloblastoma 13 years after the primary recognition. His tumor was completely resected. Gerlach et al[11] reported the case of a 15-year-old girl presenting with nausea and headache. A brain MRI scan revealed a leptomeningeal spread five years after a surgery for posterior fossa medulloblastoma and following chemoradiotherapy. The biopsy of the left frontal mass showed an extension of the tumor. The histopathological features of the tumor were similar to that of the primary one.

The metastases of medulloblastomas usually happen through the pathway of the cerebrospinal fluid, the ventricular system, and the spinal cord. The extra-neural metastases of primary tumors of the brain are relatively uncommon, and most regularly arise from medulloblastomas in children, and after the adjustment to the incidence of the primary tumor in adults.[12] The mechanisms of extra-neural medulloblastoma spread remain unknown. Surgical interventions and craniotomy interrupt the blood-brain barrier mechanically and enable the immigration of the tumor cells. Lymphatic and hematogenic (including the retroauricular and cervical lymph nodes) extensions of the primary tumor of the brain have already been proposed.[13,14] Another often proposed mechanism for the extra-neural extension of the medulloblastoma is iatrogenic diffusion through ventriculo-peritoneal shunts, which are primarily likely to result in peritoneal metastases.[14] Many extra-neural medulloblastoma metastases happen relatively early after the primary diagnosis. While in 80% to 85% of the pediatric cases the posterior-fossa and leptomeningeal metastases are diagnosed in the first 5 years, nearly 80% of the extra-neural metastases are observed within the first 3 years after the primary diagnosis.[13,14] Simultaneous involvement of the central nervous system and the liver or pulmonary metastasis, early expansion of the extra-neural metastasis (less than 18 months after the primary diagnosis), and patients younger than 16 years of age during the time of the diagnosis of the extra-neural metastasis are typically related to more mediocre forecasts.[14]

Conclusion

We conclude that the possibility of tumor recurrence or intra-cranial metastasis should always be considered in children with medulloblastoma, and it is recommended that the patients continue to undergo regular treatments and follow-ups for early diagnosis.

Conflict of Interests

The authors have no conflict of interests to declare.

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Adult Nasoethmoidal Encephalocele Corrected by Supraorbitary Approach: Case Report and Literature Review

Encefalocele nasoetmoidal de adulto corrigida por acesso supraorbitário: Relato de caso e revisão de literatura

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Arq Bras Neurocir 2020;39(3):239–242.

Abstract

Encephalocele is a protrusion of the central nervous system elements through a defect in the dura mater and in the cranium. The prevalence of encephalocele ranges from 0.08 to 0.5 per 1,000 births. The posterior encephaloceles are more common in North America and Europe, while frontal defect is frequently found in Asia. The present paper describes a 26-year-old male patient presenting with cerebrospinal fluid leak and meningitis symptoms. He was diagnosed with congenital nasoethmoidal encephalocele and treated surgically using a supraorbital approach without complications.

Keywords
- encephalocele
- supraorbitary craniotomy
- nasal fluid leak

Resumo

Encefalocele é definida como uma protrusão dos elementos do sistema nervoso central por um defeito localizado na dura máter no crânio. Sua prevalência apresenta-se entre 0.08 e 0.5 casos a cada 1.000 nascimentos. As encefaloceles posteriores são mais comuns na América do Norte e na Europa, já os defeitos frontais são frequentemente encontrados na Ásia. O presente artigo descreve o caso de um paciente do sexo masculino de 26 anos de idade com quadro de fístula liquórica nasal associada a meningite de repetição. Ele foi diagnosticado com encefalocele nasoetmoidal congênita, e tratado de forma cirúrgica com um acesso via supraorbital, sendo realizada a correção completa da falha sem intercorrências.

Palavras-chave
- encefalocele
- craniotomia supraorbitária
- fístula liquórica nasal

Introduction

Encephalocele is a type of cranial dysraphism that occurs as a protrusion of intracranial content through a defect in the cranial floor, thus leading to the formation of a herniary sac. Defects in the embryogenesis process, viral infections, hyperthermia, radiotherapy, hypervitaminosis, and the use of salicylates in early pregnancy have been implicated in its pathogenesis.[1] The prevalence of encephalocele ranges from 0.08 to 0.5 per 1,000 births.[2] Suwanwela et al[3] classified encephaloceles based on the location and type of skull defect as occipital, basal and frontoethmoidal encephalocele. In frontoethmoidal encephalocele, a congenital disorder characterized by structural changes at the junction of the frontal and ethmoid bones, internally, and in the frontonaso-orbital region, externally, which results in facial disfigurement. It is further divided into three subtypes:

received
March 31, 2020
accepted
May 12, 2020

DOI https://doi.org/10.1055/s-0040-1713919.
ISSN 0103-5355.

nasofrontal (NF), nasoethmoidal (NE), and naso-orbital (NO).[3]

Only ~ 50% of fetuses with encephaloceles survive until birth. Most surviving infants with encephaloceles have cognitive deficits, and hydrocephalus, spasticity, and seizures are also common in these children. Up to half of these children have chromosomal abnormalities.[2]

Imaging exams, such as head tomography with thin slices of skull base or magnetic resonance, are indispensable to diagnoses. In some cases, confusion may occur, mainly when the skull defect is very small.[4,5]

The treatment of choice is surgery, which consists in repairing the skull base defect with or without resection of the herniary sac. Many endoscopic and open surgical approach techniques have been described in the literature with good results.[6–9]

The present case report describes a 26-year-old male patient with nasoethmoidal encephalocele corrected with a transcranial supraorbitary approach.

Case Report

A 26-years-old male patient was admitted in an emergency room with 2 days of headache, stiff neck, and fever. He reported a periodic fluid nasal secretion and 3 previous meningitis episodes in the past 3 years. Physical examination did not show any type of cranial abnormality, despite the presence of fluid leak. A liquor sample was collected whose result showed meningitis, and a head computed tomography (CT) presented a skull base defect measuring 1.4 × 0.6 cm with a large herniation sac with brain tissue from the ethmoidal bone to the nasal cavity measuring 3.6 × 1.8 × 1.3 cm. After treatment of the central nervous system infection, the patient underwent a surgical correction of the skull base and excision of the intracranial herniary sac (►**Fig. 1**).

Due to a large skull base defect with more than 1 cm, a supraorbital approach was performed, which provided a better exposition of bone defect and hernial sac with good aesthetic results. The dura-mater was dissected from the bone and herniary sac, and ethmoidal bone defects next to the cribriform plate were observed. The amputation of the intracranial herniary content was performed with primary duraplasty using first suture and, after, a dural substitute. The repair of the anterior skull base bone was made with bone cement (►**Fig. 2**).

The patient evolved without complications and was discharged after 4 days, no longer reporting CSF leak or any other symptoms. The postoperative head CT showed complete closure of the ethmoidal bone defect (►**Fig. 3**).

Discussion

Encephaloceles are more common in Southeast Asia, with a related incidence from 1:3,500 to 1:6,000 births.[10] In Western countries, this pathology is rare, with an incidence of 1 to 40,000 births.[11,12] In general, it is associated with others brain alterations, like corpus callosum agenesis, hydrocephalus, singles ventricle, Dandy-Walker malformation,[13] microcephaly, epilepsy,[14] cavum vergae, and arachnoid cyst.[6] In our case, a central nervous system defect was not found.

The occipital encephaloceles are described as the most common type.[14,15] However, the frontoethmoidal type is the most described in the literature; of these, nasoethmoidal is the most commonly found in studies.[6,13,14,16]

Mahatamarat et al[7] classify frontoethmoidal encephalocele in some subtypes: nasofrontal, in which the defect is localized between the nasal and frontal bones; nasoorbital with herniation through the medial orbital wall; nasoethmoidal was characterized by hernial sac between the nasal bones and nasal cartilages; Combined nasoethmoidal and naso-orbital; and abortive, when the defect is unidentifiable.[7]

Many surgical techniques were described to correct meningoencephaloceles with an intracranial or an endoscopic approach. The endonasal endoscopic approach is preferred in smaller defects and cases without facial deformations or external tumor mass. The skull deformities reconstruction

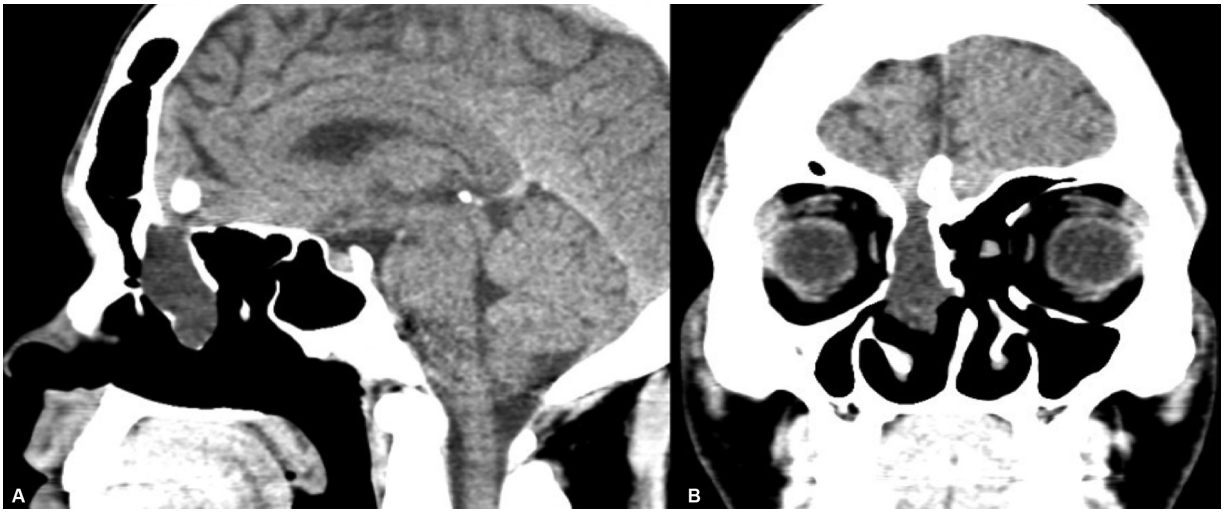

Fig. 1 A and B - Head computed tomography shown in sagittal and coronal sequences with an anterior skull base encephalocele with large bone defect connecting the intracranial anterior floor with the nasal region.

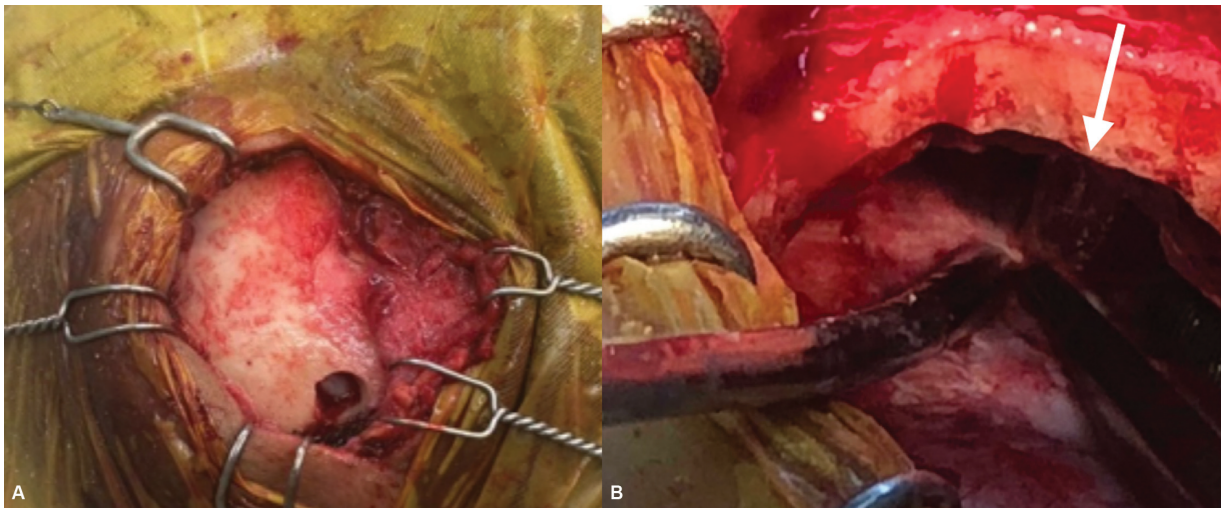

Fig. 2 A - Right supraorbital craniotomy with one burr hole. B - Anterior extradural space with encephalocele (white arrow) connecting the intracranial and nasal spaces.

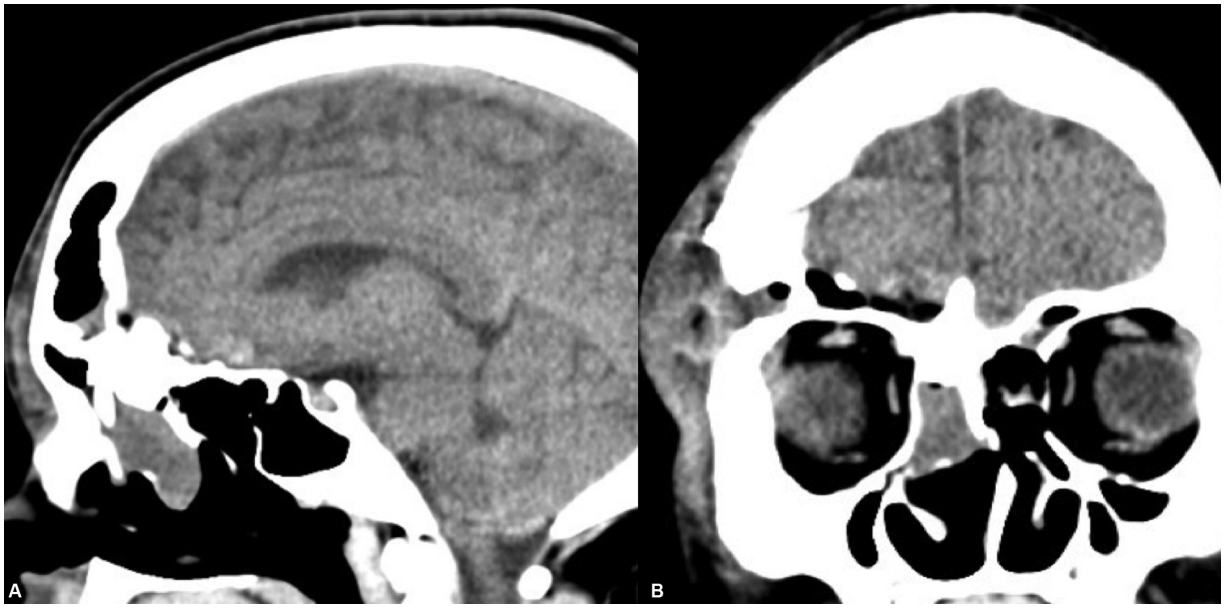

Fig. 3 A and B - Postoperative head computed tomography in sagittal and coronal sequences showing a complete correction of anterior fossa floor with bone cement and cerebrospinal fluid leak resolution.

can be performed with fat tissue, fibrin sealant, and dural substitute.[9,17]

Otherwise, transcranial approaches like the traditional Chula technique are preferred in cases with large or ectopic mass, which need some skin removal or recidivist case with previous scar face, but it leaves an inconvenient scar on the patient's face.[6] Some authors described a modified Chula technique, made with no facial incision, using a bicoronal approach to the hernial sac, with correction of skull defect. Both techniques need a large traumatic T-shaped osteotomy in the medial portion of the superior orbital rim, upper medial orbital wall, and nasal bones.[7] Bone cement has been described in the literature to treat bone defects of encephaloceles since 1959; however, it is nowadays reserved for large skull defects.[18]

The subfrontal craniotomy was a previous transcranial approach described to treat frontoethmoidal encephaloceles with good outcomes using bone grafts, periosteum, and graft of temporal fascia to close the skull defect. This type of approach makes it possible to perform the surgery in one stage, decreasing surgical risks.[16,19]

The amputation of the herniary sac in frontoethmoidal encephalocele is considered secure because the brain tissue inside is almost non-functional and only rarely epileptogenic.[16]

Conclusion

Adult encephalocele cases are rare and need to be investigated in patients with liquoric fistula without traumatic or iatrogenic history.

The supraorbitary approach should be considered to treat unilateral nasoethmoidal encephaloceles because it provides

good exposition and has the advantage of being less traumatic with better aesthetic results.

Conflict of Interests

The authors declare that they have no conflict of interests.

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ISSN 0103-5355

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Book

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Theses and dissertations

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