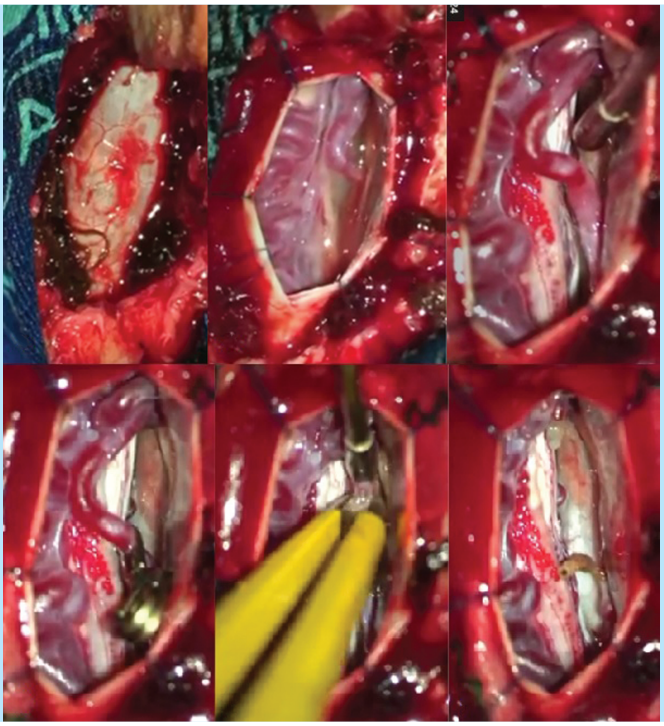
ISSN 0103-5355

Brazilian Neurosurgery

Arquivos Brasileiros de Neurocirurgia

Number 4 • Volume 43 • Pages 237–380 • December 2024



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ISSN 0103-5355

Brazilian Neurosurgery
Arquivos Brasileiros de Neurocirurgia

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Arquivos Brasileiros de Neurocirurgia

Volume 43, Number 4/2024

Brazilian Neurosurgery
Arquivos Brasileiros de Neurocirurgia

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(Souza TM, Silva PGS, Paula F, Ghizoni E, Joaquim AF. Spinal Dural Arteriovenous Fistula, a Rare and Frequently Misdiagnosed Cause of Mielopathy – Case Report and Review of the Literature. Arq Bras Neurocir 2024;43(4):e355–e359)

 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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Arquivos Brasileiros de Neurocirurgia is an official publication of the Brazilian Neurosurgery Society (Sociedade Brasileira de Neurocirurgia) and the Portuguese Language Neurosurgery Societies. It is listed in LILACS and LILACS-Express (Latin-American and Caribbean Center on Health Sciencies Information), and Latindex (Regional Cooperative Online Information System for Scholarly Journals from Latin America, the Caribbean, Spain and Portugal). Thieme Medical Publishers is a member of the CrossRef initiative.

ISSN 0103-5355

Endoscopic Septostomy for Treatment of Complex Hydrocephalus: A Single Center Retrospective Cohort

Septostomia Endoscópica para tratamento da Hidrocefalia Complexa: Uma coorte retrospectiva de um único centro

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Arq Bras Neurocir 2024;43(4):e237–e244.

Abstract

Objective The objective was to present the initial experience with endoscopic septostomy in a Brazilian public hospital.

Methods A retrospective analysis was conducted on patients who underwent neuroendoscopic septostomy at the Department of Neurosurgery of Cristo Redentor Hospital in Porto Alegre from 2015 to 2021.

Results In the period analyzed, 14 patients underwent endoscopic septostomy. The mean age of the patients was 41.86 years; 11 were male and 3 were female. The etiologies of hydrocephalus included ventricular inflammatory conditions, neoplasms, neurocysticercosis, and intraventricular cysts. Following septostomy, 64% of the patients exhibited clinical and radiological improvement. Complications occurred in 29% of the cases, including intraventricular hemorrhage and thalamic contusion. Four deaths were observed, all related to clinical complications or progression of the underlying disease.

Conclusion Endoscopic septostomy is an effective and safe procedure for treating complex hydrocephalus of different etiologies. Surgical outcomes are related to the learning curve with neuroendoscopy, and the benefits for patients are evident, considering the possibility of safely and effectively performing simultaneous endoscopic procedures with septostomy.

Keywords
- neuroendoscopy
- hydrocephalus
- Foramen of Monro
- septum pellucidum

Resumo

Objetivo O objetivo foi apresentar a experiência inicial com septostomia endoscópica em um hospital público brasileiro.

received
July 4, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1793955.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Métodos Uma análise retrospectiva foi conduzida em pacientes submetidos à septostomia neuroendoscópica no Departamento de Neurocirurgia do Hospital Cristo Redentor em Porto Alegre, de 2015 a 2021.

Resultados No período analisado, 14 pacientes foram submetidos à septostomia endoscópica. A média de idade dos pacientes foi de 41,86 anos; 11 eram do sexo masculino e 3 do sexo feminino. As etiologias da hidrocefalia incluíram condições inflamatórias ventriculares, neoplasias, neurocisticercose e cistos intraventriculares. Após a septostomia, 64% dos pacientes apresentaram melhora clínica e radiológica. Complicações ocorreram em 29% dos casos, incluindo hemorragia intraventricular e contusão talâmica. Quatro óbitos foram observados, todos relacionados a complicações clínicas ou à progressão da doença subjacente.

Conclusão A septostomia endoscópica é um procedimento eficaz e seguro para o tratamento da hidrocefalia complexa de diferentes etiologias. Os resultados cirúrgicos estão relacionados à curva de aprendizado com a neuroendoscopia, e os benefícios para os pacientes são evidentes, considerando a possibilidade de realizar procedimentos endoscópicos simultâneos com a septostomia de maneira segura e eficaz.

Palavras-chave
- neuroendoscopia
- hidrocefalia
- Forame de Monro
- septo pelúcido

Introduction

Complex Hydrocephalus promoting mono or biventricular hydrocephalus is usually caused by obstruction, congenital or acquired, from one or both foramen of Monro. Tumors, vascular malformations, infections, and inflammatory diseases are acquired pathologies associated with this form of hydrocephalus.[1–5] The spread of neuroendoscopy in the last decades has allowed its use as an alternative to shunt in treating obstructive hydrocephalus of different etiologies.[6–12]

Endoscopic septostomy (ES) allows for bypass a monolateral obstruction of the foramen of Monro creating a cerebrospinal fluid (CSF) circulation between the obstructed ventricle and the opposite, communicating with the third ventricle by the normal foramen of Monro.[13] It could also be proposed in case of bilateral obstruction of the foramen of Monro when followed by foraminoplasty or a ventriculoperitoneal shunt (VPS).[14]

In this study, we aim to present our initial experience with endoscopic septostomy in a Brazilian public hospital.

Methods

Patients Review

A retrospective analysis was conducted on patients who underwent neuroendoscopic septostomy at the Department of Neurosurgery of Cristo Redentor Hospital in Porto Alegre from 2015 to 2021. Fourteen patients who underwent endoscopic septostomy procedures were included in the study. The medical records of these patients were retrospectively analyzed to collect the following data: age, sex, etiology of hydrocephalus, radiological findings, previous shunt history, simultaneous endoscopic procedures, clinical and radiological improvements, postoperative complications, and reoperations.

Patients presenting with clinical symptoms such as headache and/or altered state of consciousness, along with imaging findings indicative of mono or biventricular hydrocephalus, were selected for the procedure. Simultaneous procedures performed alongside endoscopic septostomy included monroplasty, endoscopic third ventriculostomy (ETV), tumoral biopsy, removal of previously implanted ventricular catheters, and opening of intraventricular cysts.

Endoscopic Septostomy Technique

Various techniques have been described for performing septostomy to treat univentricular hydrocephalus. The most commonly used approach for accessing the lateral ventricle is through coronal trepanation in the mid-pupillary line.[13] Alternatively, lateral access about the Kocher point can be utilized, allowing for a more perpendicular trajectory about the septum pellucidum (SP), thereby facilitating visualization of midline structures.[5,15,16] When accessing the frontal horn, it can be done through both normal and incarcerated ventricles, although caution must be exercised to avoid inadvertent injury to the contralateral ventricle wall during procedures conducted through incarcerated ventricles.[16]

The identification of avascular areas of the septum pellucidum is essential for successful fenestration. The ideal point for fenestration via frontal access is described as 1.0 cm superior and 2.0 cm anterior to the superior margin of the foramen of Monro.[15,16] Some authors describe the ideal location generically as the region above and before the Monro foramen.[14,16] According to Vinas et al.,[13] there are only 2 to 3 vascular areas susceptible to the procedure, with the ideal area often found in the frontal segment limited by the inferior septal vein, frontal horn floor, and corpus callosum. This area is often transparent and allows, through translucency, a view of the other ventricle. However, other

authors argue that there is no specific area for fenestration.[17] The anatomical individuality must be respected, looking for the best area according to the instant analysis.

Incisions in the septum close to the fornix and corpus callosum increase the risk of damaging structures and may not create effective communication between the ventricles. Fenestrations placed more posteriorly are associated with a higher risk of failure or complications.[17]

The occipital horn of the normal lateral ventricle can also be accessed through occipital trepanation, allowing fenestration of the septum pellucidum and establishing communication with the incarcerated ventricle.[15,18]

Regarding the ideal size of the perforation, there is no defined consensus. Descriptions range from 7 mm to 1.5 to 2.0 cm.[15,18] Schroeder et al. describe the ideal size as 1 cm in diameter, especially in thick septa where the chances of closing the stoma are higher.[19]

Details of The Septostomy Performed

Following general anesthesia and proper positioning, the surgery is performed based on radiological exams. In most of our cases, a more lateral burr hole than the standard Kocher's point was utilized to achieve a more perpendicular angle to the SP.[5,15,16,20]

When performing ESP alongside ETV or Biopsy, the trajectory is planned according to MRI findings. Neuronavigation was not available in our institution; therefore, all approaches were performed using the largest ventricle available. After ventriculoscopy and identification of anatomical landmarks, openings are made in the septum pellucidum in the avascular area at the level of foramen de monro.[14,16,20]

The chosen area of the SP is coagulated using a monopolar to create a small opening, (►**Fig. 2B**) followed by the careful introduction of a Fogarty catheter to complete the ostomy after it is filled (►**Fig. 2C**). Visualization of anatomical structures of the contralateral lateral ventricle is considered essential to ensure the adequacy of the opening (►**Fig. 2D**).

Results

Between 2015 and 2021, 14 endoscopic septostomy procedures were performed at our institution. The mean age of the patients was 41.86 years (median 1.9 years, range 1 week to 18 years); 11 were male and 3 were female.

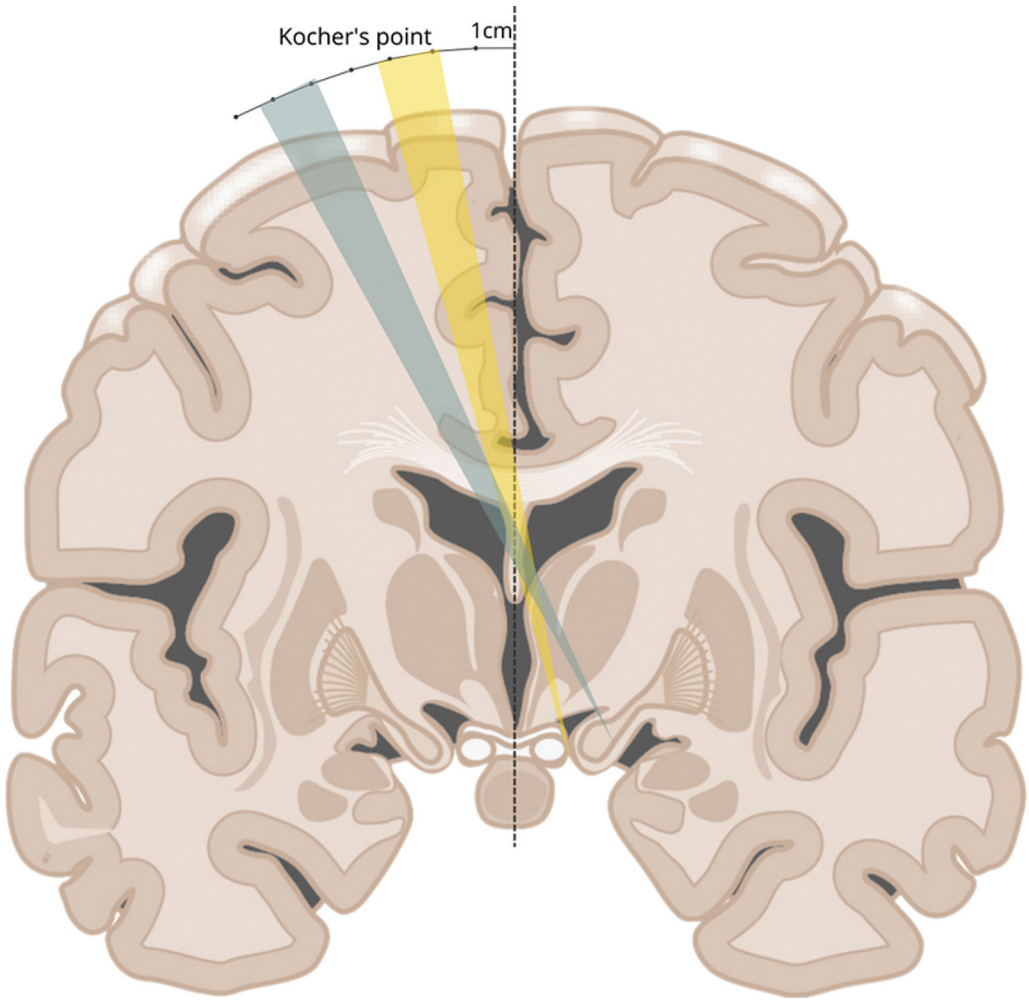

Fig. 1 Illustration of the surgical approach. Trepanation 2 cm lateral to Kocher's point (blue triangle). Image modified from "Slagter - Drawing Coronal section of the brain - no labels" by Ron Slagter, license: CC BY-NC-SA.[21]

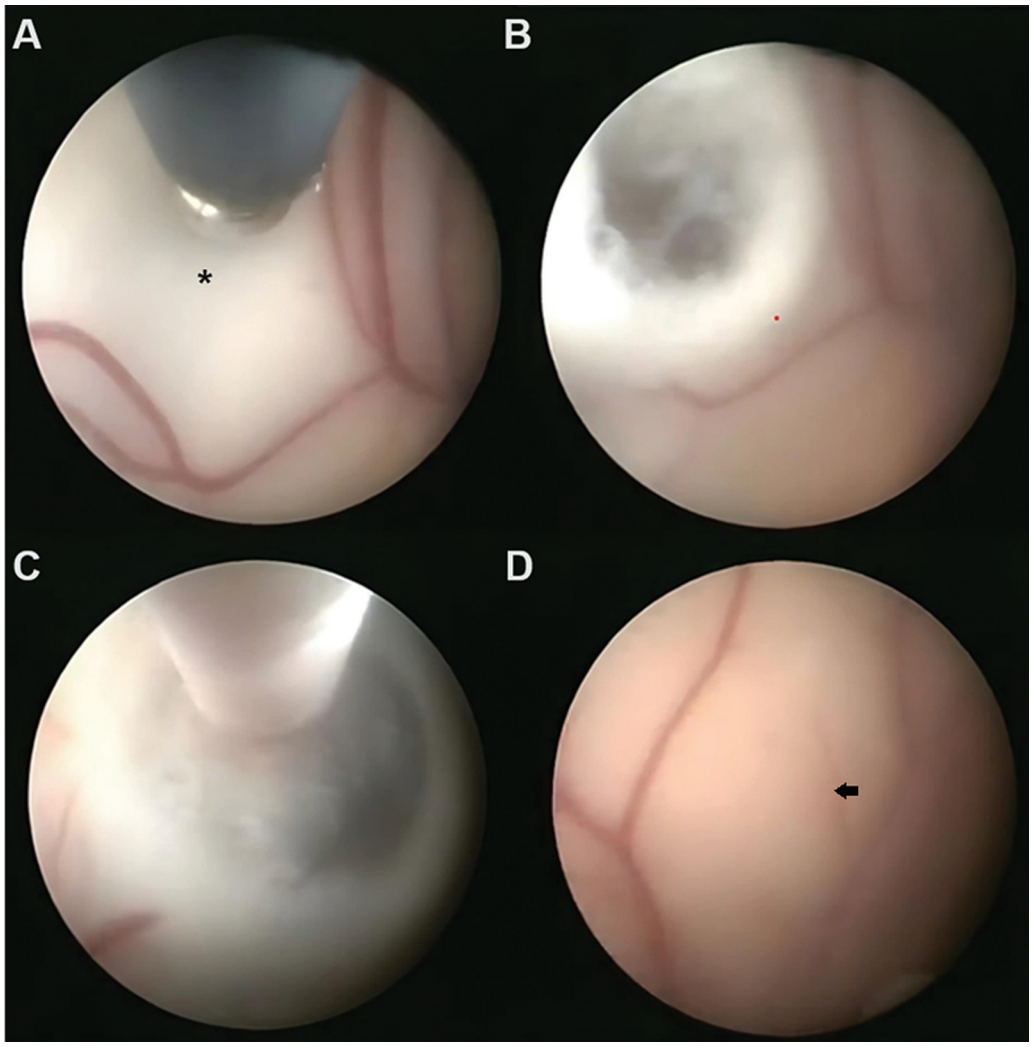

Fig. 2 Neuroendoscopic view of septostomy with anatomic landmarks. **A.** Septum pellucidum (black asterisk) **B.** Opening of the septum pellucidum **C.** Introduction of the Fogarty catheter and completion of the ostomy **D.** View of the lateral wall of the contralateral ventricle (black arrow).

Regarding the type of hydrocephalus, we found 8 patients (57%) with bilateral obstruction and 6 patients (43%) with unilateral obstruction (isolated ventricular hydrocephalus) (►**Table 1**).

The etiologies of hydrocephalus found were related to ventricular inflammatory conditions (7 cases), neoplasms (4 cases), neurocysticercosis (2 cases), and intraventricular cyst (1 case) (►**Table 1**) (►**Figs. 3** and **4**).

Altered consciousness (8 of 14 cases, 57%) was the most common symptom, ranging from confusion, drowsiness/lethargy, to coma, followed by headache found in 6 of 14 cases (42%) (►**Table 2**).

Surgical Results and Complications

Overall, right after septostomy, 9 patients (64%) exhibited patent septostomy with clinical and radiological improvements. One patient with unilateral hydrocephalus initially showed improvement after septostomy. However, after 6 months, they were readmitted with symptoms like those observed before the initial surgery. At that point, it was decided to implant a ventriculoperitoneal shunt.

Related to the previous history of CSF shunting, 3 patients had successful outcomes while 1 patient presented with technical failure.

Nine patients underwent 12 simultaneous procedures in addition to ESP: 4 foraminoplasties, 3 biopsies, 2 removals of ventricular catheters, one ETV, one cyst-ventriculostomy, and one cysticercal removal.

Regarding the type of hydrocephalus, postoperative septostomy patency was observed in 6 patients (42.8%) with bilateral hydrocephalus and 3 patients (21.4%) with unilateral hydrocephalus. In one patient with bilateral hydrocephalus secondary to a tumor, fenestration of the septum pellucidum combined with foraminoplasty allowed for the restoration of physiological CSF circulation, eliminating the need for shunt placement.

Regarding the etiology of hydrocephalus, septostomy patency was observed in 3 patients (42%) from the group of patients with hydrocephalus secondary to inflammatory causes, 4 patients (100%) with brain tumor, 1 patient (50%) with neurocysticercosis, and 1 patient (100%) with ventricular cyst. (Details in ►**Table 1**).

Table 1 Summary of patient's data and results

Patient	Age/Sex	Type of hydrocephalus	Eiology of hydrocephalus	Clinical improvement	Radiological improvement	Previous shunt	Concomitant endoscopic procedure	Complications	Subsequent surgery	Follow up
1	46/M	Unilateral	Post inflammatory	No	No	No	Foraminoplasty	No	No	2 months (death)
2	52/M	Bilateral	Tumor	Yes	Yes	No	Biopsy	No	No	3 months (death)
3	57/M	Bilateral	Tumor	Yes	Yes	No	Foraminoplasty and biopsy	No	No	1 month (death)
4	69/F	Bilateral	Tumor	Yes	Yes	No	Biopsy	No	VPS	3 years
5	71/M	Unilateral	Post inflammatory	Yes	Yes	Yes	No	Minor thalamic contusion	VPS (after 6 months)	2 years
6	13/M	Unilateral	Intraventricular cyst	Yes	Yes	No	Cyst fenestration	No	No	3 years
7	45/M	Bilateral	Post inflammatory	Yes	Yes	Yes	ETV/ventricular catheter removal	Intraventricular hemorrhage	VPS	4 years
8	49/M	Bilateral	Tumor	Yes	Yes	No	Biopsy	No	VPS	2 years (death)
9	42/M	Unilateral	Post inflammatory	No	No	No	Monroplasty	Insufficient septostomy	VPS	2 months (death)
10	2 months/M	Unilateral	Post inflammatory	No	No	No	No	No	No	6 months
11	44/M	Unilateral	Neurocysticercosis	Yes	Yes	No	No	No	No	3 years
12	21/F	Bilateral	Post inflammatory	No	No	Yes	Ventricular catheter removal	Intraventricular hemorrhage	VPS	6 months
13	42/M	Bilateral	Post inflammatory	Yes	Yes	Yes	No	No	VPS	3 years
14	35/F	Bilateral	Neurocysticercosis	No	No	No	Foraminoplasty/ cysticercal removal	No	VPS	6 years

Abbreviations: ETV, endoscopic third ventriculostomy; VPS, ventriculo-peritoneal shunt.

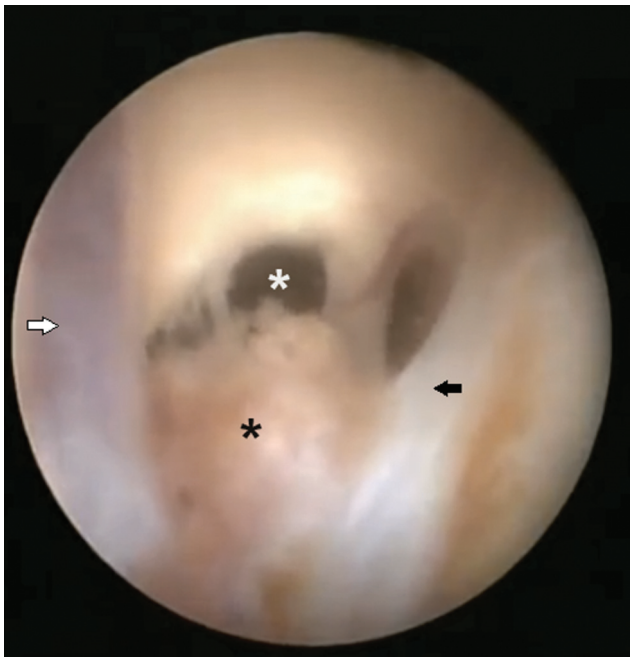

Fig. 3 Obstruction of the foramen of Monro due to inflammatory etiology. Foramen of Monro partially obstructed (white asterisk), choroid plexus (black asterisk), septal vein (white arrow), and thalamostriate vein (black arrow).

Out of 14 patients, 4 (29%) experienced complications. Two patients with post-inflammatory hydrocephalus and a history of previous shunt surgery presented with intraventricular hemorrhage during maneuvers to remove the previous ventricular catheter. In both cases, lavage was performed with saline solution, and an external ventricular shunt catheter was utilized postoperatively. Both patients showed good outcomes and were promptly referred for placement of a ventriculoperitoneal shunt.

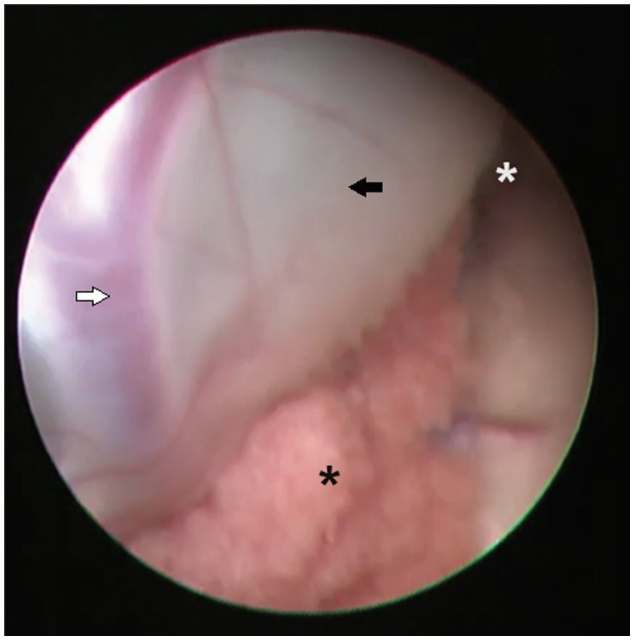

Fig. 4 Foramen of Monro (white asterisk), choroid plexus (black asterisk), septal vein (white arrow), septum pellucidum displaced by tumor (black arrow).

Table 2 Main preoperative symptoms

Symptom	Number of patients (%)
Mental confusion	4 (29)
Drowsiness/torpor	2 (14)
Coma	2 (14)
Headache	6 (43)
Total	14 (100)

A third patient with post-inflammatory hydrocephalus exhibited severe ependymal scarring and thick septum pellucidum. The ostomy opening was insufficient, and the patient was referred early for placement of a ventriculoperitoneal shunt. Another patient suffered minor thalamic contusion presenting satisfactory neurological evolution during the follow-up period.

Four deaths were observed in the postoperative period (between 30 and 90 days). None of these deaths were directly related to the surgical procedure; all were associated with clinical complications or progression of the underlying disease.

The mean follow-up after septostomy was 23.7 months (range 1 month to 6 years).

Discussion

Endoscopic septostomy emerges as a promising alternative for treating hydrocephalus related to obstruction of one or both Monro foramen.[14] The patency of this membrane opening facilitates the restoration of physiological cerebrospinal fluid circulation, potentially reducing the need for shunt placement[13,14] or even obviating its necessity in cases of isolated lateral ventricle hydrocephalus.

In this small series, we present a sample of cases from our initial experience with this technique in a public hospital neurosurgery service. Our success rate achieved with the procedure (64%) is like previous described series.[15]

The etiology of hydrocephalus is described as the main factor related to the success of the procedure.[21] We observed in our series that in the group of patients with brain tumors, the high success rate of septostomy is similar to previous descriptions.[22] On the other hand, we observed a high rate of procedural failure (57%) in the group of patients with post-inflammatory hydrocephalus. According to Aldana et al, in these cases, anatomical distortion making it difficult to identify anatomical structures, as well as scar tissue from the ependyma, may even prevent the procedure from being carried out.[15]

A previous history of ventricular surgeries such as shunts is also described as a greater risk of the septostomy not being effective, though, in the present series, we did not observe this relationship.[15]

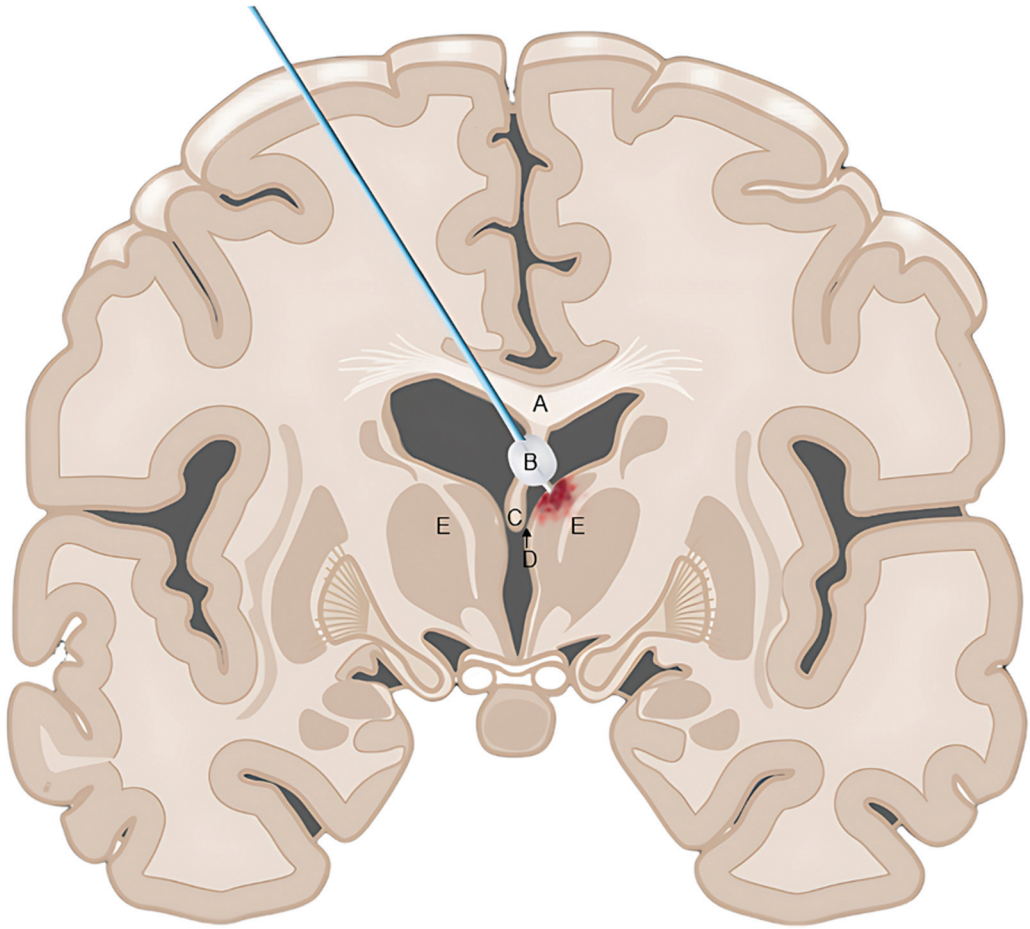

Fig. 5 Illustration of potential brain injury during endoscopic septostomy. When the tip of the fogarty catheter is larger than the distance between the septum pellucidum and the contralateral ventricle wall, it can cause trauma (indicated by the red-shaded area). Corpus callosum (A), fogarty catheter balloon crossing septum pellucidum (B), fornix (C), foramen of Monro (D), and thalamus (E). Image modified from "Slagter - Drawing Coronal section of the brain - no labels" by Ron Slagter, license: CC BY-NC-SA.[21]

Contemporary ventricular neuroendoscopy permits the performance of multiple additional procedures alongside septostomy. In our series, 9 patients (64%) underwent additional endoscopic procedures concomitant with septostomy. The relevance of neuroendoscopy in the current management of hydrocephalus of different etiologies is emphasized.[23] Although endoscopic septostomy is a simple and effective procedure, it is not without its share of complications.[20] Our complication rate (29%) is consistent with previous reports.[24]

Neuroendoscopy allows the surgeon to safely remove previously implanted ventricular catheters that have been left in the ventricular system.[25]

In two patients, during coagulation maneuvers of the choroid plexus, adhered to the tip of the ventricular catheter, a small intraventricular hemorrhage was observed and controlled after continuous irrigation and compression of saline solution for a few minutes. In the end, the removal of the catheter was successfully performed.

Performing a septostomy in patients with post-inflammatory complex hydrocephalus can also be a challenging procedure considering the thickness of the septum pellucidum and the possibility of multiple membranes or layers adjacent to it.[26] In a patient with post-inflammatory hydrocephalus, we observed this condition. The poor outcome of the procedure in this case was related to this finding.

The prevention of complications necessitates a detailed preoperative analysis of imaging examinations. In a patient with unilateral hydrocephalus, we observed a small traumatic lesion in the contralateral thalamus related to the introduction of the fogarty catheter into the opening made in the septum pellucidum.

When using the large ventricle to perform ESP, we must evaluate in imaging tests whether the tip of the fogarty catheter is larger than the distance between the septum pellucidum and the wall of the contralateral ventricle. In our opinion when it happens the use of fogarty should be avoided, and the opening of the septum pellucidum should be widened with the monopolar coagulator in a safe way (►**Fig. 5**).

Conclusion

Endoscopic septostomy is an effective and safe procedure in the treatment of complex hydrocephalus of different etiologies. Our surgical results are related to our learning curve

with neuroendoscopy. The benefit for patients is evident considering the possibility of carrying out endoscopic procedures simultaneously with septostomy in a safe and effective way.

Conflict of Interests

The authors have no conflict of interest to declare.

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Comparison of Premature Ejaculation in Men with Focal Epilepsy and Generalized Tonic-Clonic Epilepsy

Comparação da ejaculação precoce em homens com Epilepsia Focal e Epilepsia Tônico-Clônica Generalizada

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Arq Bras Neurocir 2024;43(4):e245–e250.

Abstract

Introduction premature ejaculation (PE) is one of the most common sexual disorders in men.

Objectives Considering the importance of sexual health in men, especially patients with epilepsy, this study was conducted with the aim of comparing premature ejaculation in men with focal epilepsy and generalized tonic-clonic seizure (GTCS).

Methods In this cross-sectional and observational study, patients with epilepsy were included in the study. The examined patients were examined by psychiatrists and neurologists, and sampling was done according to the entry and exit criteria. The total sample size was 200 people, including 100 patients with focal epilepsy and 100 patients with GTCS. The tools used included demographic profile form, Men Sexual Health Questionnaire (MSHQ), Sexual Quality of Life-Men (SQOL-M), and Premature Ejaculation Diagnostic Tool (PEDT). The study was conducted to include patients referred to specialized clinics and hospitals and who had the necessary conditions to participate in the study. Considering that all the patients were male, the questioning was done by a male researcher. Then, the extracted data were entered into SPSS statistical software.

Results Result showed, the M(SD) age of the patients in the focal epilepsy group was equal to 30.18(3.85). M(SD) score of MSHQ tool was equal to 51.81 (11.98), SQOL-M tool was equal to 34.75 (9.36) and PEDT tool was equal to 8.63 (4.79). In this study, although the M(SD) of the PE score in the focal epilepsy group was reported to be 9.17 (4.49) higher than that of the GTCS group with a rate of 8.09 (5.04), but this difference was not significant. also, the findings showed that there was a significant relationship between the status of the PEDT score, the status of the SQOL-M score, and the MSH

Keywords
- Premature Ejaculation
- Focal Epilepsy
- Epilepsy

received
July 2, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1796654.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

score ($p < 0.05$). MSHQ score and SQOL-M score were reported to be lower in patients with PE disorder.

Conclusion According to the findings, the prevalence of sexual disorders including PE in both groups of patients with epilepsy is significant. For this reason, it is necessary to carry out pharmacological and non-pharmacological interventions to reduce the rate of PE in these patients.

Resumo

Introdução A ejaculação precoce (EP) é um dos distúrbios sexuais mais comuns em homens.

Objetivos Considerando a importância da saúde sexual em homens especialmente pacientes com epilepsia este estudo foi conduzido visando comparar a ejaculação precoce em homens com epilepsia focal e crise tônico-clônica generalizada (CTCG).

Métodos Neste estudo transversal e observacional pacientes com epilepsia foram incluídos no estudo. Os pacientes examinados foram examinados por psiquiatras e neurologistas e a amostragem foi feita conforme os critérios de entrada e saída. O tamanho total da amostra foi de 200 pessoas incluindo 100 pacientes com epilepsia focal e 100 pacientes com CTCG. As ferramentas utilizadas incluíram formulário de perfil demográfico Questionário de Saúde Sexual Masculina (MSHQ) Qualidade de Vida Sexual-Masculina (SQOL-M) e Ferramenta de Diagnóstico de Ejaculação Precoce (PEDT). O estudo foi conduzido de forma a incluir os pacientes encaminhados para clínicas e hospitais especializados e que tivessem as condições necessárias para participar do estudo. Considerando que todos os pacientes eram do sexo masculino o questionamento foi feito por um pesquisador do sexo masculino. Em seguida os dados extraídos foram inseridos no software estatístico SPSS.

Resultados Os resultados mostraram que a idade M(DP) dos pacientes no grupo de epilepsia focal foi igual a 30.18 (3.85). A pontuação M(DP) da ferramenta MSHQ foi igual a 51.81 (11.98)a ferramenta SQOL-M foi igual a 34.75 (9.36) e a ferramenta PEDT foi igual a 8.63 (4.79). Neste estudo embora a M(DP) da pontuação PE no grupo de epilepsia focal tenha sido relatada como 9.17 (4.49) maior do que a do grupo GTCS com uma taxa de 8.09 (5.04) mas essa diferença não foi significativa. Além disso os resultados mostraram que houve uma relação significativa entre o *status* da pontuação PEDT o status da pontuação SQOL-M e a pontuação MSH ($p < 0.05$). A pontuação MSHQ e a pontuação SQOL-M foram relatadas como sendo menores em pacientes com transtorno de EP.

Conclusão Segundo as descobertas a prevalência de transtornos sexuais incluindo EP em ambos os grupos de pacientes com epilepsia é significativa. Por esse motivo é necessário realizar intervenções farmacológicas e não farmacológicas para reduzir a taxa de EP nesses pacientes.

Palavras-chave
- Ejaculação Precoce
- Epilepsia Focal
- Epilepsia

Introduction

In men, there are different types of sexual disorders including libido disorder, erectile dysfunction (ED), and ejaculation disorder. Premature ejaculation (PE) is one of the most common sexual disorders in men.[1] Due to the existence of different definitions for the diagnosis of PE, for this reason, its prevalence has been reported differently in different studies. PE has many negative effects on the quality of sexual life of a person and his sexual partners and has reduced their mental health. Also, if PE is associated with ED disorder, the patient's depression worsens.[2,3]

There are different definitions for PE. If the time interval from penetration to ejaculation is short and ejaculation occurs before or shortly after penetration, it is defined as premature ejaculation. On the other hand, in some sources, if ejaculation occurs less than one minute from the beginning of intercourse, it is considered premature ejaculation, and in some other definitions, time less than two minutes is considered abnormal and premature. Also, in premature ejaculation, a man intermittently or permanently reaches orgasm before the desired time and ejaculation occurs.[4–6]

PE is divided into two categories. One of the types related to those men who are physiologically prone to rapid peak sexual pleasure due to the shorter time of neural latency. In the second type, some cases are conditioned by psychological or behavioral causes and suffer from premature ejaculation.[7]

In the diagnosis of PE, the doctor should consider the age, the novelty of the sexual partner, the frequency and duration of intercourse, which affect the duration of stimulation.[8,9] The basis of PE diagnosis is based on taking a history from the patient or the person's sexual partner, and it has even been shown that if the doctor wants to measure the ejaculation time in his clinic, this time is normal or more than the time indicated by the person. Has done, is, for this reason, its routine evaluation is not suggested, and it is only based on the time mentioned by Fer himself or his wife.[10,11]

The causes of male sexual dysfunction may be due to physical, mental or a combination of these two causes. The physical causes of sexual disorders include chronic diseases including diabetes, tumors of the reproductive system, blood pressure, urinary infections, and nerve and organ surgeries. From mental problems, it is possible to mention psychiatric disorders including the use of psychoactive drugs, anxiety, depression, etc.[1,12,13]

Diseases related to the brain and nervous system are a group of diseases that have a high prevalence and leave many side effects for the patient.[14–16] Epilepsy is one of the diseases of the brain and nervous system, which can affect the sexual function of the patient.[17,18] The studies conducted in the field of sexual problems of patients with epilepsy are limited and few studies have addressed this issue. However, according to the studies, the status of sexual problems in patients with epilepsy has been reported to be higher than in other patients.[19–21] In patients with epilepsy, spermatozoa concentration and seminal fluid have a lower volume and concentration, and this factor has been effective in the lack of sexual satisfaction in these patients.[22]

Aim

Considering the importance of sexual health in men, especially patients with epilepsy, this study was conducted to compare premature ejaculation in men with focal epilepsy and generalized tonic-clonic seizure (GTCS).

Methods

In this cross-sectional and observational study, patients with epilepsy were included in the study. The examined patients were examined by psychiatrists and neurologists, and sampling was done according to the entry and exit criteria. The total sample size was 200 people, including 100 patients with focal epilepsy and 100 patients with GTCS.

The inclusion criteria included the patient being between the ages of 18 and 40, male gender, married and having sex for at least 6 months, informed consent to participate in the study, and suffering from epilepsy according to the doctor's opinion. Patients who, in addition to epilepsy, suffered from other diseases such as mental retardation, had a history of sexually diagnosed diseases, or had a history of drug use, were excluded from the study.

The tools used included a demographic profile form, Men Sexual Health Questionnaire (MSHQ), Sexual Quality of Life-Men (SQOL-M) and Premature Ejaculation Diagnostic Tool (PEDT).

Demographic Information Form

It included questions about age, patient's and spouse's education, history of smoking, history of exercising, and number of children.

Men Sexual Health Questionnaire (MSHQ)

This tool includes 3 dimensions of erection, ejaculation, and satisfaction. The items of the instrument have a response range from zero to five, and higher scores indicate better sexual performance.[23] The MSHQ instrument has dimensions such as erection, which has 3 questions and the range of scores between 0-15, the state of ejaculation has 7 questions with a range of scores between 0-35, and the state of satisfaction has 6 questions, the range of scores of which is between 0-30.[23,24]

Sexual Quality of Life-Men (SQOL-M)

This tool has 11 questions whose scoring range is from completely agree (score 1) to disagree (score 6), which in total scores are between 11-66, and higher scores indicate a better quality of life.[25,26]

Premature Ejaculation Diagnostic Tool (PEDT)

This tool has 5 domains where the answer to each question is scored on a Likert scale from 0-4 and higher scores indicate higher sexual disorder. If the score obtained from the tool is less than 8, it means no PE, if the score is between 9-10, it means possible PE, and if the score is more than 11, it means PE.[27–29]

The method of conducting the study was in such a way that the patients who were referred to specialized clinics and hospitals and met the conditions for entering the study were included in the study. Considering that all the patients were male, the questioning was done by a male researcher. At first, by obtaining informed written consent from the patients, questioning began, and then the method of conducting the study was explained to the patients. Then, the extracted data were entered into SPSS statistical software while maintaining confidentiality, and data analysis was done with independent t-tests, ANOVA, regression, and descriptive tests.

Result

Result ►**Table 1** showed that the M(SD) age of the patients in the focal epilepsy group was equal to 30.09(3.66), in the GTCS group it was equal to 30.27(4.05) and in all patients, it was equal to 30.18(3.85). Also, 15% of all patients had the experience of doing sports and 15.5% of them had the experience of smoking.

According to ►**Table 2**, the M(SD) score of the MSHQ tool was equal to 51.81 (11.98), the SQOL-M tool was equal to 34.75 (9.36) and the PEDT tool was equal to 8.63 (4.79). In this study, although the M(SD) of the PE score in the focal epilepsy group was reported to be 9.17 (4.49) higher than that of the GTCS group with a rate of 8.09 (5.04), this difference was not significant.

Table 1 Demographic characteristics of patients with epilepsy in the studied groups

Variable		Focal epilepsy	GTCS	Total epilepsy
		N (%)	N (%)	N (%)
Education	High school or below	49(49)	47(47)	96(48)
	University	51(51)	53(53)	104(52)
Economic status	Weak	65(65)	54(54)	119(59.5)
	Moderate	33(33)	40(40)	73(36.5)
	Good and excellent	2(2)	6(6)	8(4)
Children	None	57(57)	64(64)	121(60.5)
	One or more	43(43)	36(26)	79(39.5)
Spouse education	High school or below	38(38)	47(47)	85(42.5)
	University	62(62)	53(53)	115(57.5)
Exercise	Yes	18(18)	12(12)	30(15)
	No	82(82)	88(88)	170(85)
Smoking	Yes	14(14)	17(17)	31(15.5)
	No	86(86)	83(83)	169(84.5)
Age	M(Sd)	30.09(3.66)	30.27(4.05)	30.18(3.85)

Table 2 Status M(SD) score of MSHQ, SQOL-M and PEDT instruments of the patients under study

Variable		Focal epilepsy	GTCS	Total epilepsy	P-Value, F
MSHQ	Erection	6.6(1.71)	6.08(1.27)	6.7(1.5)	0.04, 4.25
	Ejaculation	25.78(4.63)	21.57(6.84)	23.67(6.19)	0.000, 32.37
	Satisfaction	22.47(7.33)	20.4(7.94)	21.43(7.7)	0.05, 3.67
	MSISQ Total	54.85(10.38)	48.77(12.72)	51.81(11.98)	0.007, 7.48
SQOL-M		36.31(10.62)	33.2(7.66)	34.75(9.36)	0.001, 10.47
PEDT		9.17(4.49)	8.09(5.04)	8.63(4.79)	0.76, 0.09

The findings showed that there was a significant relationship between the status of the PEDT score, the status of the SQOL-M score, and the MSH score ($p < 0.05$). MSHQ score and SQOL-M score were reported to be lower in patients with PE disorder (►**Table 3**).

Results showed, 29.5% of patients were in Definitive PE status, 8.5% of patients were in Possible PE status, and 62% were in No PE status (►**Table 4**).

Discussion

This study aimed to compare premature ejaculation in men with focal epilepsy with GTCS. In various studies, the sexual problems of men and women in patients with epilepsy have been investigated. The results of this study will be compared with the results of other studies in several sections (general population, patients with epilepsy inside Iran and outside Iran) as follows:

In the report of the meta-analysis by Ramezani et al. in Iran, 11 articles with different types of patients including patients with heart problems, diabetes, dialysis, neurological, and other groups were reviewed. According to the findings, the prevalence of erectile dysfunction in men was equal to 56.1%.[30] In the study of Porst et al., the prevalence of PE in the United States was reported as 24%, in Germany as 20.3%, and in Italy as 20%. Also, men with PE have been exposed to other sexual disorders such as erectile dysfunction, sexual aversion, and anorgasmia.[2] Also, in Tang et al.'s study, where men aged 18-70 years were examined, the prevalence of PE in 207 examined men was reported as 46.9%.[31] The results of the aforementioned studies show the prevalence of sexual disorders, which is consistent with the results of this study on the prevalence of PE in patients with epilepsy.

In the study of Nikoobakht et al., 80 male patients between the ages of 22 and 50, who were diagnosed with epilepsy, were included in the study. 42.5% of patients had erectile function disorder and 11.3% of patients had premature ejaculation disorder. Also, the type of seizure and the frequency of epileptic seizures had a significant relationship with the state of erectile function, orgasmic function, and sexual desire.[32] In the study of Mazdeh et al., which examined 35 married patients, it was shown that erectile dysfunction was observed in 48.1% of the patients in the sodium valproate group and 51.9% of the carbamazepine group. It

Table 3 Correlation coefficient matrix of MSHQ, SQOL-M and PEDT

Variable	SQOL-M			PEDT			MSHQ		
	P	R	F	P	R	F	P	R	F
MSHQ	0.000	0.28	17.63				1	1	1
SQOL-M	1	1	1	0.03	- 0.15	4.65			
PEDT				1	1	1	0.000	0.47	58.74

Table 4 Investigation of distribution of frequency (percentage) of PE in examined patients

Variable	Focal epilepsy	GTCS	Total epilepsy
	N (%)	N (%)	N (%)
No PE	55(55)	69(69)	124(62)
Possible PE	12(12)	5(5)	17(8.5)
Definitive PE	33(33)	26(26)	59(29.5)
Total	100(100)	100(100)	200(100)

was also observed that with erectile dysfunction, there were 11 patients with moderate condition, 15 patients with moderate to mild condition, 16 patients with mild condition, and 18 patients without erectile dysfunction.[33] Previous studies have shown the presence of sexual disorders in patients with epilepsy in Iran, which is consistent with the results of this study.

In the group of women with epilepsy, in the study of Mazdeh et al., where 80 married women were included in the study, disorders in the state of Desire equal to 41%, state of arousal equal to 35%, state of lubrication equal to 48% and state of orgasm were reported equal to 41%.[34] The results of the mentioned study are consistent with the results of this study regarding the existence of sexual problems in patients with epilepsy.

Henning et al.'s study, which examined 171 patients with epilepsy, showed that the most common reported problems included erection problems, decreased libido, vaginal dryness, and problems related to orgasm. Also, the prevalence of sexual problems in men was equal to 63.3%, and in women was equal to 75.3%. The problems reported in men include sexual dysfunction with a rate of 63.3%, late ejaculation with a rate of 5.6%, reduced sexual desire with a rate of 25.6%, feeling sexually deviant with a rate of 5.6%, problems with orgasm with a rate of 13.3%, and premature ejaculation with a rate of 15.6%. It was reported.[35]

Also, in the study of Calabrò et al., in the group of 30 men with epilepsy (aged 20 to 53 years), it was shown that the rate of Retarded ejaculation equals 3.8%, the rate of Erectile dysfunction equals 3.3%, the rate of Premature ejaculation equals 6.7%, the rate of Hyperactive desire equal to 1.7%, hypoactive desire equal to 8.3% and the number of patients who reported no sexual disorders was reported equal to 21.7%.[36] Also, in another study conducted by Sureka et al., it was shown that sexual dysfunction was reported in 66% of patients. Reported sexual dysfunction included Erectile dysfunction with a rate of 36%, Hypoactive sexual desire equal to 4 hundred percent (0.04%), Premature Ejaculation equal to 26%, and the percentage of patients who reported no sexual dysfunction equal to 34%.[37]

Conclusions

According to the findings, the prevalence of sexual disorders including PE in both groups of patients with epilepsy is significant. For this reason, it is necessary to carry out pharmacological and non-pharmacological interventions to reduce the rate of PE in these patients.

Authors' Contribution

SHA, MO, and AD conceived the study, performed data analysis, and wrote the manuscript. SHA, MO, and AD collected data and wrote the manuscript. SHA, MO, and AD interpreted the results and wrote the manuscript. SHA, MO, and AD designed the study, and wrote, and edited the manuscript.

Data Reproducibility

The dataset presented in the study is available on request from the corresponding author during submission or after its publication. The data are not publicly available due to [confidentiality].

Ethical Approval

The current study was conducted after obtaining approval by the Ethics Committee of ilam University of Medical Sciences (IR.MEDILAM.REC.1403.027).
https://ethics.research.ac.ir/ProposalCertificateEn.php?id=463349&Print=true&NoPrintHeader=true&NoPrintFooter=true&NoPrintPageBorder=true&LetterPrint=true

Informed Consent

Informed consent was obtained.

Funding

No funding was received.

Conflict of Interests
No conflict of interest.

Acknowledgments
We thank the ilam University of Medical Sciences.

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Endovascular Treatment of Idiopathic Intracranial Hypertension Secondary to Venous Stenosis

Tratamento endovascular da Hipertensão Intracraniana Idiopática Secundária à Estenose Venosa

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Arq Bras Neurocir 2024;43(4):e251–e257.

Abstract

Introduction Idiopathic intracranial hypertension (IIH) is a condition characterized by signs and symptoms of elevated intracranial pressure (ICP). Although the role of venous sinus stenosis in the pathophysiology of IIH is controversial, venous angioplasty with stenting has been proven to decrease cerebral venous pressure and intracranial pressure. This study aims to identify and quantify the clinical improvement obtained by patients with IIH, refractory to prior pharmacological treatment, undergoing endovascular venous angioplasty in a neuroendovascular reference service.

Methods A retrospective analytical study of 25 cases of IIH with transverse sinus stenosis operated on in a reference service using the endovascular method, in which clinical data from medical records and information about the procedure were analyzed.

Results Of the 25 patients, 22 were women, and the mean age was 42 years. All patients were refractory to prior clinical treatment. At the clinical presentation, all had headaches. There were no complications or failures from the procedures performed. In the 30-day evaluation, there was a significant decrease in all the symptoms reported.

Conclusion Venous sinus stenting is safe and effective in patients with IIH with transverse sinus stenosis refractory to clinical treatment, with substantial symptomatic improvement and good evolution in the postoperative follow-up period.

Keywords
- stenosis
- endovascular
- idiopathic intracranial hypertension

Resumo

Introdução A hipertensão intracraniana idiopática (HII) é uma condição caracterizada por sinais e sintomas de pressão intracraniana elevada (PIC). Embora o papel da estenose dos seios venosos na fisiopatologia da HII seja controverso, a angioplastia venosa com

received
June 5, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1793956.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

colocação de stent tem se mostrado eficaz na redução da pressão venosa cerebral e da pressão intracraniana. Este estudo visa identificar e quantificar a melhoria clínica obtida por pacientes com HII, refratários ao tratamento farmacológico prévio, submetidos à angioplastia venosa endovascular em um serviço de referência neuroendovascular.

Métodos Um estudo analítico retrospectivo de 25 casos de HII com estenose do seio transverso operados em um serviço de referência utilizando o método endovascular, no qual foram analisados dados clínicos dos prontuários médicos e informações sobre o procedimento. Resultados: Dos 25 pacientes, 22 eram mulheres, com idade média de 42 anos. Todos os pacientes eram refratários ao tratamento clínico prévio. Na apresentação clínica, todos tinham cefaleia. Não houve complicações ou falhas nos procedimentos realizados. Na avaliação de 30 dias, houve uma diminuição significativa em todos os sintomas relatados.

Conclusão A colocação de stent nos seios venosos mostrou-se segura e eficaz em pacientes com HII com estenose do seio transverso refratários ao tratamento clínico, com melhoria sintomática substancial e boa evolução no período de acompanhamento pós-operatório.

Palavras-chave
- estenose
- endovascular
- hipertensão intracraniana idiopática

Introduction

Idiopathic intracranial hypertension (IIH), also known as brain pseudotumor, is a condition characterized by signs and symptoms of elevated intracranial pressure (ICP) without an established pathophysiology.[1] It is an uncommon disorder whose worldwide incidence ranges from 1 to 3 cases per 100,000 population per year and can affect both children and adults.[2] This disorder is strongly associated with obesity and affects mainly female patients of childbearing age.[1]

The clinical picture is nonspecific, which leads to late recognition, as well as underdiagnosis. Most patients with IIH have progressive, sometimes migraine-like headaches. Common findings include papilledema, visual blurring, tinnitus, dizziness, and cognitive disturbances.[2]

While the role of venous sinus stenosis in the pathophysiology of IIH is controversial, venous angioplasty with stenting has been shown to decrease cerebral venous pressure and intracranial pressure by improving cerebrospinal fluid (CSF) absorption.[3] Currently available literature provides increasing evidence that this procedure is associated with important symptomatic relief and long-term disease control.[4]

This study aims to identify and quantify the clinical improvement of patients with IIH who are refractory to prior pharmacological treatment and underwent endovascular venous angioplasty in a neuroendovascular reference service. Moreover, the study seeks to develop the epidemiological profile and survey the main comorbidities in patients with IIH, as well as symptoms, prior treatments, stenosis characteristics, materials used in surgery, and surgical success rate and complications.

Methods

Design and Sample

This is a retrospective analysis of 25 cases of IIH with transverse sinus stenosis operated on using the endovascular method in a neurosurgery reference service in Blumenau - SC, Brazil.

Inclusion and Exclusion Factors

Symptomatic individuals diagnosed with IIH according to Dandy's criteria, with transverse sinus stenosis shown on venography and undergoing endovascular stenting between August 2015 and August 2023 were included. Insufficient medical data, such as segment loss and absence of radiological reports, were considered exclusion factors.

Data Analysis

Based on clinical data from medical records, information on the endovascular procedure and radiological findings in the reports, we calculated sums and the percentage of patients who matched each of the variables analyzed in the study. Results concerning symptomatology data were temporally compared to measure the decrease in their absolute values 30 days after the surgical intervention. The analyses were tabulated and calculated using Microsoft Excel 2020®.

Variables

The variables studied were sex, age, prior comorbidities, clinical presentation, prior treatment, location and degree of venous stenosis, diagnostic tests, stent used in the endovascular intervention -Casper® (Microvention™, Schnapper 78100 Saint-Germain-en-Laye France), Precise (Cordis®, 14201 Northwest 60th Avenue Miami Lakes, USA) and Carotid Wall (Boston Scientific™, 300 Boston Scientific Way Marlborough, MA 01752-1234, USA)-, balloons selected for the dilation of the Falcon RX stent (Scitech Medical Products®. Rua 18, Lote 06 Polo Empresarial Goiás, state of Goiás, Brazil), Aviator Plus (Cordis®, 14201 Northwest 60th Avenue Miami Lakes, USA), Viatrac 14 Plus (Abbot®, 100 Abbot Park Road, IL, 60064, USA) and Sterlin (Boston Scientific™, 300 Boston Scientific Way Marlborough, MA 01752-1234, USA), complications and post-procedure evolution.

Procedure

All patients were started on dual antiaggregation therapy with aspirin 200 mg daily and clopidogrel 75 mg, 1 week prior to the procedure. They remained on dual antiaggregation for 3 months and are still on 100 mg of aspirin continuously.

Initially, total sedation and heparinization were performed, with instillation of intra-arterial and intra-venous low osmolarity non-ionic contrast, femoral artery through a guide catheter. Next, cerebral angiographies were performed to establish the location and degree of stenosis, and the venous pressure was measured pre- and post-angioplasty. Using a micro-guide, a stent was inserted that fitted the stenosis level, thus correcting the affected region of the transverse sinus. Then, an Angioplasty Balloon was inflated twice for post-dilatation. Postoperative angiographies showed the correct permeability of the device.

Ethics

The study was conducted according to SPIRIT and approved by the local ethics committee under CAEE 31683520.0.0000. 5370. The Informed Consent Form (ICF) was presented and made available to all individuals who took part in the study.

Results

Of the 25 patients, 22 (88%) were female, and the mean age of the study population was 42 (range, 12-72 years old). Obesity was found in 3 (12%) individuals. All patients were refractory to prior clinical treatment; 12 (48%) had topiramate alone, 4 (16%) had acetazolamide alone, 1 (4%) had only ventriculoperitoneal shunting (VPS); 6 (24%) were on a combination of topiramate and acetazolamide, and 2 (8%) were treated with topiramate and VPS.

At clinical presentation, 21 patients (84%) had papilledema, 1 (4%) had abducent cranial nerve (VI nerve) involvement, 9 (36%) had visual loss, 22 (88%) complained of visual clouding, 5 (20%) had tinnitus, 11 (44%) had nausea and vomiting, 2 (8%) had mental confusion, 3 (12%) had syncope, 13 (52%) had dizziness, 1 (4%) had dysphasia, 2 (8%) had memory loss, and all 25 (100%) complained of headache. As for diagnostic tests, skull MRI was performed in 7 (28%) cases, skull CT scan in 1 (4%), venous angioresonance in 22 (88%), and arteriography in 25 (100%). The mean degree of stenosis of the affected TS was 95%; 6 (24%) patients had bilateral stenosis and 2 (8%) had occlusion of the contralateral TS (►**Table 1**).

The stents used were Casper in 23 (92%) patients, Precise in 1 (4%), and Carotid Wall in 1 (4%). The balloon used was Falcon RX in 16 (64%) cases, Aviator Plus in 5 (20%), Viatrac 14 Plus in 3 (12%) and Sterlin in 1 (4%). Femoral surgical access was chosen in all interventions. No complications or failures were observed in the procedures performed.

In the 30-day evaluation, we found a 78% decrease in papilledema, 44% in visual loss, resolution of 50% of visual clouding symptoms, 60% in tinnitus, 63% in emesis, 84% in dizziness, and a 72% decrease in headache complaints. There was a complete remission of confusion, syncope, and memory loss. The mean opening pressure on lumbar puncture before venoplasty was 27.68 cmH2O, and after venoplasty it was 5.84 cmH20, with a mean decrease of 78.17% from the level found at clinical presentation (►**Table 2**; ►**Figs. 1**–**6**).

Discussion

Previously called "benign intracranial hypertension", which expressed the absence of tumors and frequent clinical remission, this disorder was renamed to portray its association with severe morbidities, such as permanent visual loss.[5] It predominantly affects women, who, according to the figure found in this study (88%), make up about 90% of the population with IIH.[4] The mean age at diagnosis is about 30,[5] an age slightly lower than that found in the study sample (42).

In the literature, there are reports of visual clouding (68%) and pulsatile tinnitus (58%) in patients with IIH. In our sample, the prevalence was 88% and 20%, respectively, showing lesser importance of tinnitus at clinical presentation. Headache is the most common symptom, with a prevalence of 93% according to surveys, routinely characterized as severe daily pulsatile pain. In this study, this symptom was also the most prevalent, found in all (100%) patients. The estimated prevalence of visual loss is 30%, similar to what was observed in this sample (36%). Papilledema is often considered a defining sign of IIH, with an incidence of 95%, also close to the rate found in this study (86%). Abducent nerve palsy is limited to severe cases, seen in 1 of our patients.[4]

IIH pathogenesis is not fully understood. Dural venous sinus occlusion secondary to thrombosis or compressive injury, most commonly in the transverse sinus (TS), is known to lead to increased ICP and IIH. However, primary TS stenosis has been increasingly identified in patients with IIH,[6] with incidences ranging from 30% to 93%[4] compared with 6.8% in the general population.[7] Some consider such alteration to be the underlying cause of IIH, although its possibly being a consequence of refractory disease is still in discussion.[3]

Other contributing factors to its pathophysiology are also considered, such as overweight or obesity and hormonal disorders.[2] Higher increased intra-abdominal and cardiac filling pressures found in obese individuals hinder cerebral venous return, leading to increased ICP.[8] Several epidemiological studies found that 80-90% of IIH patients have some degree of obesity,[9] an estimate that is higher than the value found in this sample, of only 12%.

IIH is a diagnosis of exclusion, usually established based on the modified Dandy criteria, which include elevated ICP ($>$ 25 cm H2O on lumbar puncture, performed in lateral decubitus), with papilledema typically present (not a mandatory criterion, though), and normal neuroimaging and CSF.[5] No individuals in this study had changes in neuroimaging, and all of them had opening pressure on initial lumbar puncture above 25cm of H20, the average being 27.68. There is research work describing a higher mean value, around 40cm of H20,[8,10] but with a smaller patient sample.

Table 1 Characteristics of patients undergoing endovascular therapy for IIH

Variable	Classification	n	Percentage (%)
Sex	Female	22	88%
	Male	3	12%
Age			
	Mean	42	
	Under 40 Over 40	12 13	48% 52%
Prior clinical treatment			
	Topiramate	12	48%
	Acetazolamide	4	16%
	VPS	1	4%
	Acetazolamide + Topiramate	6	24%
	Topiramate + VPS	2	8%
Clinical Presentation			
	Headache	25	100%
	Papilledema	21	84%
	Visual Clouding	22	88%
	Nausea/Vomiting	13	52%
	VIsual loss	11	44%
	Tinnitus	9	36%
	Syncope	5	20%
	Mental confusion	3	12%
	Memory loss	2	8%
	Dysphasia 6th nerve involvement	2 1	4% 4%
30-dayevaluation			
	Papilledema	–	78% decrease
	VIsual loss	–	44% decrease
	Visual Clouding	–	50% decrease
	Headache	–	72% decrease

There are no widely accepted standardized guidelines for treating IIH.[8] The main therapeutic goals are lowering ICP and resolving potential etiologic factors, through which symptomatic relief and vision preservation will be achieved. Weight loss, medication use, serial lumbar punctures, VPS, bariatric surgery, and venous angioplasty are alternatives currently used for this purpose.[11]

The most widely used drug for clinical treatment is acetazolamide, a carbonic anhydrase inhibitor that reduces CSF production in the choroid plexus and, therefore, decreases ICP. Topiramate has similar effects and promotes weight loss.[12] Both drugs have potential side effects that include allergic reactions, fatigue, paresthesia, nausea, vomiting, cognitive impairment, and teratogenicity, which cause a significant percentage of patients to discontinue therapy.[2] The authors of a Cochrane review based on two randomized clinical trials conducted to study the effect of acetazolamide versus placebo were unable to recommend or reject acetazolamide for the treatment of IIH.[13]

Patients who develop rapid progression of visual loss, are clinically refractory, or present with severe acute symptoms require urgent temporary measures such as repeated lumbar puncture, cerebrospinal fluid drainage, or optic nerve sheath fenestration (ONSF). It is known that such management options are not definitive treatments; moreover, these measures are associated with multiple complications such as orbital cellulitis, traumatic optic neuropathy, drain obstruction, subdural hemorrhages, and tonsillar hernia, according to the procedure that is performed.[12]

Based on recent pathophysiological concepts, venous sinus stenting has been widely recommended as a safe method to prevent sequelae and restore CSF drainage.[10] Knowing that venous stenosis and the ensuing elevation of ICP may play a role in IIH etiology, it can be proposed that the

Table 2 Variation from pre- to post-stenting venous pressures

N°	Pre-stenting venous pressure	Post-stenting venous pressure	Decrease (%)
1	50	4	92.0%
2	30	5	83.3%
3	24	6	75.0%
4	24	6	75.0%
5	25	5	80.0%
6	42	7	83.3%
7	32	4	87.5%
8	28	5	82.1%
9	26	6	77.0%
10	24	7	70.8%
11	21	10	52.4%
12	20	4	80.0%
13	16	3	81.2%
14	19	2	89.5%
15	28	12	57.1%
16	55	14	74.5%
17	15	3	80.0%
18	32	4	87.5%
19	23	6	74.0%
20	28	5	82.1%
21	25	6	76.0%
22	22	7	68.1%
23	24	4	83.3%
24	30	5	83.3%
25	29	6	79.3%

most appropriate intervention for a patient with identified venous sinus stenosis is one that acts directly on its hemodynamics, through stenting. Other surgical options, such as ONSF and VPS, decrease CSF pressure; however, they do not act directly on venous sinus hemodynamics and, therefore, may not modulate the underlying cause of the problem. [5]

There are favorable data in the literature on the efficacy of venous sinus stenting. A systematic review and meta-

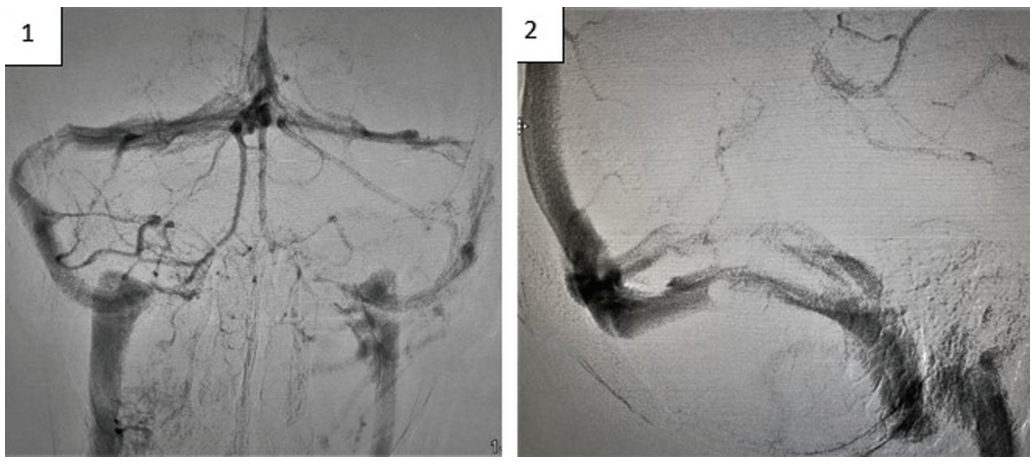

Fig. 1–2 Pre-Stenting exams for evaluation of Stenosis.

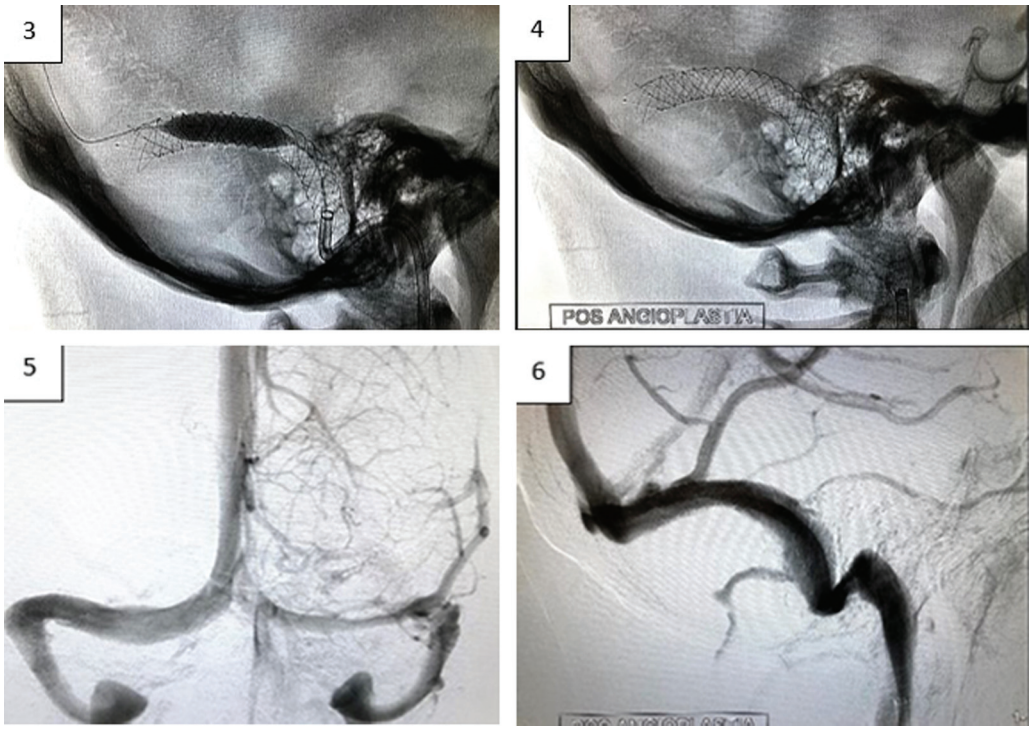

Fig. 3–6 Post-Stenting exams for procedure evaluation.

analysis of data from 473 patients in 24 trials concluded that this procedure is associated with lower ICP, improved symptoms, and low complication rates in patients with refractory IIH and evidence of venous sinus stenosis.[14] Likewise, a systematic review of data from 185 patients who had undergone stenting suggested that this method may be a safe and effective therapeutic option for IIH refractory to clinical treatment.[15,16]

As for the patients in this study, a lower ICP (observed through lower opening pressure on the post-procedure lumbar puncture), as well as a substantial remission of complaints,

were achieved after venous angioplasty with stenting in the transverse sinus in cases already refractory to prior therapeutic attempts. The absence of surgical complications and a favorable evolution after the intervention show that this approach yields promising results, especially in patients unresponsive to medication, with contraindications to their use, or with greater clinical severity.

Conclusion

This study shows that venous sinus stenting is safe and effective in patients with IIH and with transverse sinus stenosis refractory to prior treatment, with significant symptomatic improvement and good evolution during the postoperative follow-up period. Accordingly, the literature has shown that this therapeutic approach achieves good outcomes. However, further studies are needed to provide prospective data and evaluate its long-term clinical outcomes.

Conflict of Interest
None declared.

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Analysis of the Molecular Profile of Melanoma Brain Metastases using Immunohistochemistry

Análise do perfil molecular das metástases cerebrais de melanoma no exame de imuno-histoquímica

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Arq Bras Neurocir 2024;43(4):e258–e261.

Abstract

Brain metastases from melanoma represent an advanced and aggressive form of the disease. Understanding their molecular characteristics is crucial for improving diagnosis, prognosis, and treatment. The main objectives of this study were to identify and characterize molecular alterations present in brain metastases from melanoma and to clinically correlate them. The clinical-epidemiological information was anonymously and retrospectively obtained. Brain metastases from melanoma were collected through surgical biopsies, which were processed and analyzed using immunohistochemical markers. A total of 132 samples were initially selected, resulting in 8 samples of metastatic melanoma in the brain region included in this analysis. Regarding the frequency of immunohistochemical markers in brain samples of melanoma metastasis, 75% showed positive BRAF V600R, 62% contained positive SOX10, 37% positive HMB45, and 25% positive Melan-A. Regarding the location, 4 of them were in the frontal lobe, 3 in the parietal lobe, and 1 in the cerebellum. Among the samples, 87.5% originated from the supratentorial region of the brain, while 12.5% came from the infratentorial region. At the time, half of the patients were under 65 years old, with a significant proportion of 25% of individuals being below 40 years old. Moreover, 87.5% had two or more brain lesions at the time of diagnosis. Among the 12.5% that comprised the single lesion group at the time of analysis, the frontal lobe location

Keywords

- neurosurgery
- brain metastase
- immunohistochemistry

Instituição de realização do trabalho: AC Camargo Cancer Center, São Paulo, São Paulo, Brasil.

received
May 9, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1796655.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

stands out. The findings indicate heterogeneity among tumors and metastases in different anatomical locations. Further investigations are needed to validate these findings and elucidate their clinical applicability.

Resumo

As metástases cerebrais de melanoma representam uma forma avançada e agressiva da doença. Compreender suas características moleculares é crucial para melhorar o diagnóstico, prognóstico e tratamento. Os principais objetivos deste estudo foram identificar e caracterizar as alterações moleculares presentes nas metástases cerebrais de melanoma e correlacioná-las clinicamente. As informações clínico-epidemiológicas foram obtidas anonimamente e retrospectivamente. As metástases cerebrais de melanoma foram coletadas por meio de biópsias cirúrgicas, que foram processadas e analisadas utilizando marcadores imuno-histoquímicos. Um total de 132 amostras foram inicialmente selecionadas, resultando em 8 amostras de melanoma metastático na região cerebral incluídas nesta análise. Em relação à frequência dos marcadores imuno-histoquímicos nas amostras cerebrais de metástase de melanoma, 75% apresentaram BRAF V600R positivo, 62% continham SOX10 positivo, 37% HMB45 positivo e 25% Melan-A positivo. Quanto à localização, 4 delas estavam no lobo frontal, 3 no lobo parietal e 1 no cerebelo. Entre as amostras, 87,5% originaram-se da região supratentorial do cérebro, enquanto 12,5% provinham da região infratentorial. No momento, metade dos pacientes tinha menos de 65 anos, com uma proporção significativa de 25% de indivíduos abaixo de 40 anos. Além disso, 87,5% tinham duas ou mais lesões cerebrais no momento do diagnóstico. Entre os 12,5% que compunham o grupo de lesão única no momento da análise, destaca-se a localização no lobo frontal. Os achados indicam heterogeneidade entre tumores/metástases em diferentes locais anatômicos. Mais investigações são necessárias para validar esses achados e elucidar sua aplicabilidade clínica.

Palavras-chave
- neurocirurgia
- metástases cerebrais
- imuno-histoquímica

Introduction

Melanoma is a type of skin cancer that can spread to other tissues, including the central nervous system. This stage represents an advanced stage of the disease and is associated with an unfavorable prognosis. Understanding the molecular characteristics of brain metastases from melanoma is essential for the diagnosis, treatment, and prognosis of these patients.[1]

The incidence of melanoma is 100,000 new cases per year in the United States alone. Among patients with advanced melanoma, approximately 50% develop brain metastases, resulting in significant morbidity and mortality. Local therapy, including surgery and radiation, has historically resulted in an overall survival of 4 to 6 months for patients with melanoma brain metastases.[2]

Until now, primary melanomas have been extensively studied; in contrast, the biology of melanoma brain metastasis remains poorly understood. There is increasing evidence of the emergence of metastatic tumor clones in the central nervous system distinct from the primary site throughout tumor progression. This tumoral heterogeneity occurs in more than 50% of cases and may drive the development of metastatic disease as well as resistance to cancer therapy.[3]

Immunohistochemistry is a widely used technique in the molecular characterization of different types of cancer. It involves the detection of specific proteins in tissue samples using antibodies that bind to these proteins of interest. This technique provides information about the molecular profile of the sample and aids in the identification of potential therapeutic targets.[4,5]

Understanding the molecular alterations present in these lesions can provide insights into tumor biology, enabling the identification of specific molecular markers and the development of more targeted therapeutic strategies.[6]

In this context, this research aimed to investigate the molecular profile of melanoma brain metastases through immunohistochemistry examination, aiming to identify the expressions of key proteins involved in melanoma brain metastases, as well as to identify the age, location, and number of lesions in the collected samples, allowing for the acquisition of relevant information for patient stratification and selection of targeted therapies.

Methods

A retrospective observational study was conducted through the review of anonymous databases of patients from AC Camargo Cancer Center diagnosed with

Sample	Age	Localization	2 or more lesions	Positive markers
16024821	46	left front	yes	BRAF V600E
96015659	78	left front	yes	BRAF V600E SOX10 Melan A HMB45
14889910	65	right parietal	yes	S100 HMB45 Melan A
14793550	39	right parietal	yes	BRAF V600E SOX10
14834070	65	right front	no	BRAF 600? SOX10
16029252	59	left parietal	yes	BRAF V600E SOX10
16027675	75	right front	yes	BRAF V600E – HMB45 S100
13960510	38	cerebellum	yes	BRAF V600E SOX10

Fig. 1 Characteristics of melanoma brain metastasis samples.

metastatic brain tumors with a primary focus on melanoma who underwent biopsy or surgery followed by immunohistochemistry examination from March 2022 to November 2023, aiming to collect clinical and histopathological data. The anonymous database was analyzed, and the data were collected in an academic environment from September to October 2023. All data are confidential, and no participant names or any other form of identification are exposed.

The present study will analyze the markers BRAF V600E, SOX 10, HMB45, and Melan-A. These are the most common alterations observed among metastatic melanoma samples in previous studies in the field. As the study is retrospective, the listed markers are already specified in the issued reports, and no new tests or samples will be manipulated or conducted from the present date. The pathology medical professional will have already been designated at the time of the report when the individual was under treatment. Only the data from the tests conducted during the period will be collected and analyzed.

The inclusion criteria used were samples from participants aged 18 years or older, admitted to the AC Camargo Cancer Center with a diagnosis of metastatic brain tumor with a primary focus of melanoma, subjected to biopsy or surgery, followed by immunohistochemical examination. As exclusion criteria, results from non-melanoma brain metastases, participants outside the age range, and/or those without the immunohistochemical examination were used.

Results

A total of 132 samples of melanoma metastases were initially selected, resulting in 8 samples of metastatic melanoma in the cerebral location that were included in this analysis. Age, location, number of brain lesions, and the markers present in the immunohistochemical sample were collected (►**Fig. 1**).

Regarding the location, 4 of them were in the frontal lobe, 3 in the parietal lobe, and 1 in the cerebellum. Among the samples, 87.5% originated from the supratentorial region of the brain, while 12.5% came from the infratentorial region.

Regarding the age of the individuals at the time of sample collection for analysis, half of them were below 65 years old, with a notable 25% of individuals falling below the age range of 40 years old.

Regarding the number of lesions observed on imaging exams at the time of diagnosis, 87.5% had one or more brain lesions. Among the 12.5% that comprised the single lesion group at the time of analysis, the location in the frontal lobe stands out.

The frequency of immunohistochemistry markers (►**Fig. 2**) in samples of brain metastatic melanoma tumors showed 75% tested positive for BRAF V600R, 62% for SOX10, 37% for HMB45, and 25% for Melan-A.

Discussion

Brain metastases result in significant mortality and morbidity for patients with advanced melanoma. A better understanding of the biology of melanoma brain metastases remains an

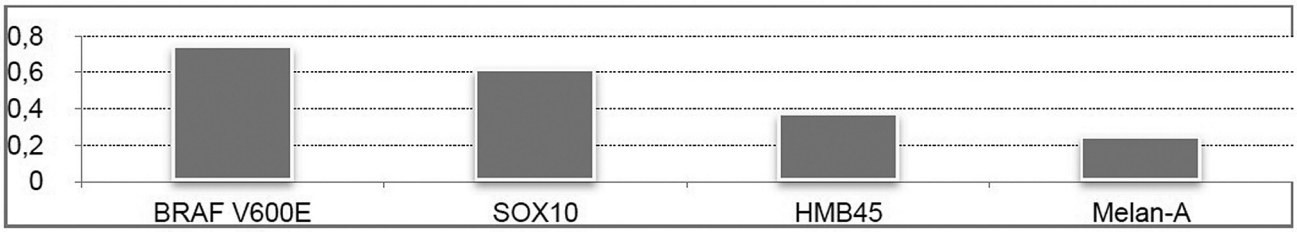

Fig. 2 Frequency of immunohistochemistry markers in brain metastasis samples.

unmet need. The age of the individual at the time of tissue sample collection, with 25% of them falling below the age of 40, highlights a progressive decrease in the average age at the time of cancer diagnosis, currently standing at 62 years.[7]

The location of brain metastases predominantly occurs in the supratentorial region of the brain, consistent with recent studies on the subject. The BRAF V600E marker was the most prevalent in the analyzed samples, similar to what has been described in the literature.

It is important to highlight the limitations of this study. Clinical data were retrieved from medical records through a retrospective analysis over time, so information on the progression and identification of the primary focus of melanoma in some cases was not found, and the diagnosis was defined through tissue analysis of the brain metastasis after surgery.

Conclusion

The retrospective analysis of tissue samples from metastatic melanoma tumors in the brain through immunohistochemistry demonstrated that the most prevalent markers present were BRAF V600E, SOX10, HMB45, and Melan-A. The preferred anatomical location of the lesions was the supratentorial region of the brain, more specifically in the frontal lobe. Our findings corroborate the existence of heterogeneity among tumors/metastases in different anatomical locations. Further investigations are needed to validate these findings and elucidate their clinical applicability.

Disclosures
The author declares that no relevant or material financial interests relate to the research described in this paper.

Conflict of Interest
The author declares no conflict of interest.

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Systematizing an Expanded Lumbar Interlaminar Endoscopic Approach: The 10 Steps of Castro-Brock for Increased Security

Sistematizando uma abordagem endoscópica interlaminar lombar expandida: Os 10 passos de Castro-Brock para maior segurança

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Arq Bras Neurocir 2024;43(4):e262–e268.

Abstract

Introduction With increasing life expectancy, there is a rising incidence of degenerative spinal pathologies, particularly in the elderly population. Minimally invasive techniques are becoming increasingly attractive due to the higher prevalence of comorbidities in older patients. Endoscopic spine surgery offers advantages such as early rehabilitation, reduced postoperative pain, minimized muscle damage, and shorter hospital stays.

Objectives To enhance the safety of the interlaminar approach and minimize complications, we propose the systematic application of an expanded interlaminar technique, termed the "Castro-Brock technique." Direct visualization of accurate anatomy is emphasized for successful endoscopic navigation.

Methods The Castro-Brock technique is described in a step-by-step manner, comprising 10 steps with illustrative images. The technique involves an initial puncture on the upper lamina, identification of bony structures, drilling and enlarging the interlaminar bone window, en bloc flavectomy, and precise identification of the descending root before accessing the disc.

Results The Castro-Brock technique facilitates improved visualization of anatomy and provides decompression of neurological structures before disc access. This systematic approach reduces the risk of inadvertent neurological injury and other surgical complications associated with interlaminar access.

Conclusions The Castro-Brock technique represents a valuable addition to the armamentarium of lumbar endoscopic spine surgery. Ensuring meticulous anatomical visualization and pre-disc decompression of neural structures enhances surgical safety and optimizes patient outcomes.

Keywords
- endoscopic spine surgery
- interlaminas approach
- minimally invasive

received
April 25, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1796658.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Introdução Com o aumento da expectativa de vida há uma incidência crescente de patologias degenerativas da coluna particularmente na população idosa. Técnicas minimamente invasivas estão se tornando cada vez mais atraentes devido à maior prevalência de comorbidades em pacientes mais velhos. A cirurgia endoscópica da coluna oferece vantagens como reabilitação precoce redução da dor pós-operatória danos musculares minimizados e internações hospitalares mais curtas.

Objetivos Para aumentar a segurança da abordagem interlaminar e minimizar complicações propomos a aplicação sistemática de uma técnica interlaminar expandida denominada "técnica Castro-Brock". A visualização direta da anatomia precisa é enfatizada para uma navegação endoscópica bem-sucedida.

Métodos A técnica Castro-Brock é descrita passo a passo compreendendo 10 etapas com imagens ilustrativas. A técnica envolve uma punção inicial na lâmina superior identificação de estruturas ósseas perfuração e ampliação da janela óssea interlaminar flavectomia em bloco e identificação precisa da raiz descendente antes de acessar o disco.

Resultados A técnica Castro-Brock facilita a visualização aprimorada da anatomia e fornece descompressão de estruturas neurológicas antes do acesso ao disco. Esta abordagem sistemática reduz o risco de lesão neurológica inadvertida e outras complicações cirúrgicas associadas ao acesso interlaminar.

Conclusões A técnica Castro-Brock representa uma adição valiosa ao arsenal da cirurgia endoscópica lombar da coluna. Garantir a visualização anatômica meticulosa e a descompressão pré-disco das estruturas neurais aumenta a segurança cirúrgica e otimiza os resultados do paciente.

Palavras-chave

- cirurgia endoscópica da coluna
- abordagem interlaminar
- minimamente invasiva

Introduction

The increased life expectancy has brought an increase in the incidence of degenerative pathologies of the spine.[1] The increment in comorbidities in the older population makes the use of less invasive techniques attractive and with lower risks.[2,3] Early rehabilitation, less post-operative local pain, minimized muscle damage, and reduced hospital stay are some advantages of endoscopic spine surgery.[4–6]

Endoscopic access to the lumbar spine essentially consists of transforaminal and interlaminar techniques. The more caudal the level, the larger the size of the interlaminar space, making it more favorable to perform the interlaminar approach, especially at the levels L4-5 and L5-S1.[7]

With the evolution of spinal endoscopy instruments, especially bone drills, the interlaminar approach has been routinely used for centrolateral disc herniations and spinal canal stenosis. The interlaminar window is the door to all kinds of pathologies and could be opened with the endoscopic burr and Kerrison, widening the interlaminar window and broadening the indications of the endoscopic lumbar spine surgery.[8]

The learning curve for the interlaminar approach requires training and getting used to handling the endoscope independently of the working cannula. Sequentially, the correct exposure and identification of the anatomy of the interlaminar window is crucial for safe access and complication reduction. Direct access with the opening of the ligamentum flavum may result in non-exposure and identification of the shoulder of the descending root, access through the axilla and an increased rate of manipulation, and injury to neurological structures.

Objectives

To increase the safety of the interlaminar approach and minimize complications, the authors propose in this paper the systematization of an expanded interlaminar approach in a pragmatic way through the Castro-Brock technique.

The main point is direct visualization of the correct anatomy is crucial for successful endoscopic navigation.

The technique described is based on 2 principles:

1. Initial puncture is on the bone (upper lamina) and not on the yellow ligament. Subsequently identification of the bone structures (spinous process basis, upper lamina, and inferior articular process in a craniocaudal direction is performed
2. Drilling and enlarging the interlaminar bone window is routinely performed, followed by en bloc flavectomy with customary identification of the descending root shoulder before accessing the disc.

Methods

Here we describe the step-by-step of the Castro-Brock technique, didactically divided into 10 steps and with representative images aiming to increase the safety of the

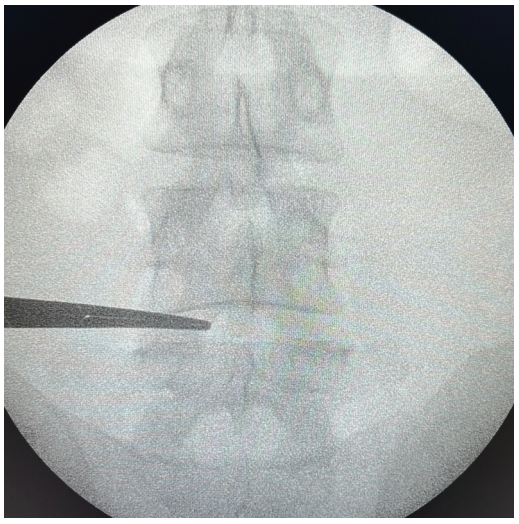

Fig. 1 Upper lamina is marked with radioscopy.

interlaminar approach and reducing the risk of injury to neurological structures.

Results

The description of this new technique for performing what we call an expanded interlaminar approach named the "Castro-Brock technique", is systematized in the following steps:

1. The upper lamina is marked with radioscopy (►**Fig. 1**) and the puncture is carried out towards the upper lamina with the dilator after incision of the skin and muscular fascia (►**Fig. 2**), feeling through the haptic with the dilator the base of the spinous process, moving in a lateral direction until feeling the step between the lamina and the interlaminar window at the junction of the lamina with the IAP (Inferior Articular Process).
2. Introduction of the working cannula and endoscope, identifying the base of the spinous process, upper lamina, and IAP as well as visualization of the interlaminar window medial to these structures (►**Figs. 3** and **4**) and creation of a virtual cavity for the flow of saline solution. The sequence of identification from medial to lateral is therefore: spinous process basis, upper lamina, IAP, interlaminar window
3. The facet capsule in de desinserted medially in a cranial-caudal direction until the tip of the IAP is identified (►**Figs. 5** and **6**), continuing with the drilling of the upper lamina and IAP in a medial-lateral direction for approximately 6 mm (twice the size of the 3mm drill), from cranial to caudal, becoming the flavum ligament and the SAP (Superior Articular Process) more evident (►**Fig. 7**); the SAP is in a deeper anatomical situation than the IAP (►**Fig. 8**).
4. Drilling of the SAP in a cranial-caudal and medial-lateral direction (►**Fig. 9**) until the disinsertion of the flavum ligament from the SAP and the inferior lamina (►**Fig. 10**).

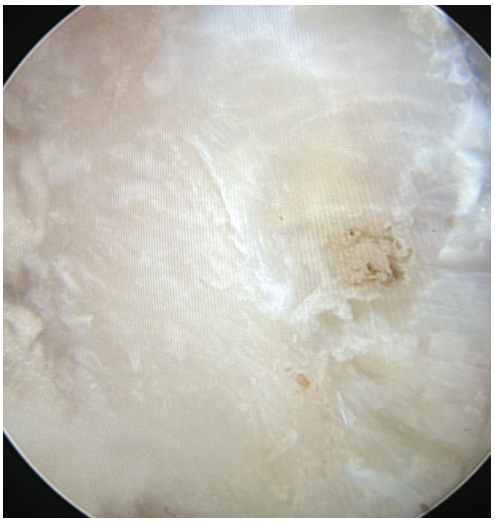

Fig. 3 After introducing the working cannula and endoscope it is crucial to identify from medial to lateral the following structures: 1. spinous process basis / 2. Upper lamina / 3. IAP / 4. interlaminar window.

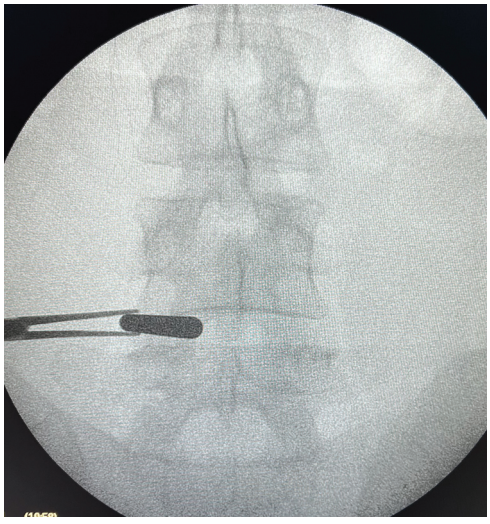

Fig. 2 Puncture of the upper lamina with the dilator.

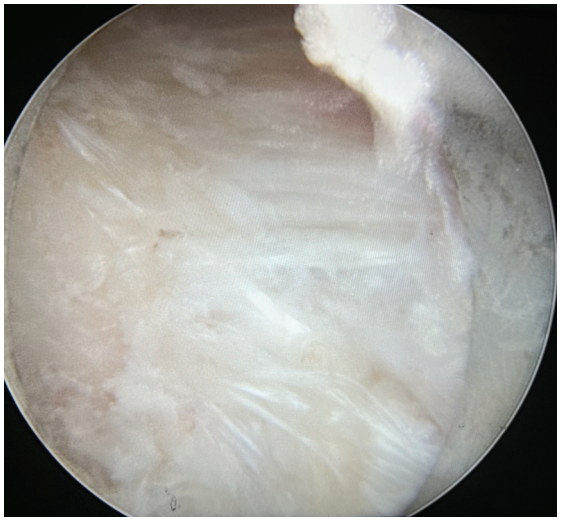

Fig. 4 IAP and facet capsule (*) and the interlaminar window medially (**).

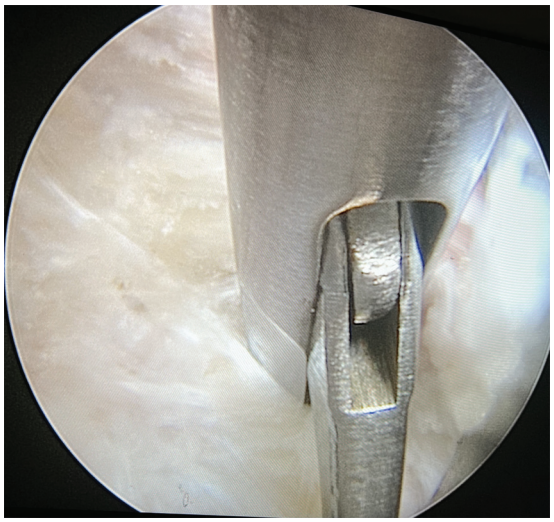

Fig. 5 The facet capsule is desinserted medially in a cranial-caudal direction with scissors.

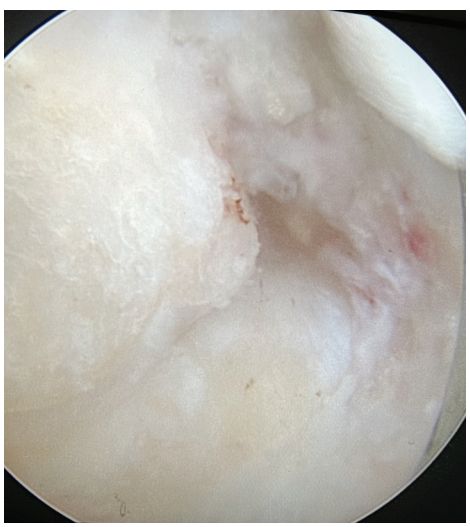

Fig. 6 The tip of the IAP is identified (*). It is also possible to visualize the inferior lamina (**).

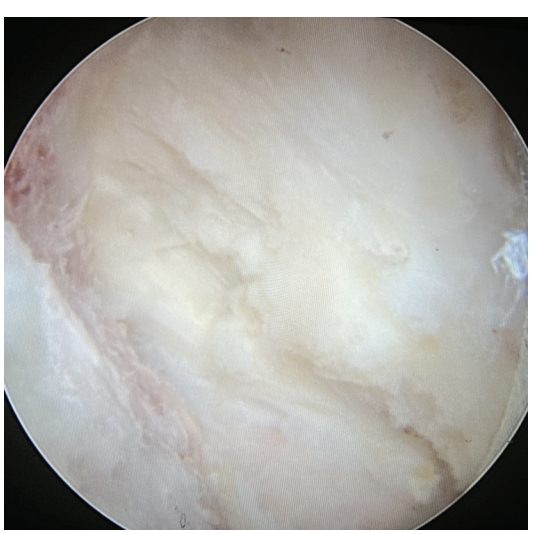

Fig. 7 Upper lamina drilled (1); IAP drilled (2); SAP bellow IAP (3); Yellow ligament exposed (4).

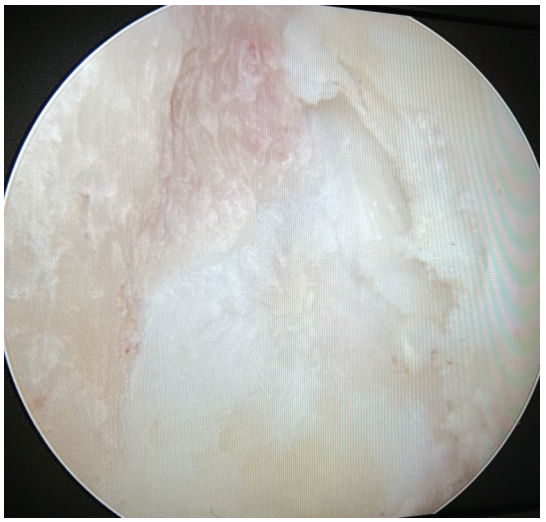

Fig. 8 IAP drilled (1); SAP deeper than IAP (2); Articular cartilage (3).

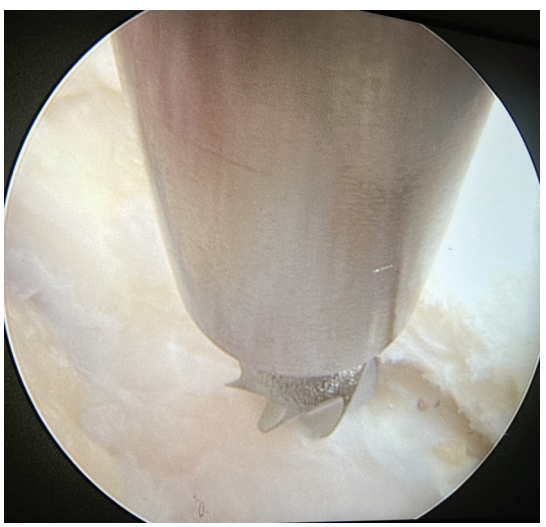

Fig. 9 SAP is drilled from medial to lateral and cranial to caudal in the direction of the inferior lamina.

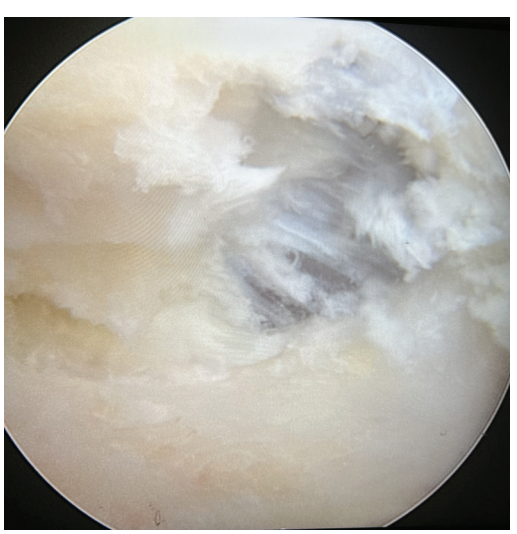

Fig. 10 Disinsertion of the yellow (flavum) ligament from the inferior lamina by drilling.

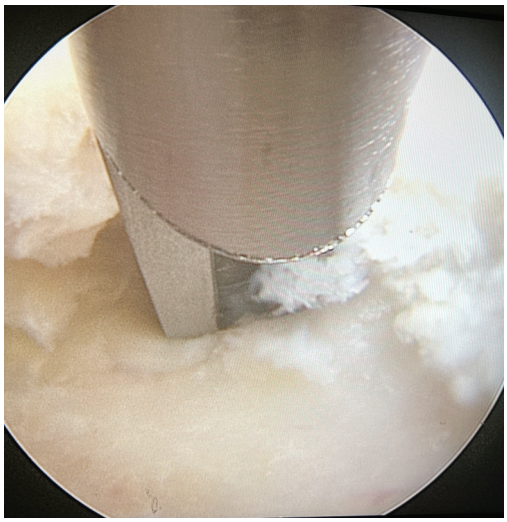

Fig. 11 Foraminotomy is performed using a Kerrison.

5. After yellow ligament disinsertion it is possible to identify the descending root and proceed with the foraminotomy using a Kerrison (►**Fig. 11**) to promptly release the compression on the descending root and locate it to avoid injury (►**Fig. 12**).
6. Opening the flavum ligament next to the superior lamina (►**Fig. 13**) in a medial to lateral direction (►**Figs. 13**–**15**) and cranial to caudal until finding the previous opening performed at the level of the SAP and inferior lamina (►**Fig. 16**)
7. Opening the flavum ligament in its medial portion in a cranio-caudal direction to the inferior lamina (►**Fig. 17**)
8. Removal of the flavum ligament en bloc (►**Fig. 18**) allowing to visualize the dural sac and descending nerve root (►**Fig. 19**), including its axila and shoulder (►**Fig. 20**)
9. The approach is mandatorily performed through the shoulder of the descending nerve root (►**Fig. 21**), with its detachment along the entire length exposed (►**Fig. 22**)

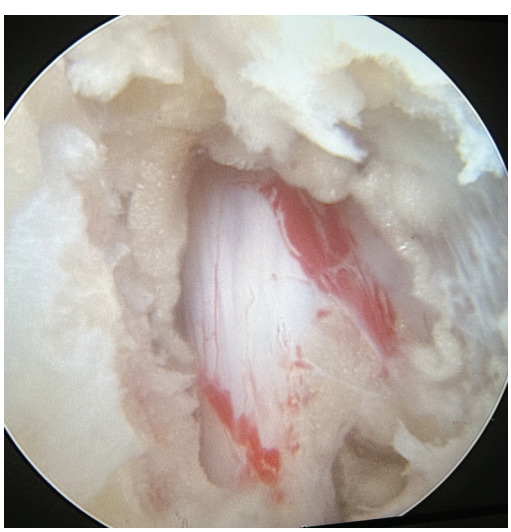

Fig. 12 Descending nerve root promptly decompressed and identified (1); SAP drilled (2); Inferior laminar drilled (3).

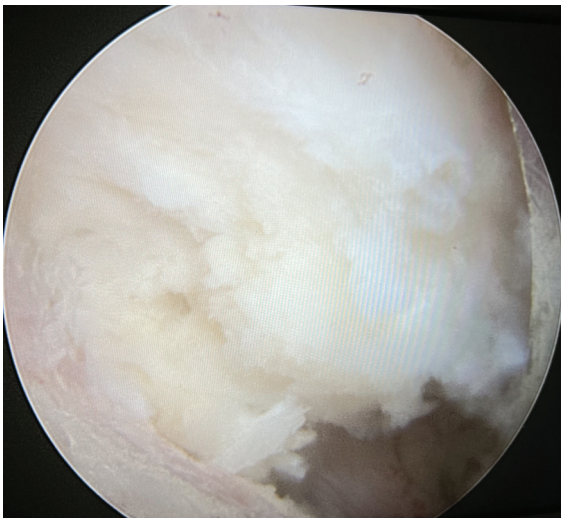

Fig. 13 Superior and medial portion of the yellow ligament will be opened (1); previous opening and descending nerve root foraminotomy (2).

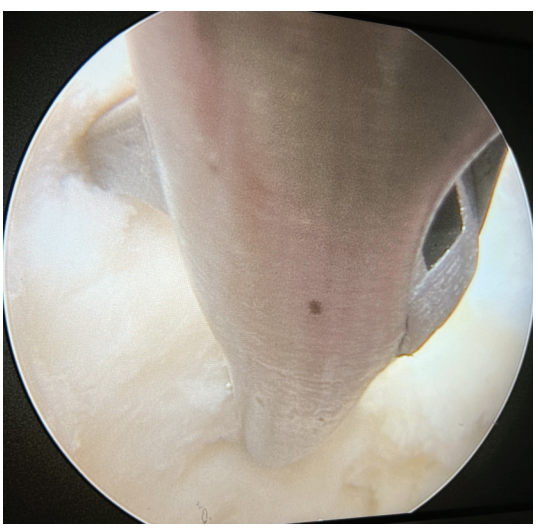

Fig. 14 The tip of the scissors must be visualized.

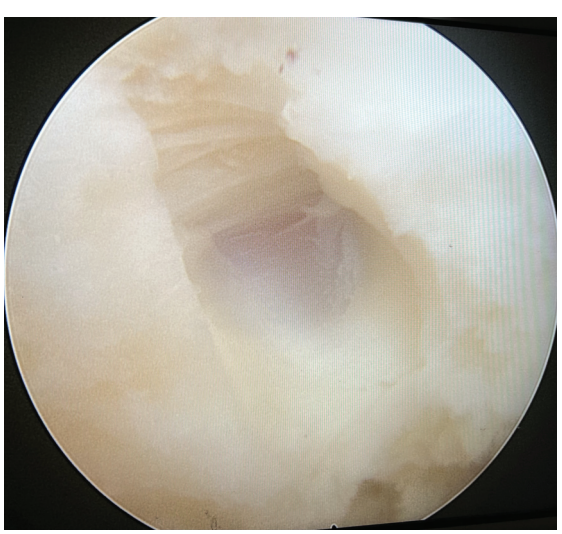

Fig. 15 The thicker superficial layer (1) and thinner deeper layer (2) of the flavum ligament.

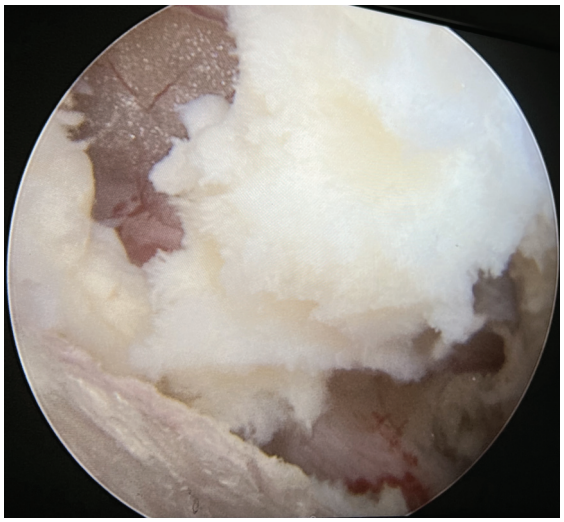

Fig. 16 The two openings are connected.

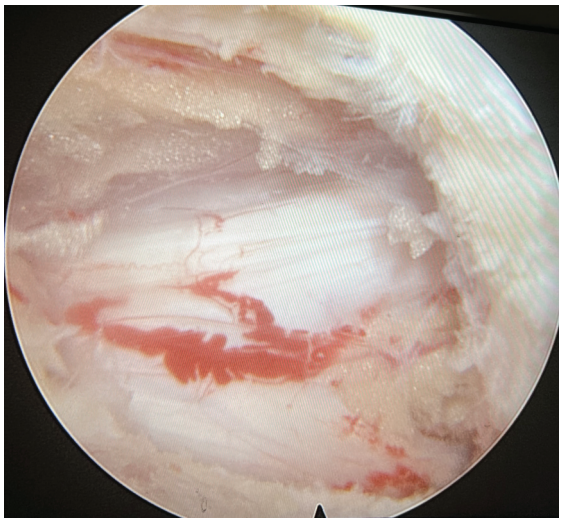

Fig. 19 After flavum ligament removal it is possible to identify the dural sac (1) the descending nerve root (2).

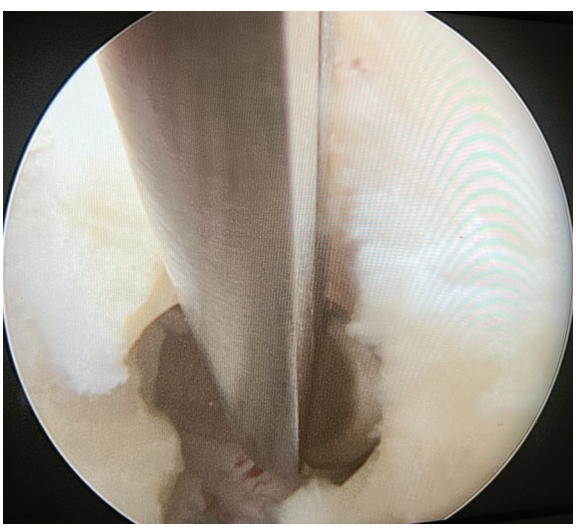

Fig. 17 The flavum ligament is divided in its medial portion in a craniocadal direction until the inferior lamina.

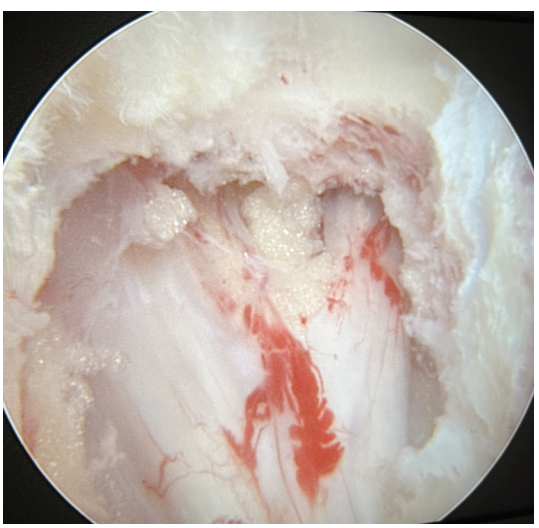

Fig. 20 Dural sac (1); descending nerve root (2) and its axila (3) and shoulder (4).

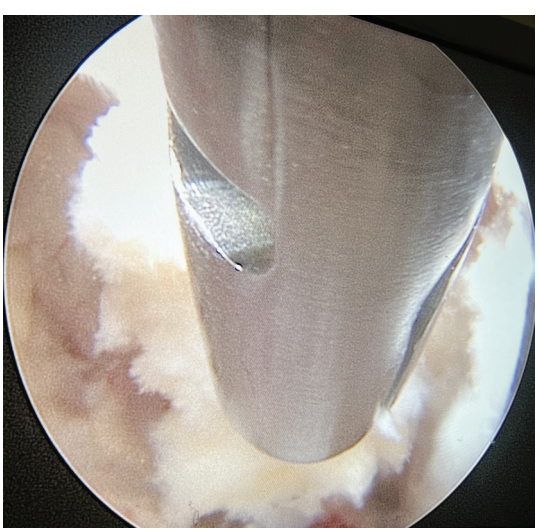

Fig. 18 After detachment, the flavum ligament is removed en bloc.

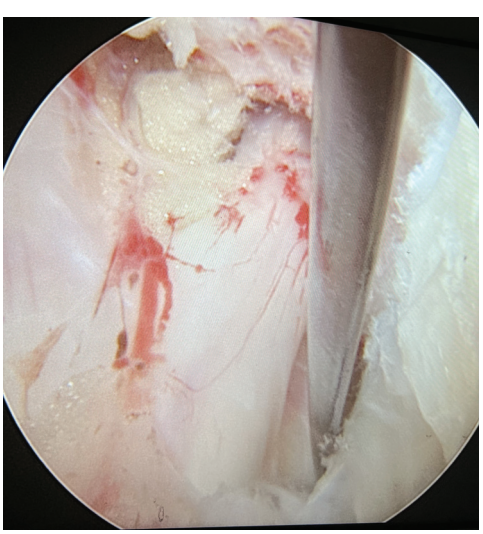

Fig. 21 A detacher/dissector is inserted through access to the descending nerve root shoulder.

10. The descending root is dislocated medially with the working cannula (the lamina is gently and cautiously rotated 180 degrees) and the disc/hernia is exposed (►**Fig. 23**)

Conclusions

The Castro-Brock technique described here provides two main advantages through an expanded interlaminar approach: it allows good visualization of the anatomy and promotes itself decompression of neurological structures before accessing the disc/herniation.

In this way, inadvertent injury to neurological structures as well as unwanted surgical complications are avoided, increasing the safety of performing the interlaminar approach.

Conflict of Interest
None declared.

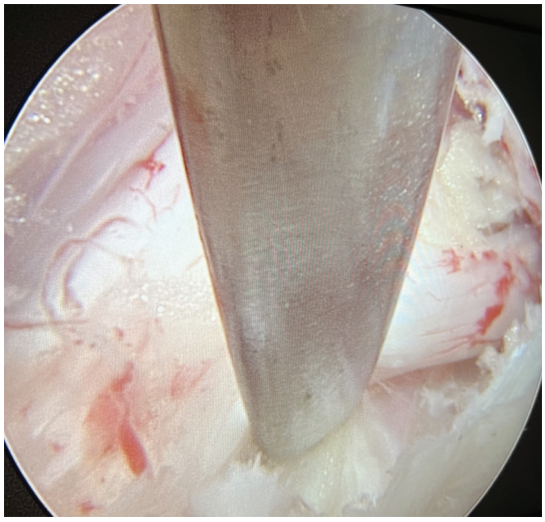

Fig. 22 The descending nerve root is detached and mobilized along its entire length.

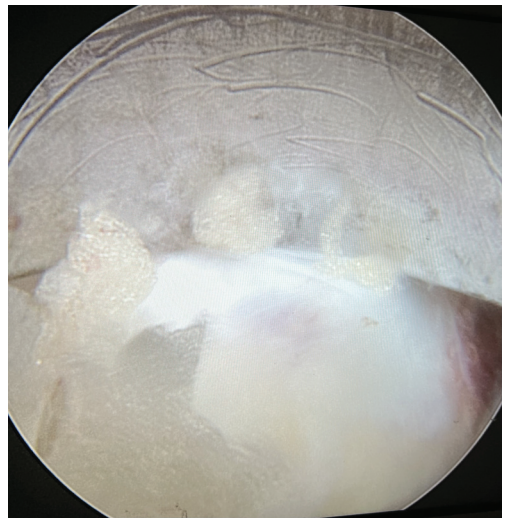

Fig. 23 Disc / herniation exposed after the root dislocation maneuvers.

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Analysis of Biochemical, Hormonal and Radiological Morphological Measurement Values in Patients with Empty Sella: A Clinical Study

Análise de valores de medidas morfológicas bioquímicas, hormonais e radiológicas em pacientes com Sela Vazia: Um estudo clínico

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Arq Bras Neurocir 2024;43(4):e269–e277.

Abstract

Objective This study investigated the relationship between radiological morphological findings and hormone levels in patients with empty sella.

Methods Patients (32 female, 3 male) with empty sella detected on radiological images were grouped as "partial empty sella (PBS) group" (subarachnoid space volume $< 70\%$) and "total empty sella (TBS) group" (subarachnoid space volume $> 70\%$). Age, gender, sella volume, pituitary gland thickness, the ratio of subarachnoid space height to pituitary gland height, and diaphragm sellae diameter were measured on radiological images. All patients' blood count results, biochemistry results, and serum hormone values were recorded.

Results Age, complete blood count, serum biochemistry parameters, and hormone levels were not different between PBS and TBS groups. Correlation analysis revealed a negative correlation between gender and subarachnoid space invasion volume, between gender and sagittal width of the sella turcica (ST), between cortisol level and ST axial diameter, between progesterone level and ST axial diameter, between testosterone level and ST axial diameter, between adrenocorticotropic hormone level

Keywords
- Empty Sella
- radiology
- morphology
- hormone
- biochemistry

The abstract of this article was accepted as oral presentation number "SS-092" at the 37th Scientific Congress of the Turkish Neurosurgical Society held between April 18-21, 2024.

received
April 20, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1796656.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

and ST axial diameter, between TSH level and subarachnoid space invasion rate, between free T4 level and diaphragm sellae sagittal width, and between free T4 level and ST sagittal width.

Conclusion This study showed that some serum hormone values may decrease when the sella tursica dimensions or the volume of subarachnoid space invading the sella tursica increase in patients with empty sella, and therefore, periodic follow-up of hormone levels and radiological images of these patients would be appropriate.

Resumo

Objetivo Este estudo investigou a relação entre achados morfológicos radiológicos e níveis hormonais em pacientes com sela vazia.

Métodos Pacientes (32 mulheres 3 homens) com sela vazia detectada em imagens radiológicas foram agrupados como "grupo sela parcialmente vazia (PBS)" (volume do espaço subaracnóideo $< 70\%$) e "grupo sela totalmente vazia (TBS)" (volume do espaço subaracnóideo $> 70\%$). Idade sexo volume da sela espessura da glândula pituitária a razão entre a altura do espaço subaracnóideo e a altura da glândula pituitária e o diâmetro do diafragma da sela foram medidos em imagens radiológicas. Os resultados do hemograma bioquímica e valores hormonais séricos de todos os pacientes foram registrados.

Resultados Idade hemograma completo parâmetros bioquímicos séricos e níveis hormonais não foram diferentes entre os grupos PBS e TBS. A análise de correlação revelou uma correlação negativa entre gênero e volume de invasão do espaço subaracnóideo entre gênero e largura sagital da sela túrcica (ST) entre nível de cortisol e diâmetro axial do ST entre nível de progesterona e diâmetro axial do ST entre nível de testosterona e diâmetro axial do ST entre nível de hormônio adrenocorticotrófico e diâmetro axial do ST entre nível de TSH e taxa de invasão do espaço subaracnóideo entre nível de T4 livre e largura sagital do diafragma da sela e entre nível de T4 livre e largura sagital do ST.

Conclusão Este estudo mostrou que alguns valores hormonais séricos podem diminuir quando as dimensões da sela túrsica ou o volume do espaço subaracnóideo que invade a sela túrsica aumentam em pacientes com sela vazia e portanto o acompanhamento periódico dos níveis hormonais e imagens radiológicas desses pacientes seria apropriado.

Palavras-chave
- Sela Vazia
- radiologia
- morfologia
- hormônio
- bioquímica

Introduction

Primary empty sella (PES) syndrome is an anatomical condition where the subarachnoid space herniates into the sella turcica.[1] Primary empty sella syndrome is a syndrome of unknown etiology in patients who have not undergone surgery, radiotherapy, or pharmacological treatments to the sellar/ parasellar region.[2] However, in secondary empty sella syndrome, patients generally have a history of central nervous system/hypothalamic-pituitary diseases, a history of pituitary surgery, a history of radiotherapy or medical treatment, and a history of functional pituitary diseases such as acromegaly, Cushing's disease or prolactinoma.[3,4] Although many hypotheses have been put forward to date regarding the pathogenesis of empty sella syndrome (such as intracranial hypertension, cerebrospinal fluid pulsatility, obesity, lactation, pregnancy, and hypophysitis), its etiopathogenesis has not been revealed yet.[3–7]

Clinical findings of empty sella are variable. It does not cause clinical findings in most patients, and empty sella is usually discovered incidentally on radiological images and is a relatively common finding in autopsies. Most patients are admitted to different departments with non-specific symptoms such as intracranial or ocular complaints and their disease are diagnosed incidentally.[5] However, empty sella syndrome can sometimes reach severe extremes in both clinical symptoms and hormonal changes. Therefore, it must be well differentiated clinically and managed appropriately based on clinical findings.[3–5] Studies have been conducted to evaluate the prevalence of primary empty sella syndrome and the hormonal status in patients with this syndrome. However, there are very few studies on the size of the pituitary gland within the sella in patients with this syndrome and the effect of empty sella syndrome on the secretory function of this gland.

This study aimed to investigate the effect of the volume of the subarachnoid space extending into the sella turcica on pituitary gland functions in patients with primary empty sella.

Materials and Methods

This retrospective clinical study was conducted after obtaining the approval of the Non-Interventional Research Ethics Committee (Decision date: 10.01.2024, decision number: 2024.01.09).

Patients

Patients with primary empty sella detected on radiologic images between 2020 and 2023 were included in the study. These patients were then grouped as follows:

- "Partial empty sella (PBS)" group (subarachnoid space volume <70%).
- "Total empty sella (TBS)" group (subarachnoid space volume >70%).

Patients were also grouped according to their gender as follows:

- Female group ($n = 32$)
- Male group ($n = 3$)

In addition, 24 participants (7 males, 17 females) who had no empty sella were included in the study to compare sella dimensions. Patients who had been previously treated for pituitary disease, patients who underwent surgery in the sellar/parasellar region, patients with adrenal gland disease/tumor, patients with non-pituitary hormonal disorders, or patients receiving hormonotherapy for various reasons, pregnant women, patients with incomplete blood or radiological imaging tests and pediatric patients were excluded.

Materials

Patients' age, gender, complaints and symptoms at the time of admission to the hospital, and medical history were recorded. In addition, the hemoglobin level values (reference range 10–18 g/dL), leukocyte (reference range 4400–11300/uL), neutrophil (reference range 1,100–9600/uL), lymphocyte (reference range 500–6000/uL), monocyte (reference range 100–1400/uL), basophil (reference range 0–300 /uL), and platelet (reference range 150000–500000/uL) count values were determined using an analyzer device (Mindray BC-6800, Shenzen, China).

Blood urine nitrogen (BUN) (reference range 17–43 mg/dL), creatinine (reference range 0.84–1.24 mg/dL), sodium (reference range 136–146 mmol/L), potassium (reference range 3.5–5.1 mmol /L), adrenocorticotropic hormone (ACTH) (reference range 7.2–63.3 pg/ mL), morning cortisol (reference range 6.2–19.4 ug/dL), total testosterone (reference range 8.4–48.1 ng/dL), estradiol (20–47 pg/mL), progesterone (ng/mL), follicle-stimulating hormone (FSH) (1.27–22.51 mIU/mL), luteinizing hormone (LH) (1.24–103.03 mIU/mL), prolactin (reference range 6–29.4 ng/mL), growth hormone (GH) (reference range 0–10 ng/mL), insulin-like growth factor-1 (IGF-1) (reference range 109–284 ng/mL), β-human chorionic gonadotropin (β-HCG) (reference range 0–5 mIU/mL), free T3 (FT3) (reference range 2–4.4 pg/mL), free T4 (FT4) (reference range 0.93–1.7 ng/mL), and thyroid stimulating hormone (TSH) (reference range 0.27–4.2 uIU/mL) levels were recorded.

Radiological Measurements

Morphologic measurements were performed on MR images of patients with primary empty sella. First, the maximum height of the subarachnoid space invading the sella tursica, the maximum height of the sella tursica, and the maximum width of the sella tursica, the maximum width of the diaphragm sella were measured on the T2 weighted sagittal MR images. Furthermore, the maximum width of the sella tursica was measured in the axial MR images (►**Figs. 1** and **2**). The ratio of the height of the subarachnoid space

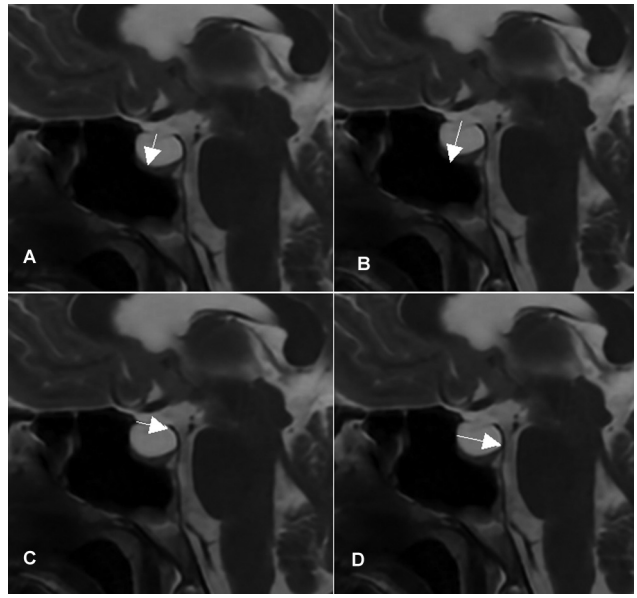

Fig. 1 The pictures obtained from the sagittal MR images show the morphological measurement methods of the subarachnoid space invading the sella tursica (**A**), the maximum height of the sella tursica (**B**), the width of the sella tursica (**C**), the width of the diaphragm sella (**D**).

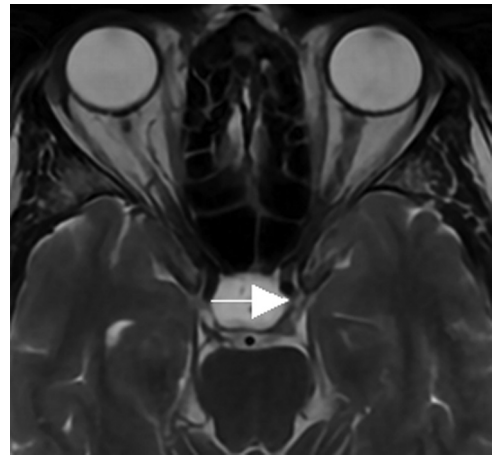

Fig. 2 The picture shows the width of the sella turcica in the axial MR image.

invading the sella tursica to the height of the sella tursica called the invasion ratio was also recorded. In addition, the volume of the subarachnoid space invading the sella tursica was also calculated and recorded. The volume was calculated as follows:

Volume = ⅓ × (maximum height of the subarachnoid space invading the sella tursica x maximum width of the sella tursica in the sagittal plane x maximum width of the sella tursica in the axial plane).

Statistical Analysis

As a result of the G*Power analysis, it was found that the minimum total study population size could be 14 (effect size d = 2.00, power = 0.95, critical t = 1.782, actual power = 0.970, total sample size = 14). Parametric data was analyzed with the *Independent Samples t-test* to evaluate group differences ($p < 0.05$). Non-parametric data was analyzed using the *Mann-Whitney U* test to compare the groups ($p < 0.05$). Categoric data were analyzed using the *Pearson Chi-square* test ($p < 0.05$). *Spearman's rho Correlation* test was used to determine the correlation between the parameters ($p < 0.05$).

Results

A total of 35 patients (3 males and 32 females) were included in the study. Almost all of the patients included in the study were female. When the anamnesis of the patients was analyzed, it was found that 14 patients had headaches for a long time, 2 patients had nausea, 2 patients had dizziness, and 1 patient who was 42 years old had menstrual irregularities. It was learned from their history that 4 patients were under treatment for hypertension, 1 patient for hypothyroidism, 1 patient for hyperthyroidism, and 2 patients for diabetes mellitus. Obesity was found in only 1 patient. It was observed that almost all patients' blood count values, blood biochemistry, and hormone values were within laboratory normal values (►**Table 1**).

There was no difference between PBS and TBS groups regarding age, complete blood count, serum biochemistry parameters, and serum hormone levels. However, subarachnoid space invasion length (t = -4.614, $p < 0.001$), sella tursica sagittal width (t = -3.338, $p = 0.002$), diaphragm sellae sagittal width (t = -3.639, $p = 0.001$), sella tursica axial width (t = -2.683, $p = 0.011$), and subarachnoid space invasion volume (t = -3.245, $p = 0.001$) values were found to be different between the two groups (►**Table 2**).

Platelet-to-lymphocyte ratio (t = 2.132, $p = 0.041$), LH (t = -3.706, $p = 0.001$), FSH (t = -4.324, $p < 0.001$), estradiol (Z = -3.571, $p < 0.001$), progesterone (Z = -2.728, $p = 0.006$), testosterone (Z = -2.036, $p = 0.042$), prolactin (Z = -2.245, $p = 0.025$), and free T3 (t = 2.651, $p = 0.012$) levels were found to be different between the age groups (►**Table 3**).

When the sella tursica dimensions of the patients were compared with the individuals without empty sella syndrome, it was found that the length of the sella tursica measured in the sagittal plane was statistically significantly different. (t = 4.807, $p < 0.001$) (►**Table 4**).

Correlation analysis revealed a negative correlation between gender and subarachnoid space invasion volume (r = -0.344, $p = 0.043$), between gender and sagittal width of the sella turcica (r = -0.364, $p = 0.032$), between cortisol level and axial diameter of the sella turcica (r = -0.348, $p = 0.041$), between progesterone level and axial diameter of the sella turcica (r = -0.346, $p = 0.042$), between testosterone level and axial diameter of the sella turcica (r = -0.426, $p = 0.012$), between adrenocorticotropic hormone level and axial diameter of the sella turcica (r = -0.478, $p = 0.008$), between TSH level and subarachnoid space invasion rate (r = -0.336, $p = 0.049$), between free T4 hormone level and sagittal width of the diaphragm sellae (r = -0.431, $p = 0.010$) and between free T4 hormone level and sagittal width of the sella turcica (r = -0.368, $p = 0.030$).

Discussion

The most common clinical finding of empty sella syndrome is headache. However, hormonal deficiencies are a rare clinical condition. Therefore, since hormonal deficiencies are rare and most likely acquired, growth and sexual development are less likely to be affected. For this reason, the empty sella diagnosis is a syndrome discovered incidentally during the examination of other neurological complaints and symptoms. Recent studies reported that PES is more than an incidental finding and the prevalence of accompanying endocrine abnormalities was found to be high.[8] For this reason, they argued in their study that these patients should be examined in more detail by endocrinologists, otherwise, the hormonal evaluation would be largely insufficient, which would lead to poor clinical management and the risk of not replacing missing hormones.[9]

Empty sella syndrome is the herniation of the subarachnoid space into the sella for various reasons and the sella is filled with cerebrospinal fluid.[1] Accordingly, normal pituitary tissue may compress and flatten, the pituitary stalk may lengthen and thin, and the sella may widen or remain normal. When the cerebrospinal fluid filling percentage is <50% or the pituitary gland thickness is measured at 3–7 mm, this is called "partial empty sella." If the cerebrospinal fluid filling percentage is >50% and the pituitary gland thickness is <2 mm, it is called "total empty sella."[3,4,10–12]

Almost all the patients included in the study were female. In the present study, many patients (14 patients) complained of headaches. In addition, two patients had nausea, two patients had dizziness, and one patient who was 42 years old had menstrual irregularities. However, only one patient was under treatment for hypothyroidism, two patients for diabetes mellitus, and one patient suffered from obesity. Almost all these patients had a subarachnoid space invasion rate of >70%. However, when the hormone levels of the patients were analyzed, it was found that all of them had serum hormone and biochemistry values within the normal laboratory result range. It was observed that subarachnoid space invasion length, sella tursica sagittal width, diaphragm sellae sagittal width, sella tursica axial width, and subarachnoid space invasion

Table 1 Descriptive table of demographic data, blood count values, blood biochemistry, and hormone levels, and radiological morphological measurements of all patients

Variable		Mean ± SD/ Median (min-max)/N (%)	Normal value
Age (year)		48.54 ± 13.76	–
Gender	Female	32 (%91.4)	–
	Male	3 (%8.6)	
Hemoglobin		13.38 ± 1.79	10-18 g/dL
Leukocyte		7722 ± 1980.01	4400-11300 /uL
Neutrophil		4610 (2140–8140)	1100-9600/uL
Lymphocyte		2532 ± 744.69	500-6000 /uL
Monocyte		437 ± 124.84	100-1400 / uL
Basophil		40 (20–110)	0-300 /uL
Platelets		272457 ± 63215.48	150000-500000 /uL
Neutrophil-lymphocyte ratio		1.93 ± 0.92	–
Monocyte-lymphocyte ratio		0.18 ± 0.07	–
Platelet-lymphocyte ratio		117.82 ± 49.62	–
Sodium		136.09 ± 23.79	136-146 mmol/L
Potassium		4.56 ± 0.35	3.5-5.1 mmol /L
Blood urine nitrogen		26.37 ± 7.22	17-43 mg/dL
Creatinine		0.71 ± 0.22	0.84-1.24 mg/dL
Adrenocorticotropic hormone		21.55 (8.20-96.20)	7.2-63.3 pg/ mL
Morning cortisol		11.28 ± 6.70	6.2-19.4 ug/dL
Luteinizing hormone		17.95 ± 12.51	1.24-103.03 mIU/mL
Follicle-stimulating hormone		26.50 (0.40-78.20)	1.27-22.51 mIU/mL
Estradiol		22 (0.00-209.00)	–
Progesterone		0.22 (0.00-21.90)	–
β-human chorionic gonadotropin		0.20 (0.00-2.35)	0-5 mIU/mL
Testosterone		18.70 (0.00-492.00)	8.4-48.1 ng/dL
Prolactin		10.50 (0.20-107.00)	6-29.4 ng/mL
Free T3		2.92 ± 0.48	2-4.4 pg/mL
Free T4		1.57 ± 1.92	0.93-1.7 ng/mL
Thyroid-stimulating hormone		1.79 (0.02-6.59)	0.27-4.2 uIU/mL
Growth hormone		0.41 (0.05-40.50)	0-10 ng/mL
Insulin-like growth factor-1		117.40 ± 60.17	109-284 ng/mL
Sella tursica sagittal length (mm)		10.40 ± 2.14	–
Subarachnoid space invasion length (mm)		7.22 ± 2.33	–
Sella tursica sagittal width (mm)		9.92 ± 2.55	–
Diaphragm sellae sagittal width (mm)		7.68 ± 1.42	–
Sella tursica axial width (mm)		11.68 ± 3.44	–
Subarachnoid space invasion volume (mm^3)		242.89 (0.00-2150.98)	–
Subarachnoid space invasion rate		68.40 ± 11.91	–

(SD: standard deviation, min: minimum, max: maximum, N: patient number)

volume (t = -3.245, $p = 0.001$) values in the subarachnoid space invasion rate >70% group were higher than those in the <70% group. However, there was no statistical difference between the two groups regarding hormone values, serum biochemistry values, and blood count values. In light of these findings, it was concluded that a subarachnoid space invasion rate >70% did not lead to decreased pituitary hormones and therefore did not cause a

Table 2 Distribution table of the patients' data according to the subarachnoid space invasion rate groups

		INVASION RATIO			
		<%70	>%70		
Variable		**Mean ± SD/ Median (min-max)/ N (%)**	**Mean ± SD/ Median (min-max)/ N (%)**	**t/Z/X²**	**p**
Age (year)		45.81 ± 15.80	50.84 ± 11.73	-1.080*	0.288
Gender	Female	15 (42.9%)	17 (48.6%)	0.203‡	0.653
	Male	2 (5.7%)	1 (2.9%)		
Hemoglobin		13.42 ± 1.86	13.34 ± 1.78	-0.361*	0.720
Leukocyte		7780 ± 2169.00	7672 ± 1865.24	0.159*	0.874
Neutrophil		4555 (2140-7640)	4610(2210-8140)	-0.199†	0.843
Lymphocyte		2498 ± 803.07	2560 ± 712.88	-0.244*	0.809
Monocyte		453 ± 94.36	424 ± 147.02	0.677*	0.503
Basophil		35 (20-70)	40 (20-110)	-0.256†	0.798
Platelets		277063 ± 54561.85	268579 ± 70942.32	0.391*	0.699
Neutrophil-lymphocyte ratio		2.08 ± 1.23	1.81 ± 0.56	0.849*	0.402
Monocyte-lymphocyte ratio		0.20 ± 0.08	0.17 ± 0.05	1.338*	0.190
Platelet-lymphocyte ratio		123.41 ± 50.36	113.109 ± 49.86	0.607*	0.548
Sodium		140.38 ± 2.99	139.79 ± 2.30	0.655*	0.517
Potassium		4.52 ± 0.39	4.60 ± 0.32	-0.655*	0.517
Blood urine nitrogen		25.25 ± 6.90	27.31 ± 7.53	-0.840*	0.407
Creatinine		0.67 ± 0.10	0.74 ± 0.28	-0.940*	0.354
Adrenocorticotropic hormone		25 (9.10-96.20)	20 (8.20-72.70)	-0.977†	0.329
Morning cortisol		12.11 ± 4.90	10.58 ± 7.97	0.667*	0.509
Luteinizing hormone		19.62 ± 14.73	16.54 ± 10.50	0.720*	0.477
Follicle-stimulating hormone		22 (1.70-78.20)	27 (0.40-61.40)	-0.364†	0.716
Estradiol		30 (5-173)	17 (0-209)	-1.335†	0.182
Progesterone		0.22 (0.05-21.90)	0.22 (0-7.73)	-0.066†	0.947
β-human chorionic gonadotropin		0.35 (0-2.35)	0.20 (0-1.60)	-0.142†	0.887
Testosterone		22.15 (7.06-492)	14.95 (0-444)	-1.277†	0.202
Prolactin		10.90 (4.40-42.40)	9 (0.20-107)	-1.275†	0.202
Free T3		2.824 ± 0.40	3.00 ± 0.54	-1.091*	0.283
Free T4		1.24 ± 0.18	1.84 ± 2.60	-0.927*	0.361
Thyroid-stimulating hormone		2.23 (1.28-6.59)	1.57 (0.02-6.45)	-1.772†	0.076
Growth hormone		0.27 (0.13-7.75)	0.50 (0.05-40.50)	-0.356†	0.722
Insulin-like growth factor-1		118.56 ± 56.53	116.52 ± 65.24	0.075*	0.941
Sella tursica sagittal length (mm)		9.69 ± 1.26	10.99 ± 2.56	-1.862*	0.071
Subarachnoid space invasion length (mm)		5.66 ± 1.18	8.54 ± 2.25	-4.614*	**<0.001**
Sella tursica sagittal width (mm)		9.81 ± 2.58	13.24 ± 3.35	-3.338*	**0.002**
Diaphragm sellae sagittal width (mm)		6.86 ± 1.91	10.89 ± 1.24	-3.639*	**0.001**
Sella tursica axial width (mm)		8.76 ± 1.85	11.01 ± 2.65	-2.683*	**0.011**
Subarachnoid space invasion volume (mm^3)		166.8 (46.56-703.41)	414.44 (111.72-2150.98)	-3.245†	**0.001**

(SD: standard deviation, min: minimum, max: maximum, N: patient number)
(*)t value, Independent Samples t-test
(†)Z value, Mann-Whitney U test
(‡)X^2 value, Pearson chi-square test, $p < 0.05$

Table 3 Distribution table of the patients' data according to the age groups

		Age <50	Age >50		
Variable		**Mean ± SD/Median (min-max)/ N (%)**	**Mean ± SD/Median (min-max)/ N (%)**	**t/Z/X^2**	**p**
Age (year)		37.53 ± 9.74	58.94 ± 7.32	–	–
Gender	Female	15 (42.9%)	17 (48.6%)	0.430‡	0.512
	Male	2 (5.7%)	1 (2.9%)		
Hemoglobin		12.91 ± 2.26	13.82 ± 1.09	-1.520*	0.138
Leukocyte		7650.59 ± 1702.00	7789 ± 2259.35	-0.204*	0.840
Neutrophil		4800 (2380-7170)	4520 (2140-8140)	-0.858†	0.391
Lymphocyte		2326 ± 595.87	2726 ± 832.35	-1.625*	0.114
Monocyte		429 ± 101.21	445 ± 146.30	-0.364*	0.718
Basophil		30 (20-110)	40 (20-70)	-0.578	0.563
Platelets		287176 ± 80909.85	258556 ± 37547.18	1.355*	0.185
Neutrophil-lymphocyte ratio		2.20 ± 1.15	1.68 ± 0.58	1.687*	0.101
Monocyte-lymphocyte ratio		0.20 ± 0.07	0.17 ± 0.06	1.087*	0.285
Platelet-lymphocyte ratio		135.33 ± 61.27	101.28 ± 28.20	2.132*	**0.041**
Sodium		139 ± 2.02	140.78 ± 2.94	-1.728*	0.093
Potassium		4.58 ± 0.33	4.55 ± 0.38	0.215*	0.831
Blood urine nitrogen		25.59 ± 6.76	27.11 ± 7.75	-0.618*	0.541
Creatinine		0.73 ± 0.21	0.69 ± 0.22	0.526*	0.602
Adrenocorticotropic hormone		21.80 (9.10-72070)	21.30 (8.20-96.20)	-0.439†	0.660
Morning cortisol		11.32 ± 7.92	11.24 ± 5.53	0.034*	0.973
Luteinizing hormone		11.07 ± 11.50	24.44 ± 9.83	-3.706*	**0.001**
Follicle-stimulating hormone		6.10 (0.40-62.40)	49 (6.60-78.20)	-4.324†	<**0.001**
Estradiol		56 (5-209)	14 (0-46)	-3.571†	<**0.001**
Progesterone		0.24 (0.05-21.90)	0.13 (0-0.39)	-2.728†	**0.006**
β-human chorionic gonadotropin		0.20 (0-2)	0.70 (0-2.35)	-2.968†	**0.003**
Testosterone		25.05 (2.50-492)	13 (0-385)	-2.036†	**0.042**
Prolactin		14.50 (0.20-42.40)	8.60 (4.40-107)	-2.245†	**0.025**
Free T3		3.12 ± 0.43	2.73 ± 0.46	2.651*	**0.012**
Free T4		1.86 ± 2.75	1.29 ± 0.25	0.868*	0.392
Thyroid-stimulating hormone		1.70 (0.02-6.59)	2.10 (0.74-6.45)	-0.776†	0.438
Growth hormone		0.93 (0.13-40.50)	0.20 (0.05-1.60)	-1.546†	0.122
Insulin-like growth factor-1		137.40 ± 70.76	99.21 ± 44.39	1.497*	0.151
Sella tursica sagittal length (mm)		10.15 ± 2.35	10.63 ± 1.96	-0.650*	0.520
Subarachnoid space invasion length (mm)		6.95 ± 2.39	7.48 ± 2.31	-0.818*	0.419
Sella tursica sagittal width (mm)		11.43 ± 3.51	11.91 ± 3.47	-1.654*	0.108
Diaphragm sellae sagittal width (mm)		7.66 ± 1.41	7.70 ± 1.47	-0.069*	0.945
Sella tursica axial width (mm)		9.20 ± 2.48	10.59 ± 2.49	-0.406*	0.688
Subarachnoid space invasion volume (mm^3)		186.12 (46.56)	310.41 (46.97-1493.61)	-1.188†	0.235
Subarachnoid space invasion rate		67.64 ± 10.58	69.11 ± 13.31	-0.360*	0.721

(SD: standard deviation, min: minimum, max: maximum, N: patient number)
(*) t value, Independent Samples t-test
(†)Z value, Mann-Whitney U test
(‡)X^2 value, Pearson chi-square test, $p < 0.05$

Table 4 Distribution table of sella tursica morphological measurement values of patients with empty sella syndrome and normal patients

	PATIENTS	CONTROL		
Variable	Mean ± SD	Mean ± SD	t	p
Sella tursica sagittal length (mm)	10.40 ± 2.14	8.08 ± 1.18	4.807	<**0.001**
Sella tursica sagittal width (mm)	9.92 ± 2.55	10.23 ± 1.42	-0.548	0.586
Diaphragm sellae sagittal width (mm)	7.68 ± 1.42	7.89 ± 1.21	-0.603	0.549
Sella tursica axial width (mm)	11.68 ± 3.44	12.52 ± 3.10	-0.959	0.342

(SD: standard deviation)
Independent Samples t-test; $p < 0.05$

metabolic disturbance. It was also argued that it did not affect blood count values.

On the other hand, platelet-to-lymphocyte ratio, prolactin, free T3, testosterone, estradiol, and progesterone serum levels were found to be low, whereas LH and FSH levels were found to be high in patients over 50 years of age. However, all these parameters were found to be within the range of normal laboratory values. It was thought that these results may be related to the fact that almost all the study group consisted of female patients and these female patients were in age-related menopause after the age of fifty.

On the other hand, the length of the sella tursica measured in the sagittal plane was different between individuals without empty sella syndrome and patients with empty sella syndrome. With these results, it was seen that the depth of the sella tursica in the sagittal plane was greater in patients with empty sella syndrome compared with normal individuals. However, the diameter of the diaphragm sellae and the axial and sagittal width of the sella tursica were like normal individuals. With these findings, it was found that there was no global enlargement in the sella tursica but the depth of the sella tursica was more in empty sella syndrome. Interestingly, the diameter of the diaphragm sellae was similar between the groups. Thus, it was suggested that there is no morphologic abnormality of the diaphragm sellae in empty sella syndrome, but there may be a structural defect in the dura mater forming the diaphragm sellae, thus, it could not prevent the passage of cerebrospinal fluid into the sella tursica and could be considered a cause of the formation of this syndrome. On the other hand, as a rule of physics, it is known that the fluid pressure in containers is similar on all surfaces of the container, but the pressure exerted on the bottom of the container by the weight of the fluid due to gravity is directly related to the height of the container. With these hypotheses, it was argued that the gravity-induced increased fluid pressure at the base of the sella tursica may increase the sagittal height of the sella in empty sella syndrome.

Based on correlation analysis, it has been established that increasing the axial diameter of the sella turcica may be directly associated with decreasing serum cortisol, progesterone, testosterone, and ACTH levels. Furthermore, an increase in the width of the sella turcica and diaphragm sellae, measured in the sagittal plane, may lead to a decrease in serum levels of free T4. Additionally, a significant decrease in TSH levels may occur with an increased subarachnoid space invasion rate. These observations strongly suggest that an increase in the dimensions of the sella turcica during follow-up periods in patients diagnosed with empty sella syndrome may lead to hypopituitarism including especially the cortisol, progesterone, testosterone, ACTH, TSH, and free T4 levels. Therefore, it is highly recommended that patients with empty sella should undergo regular follow-ups of their serum hormone levels and radiological images.

Limitations

This study has several limitations. *First*, the sample size of the study was small. *Second*, since the study was retrospective, stimulation tests for pituitary gland hormones were not performed. Therefore, detailed information about the hypothalamo-hypophyseal pathway and target organ responses could not be obtained. *Third*, due to the retrospective nature of the study, hormonal values were not monitored because the patients were not followed up. *Finally*, healthy control subjects' hormonal parameters were not included in this study, but laboratory data of the patients were compared with laboratory normal values.

Conclusion

With these findings, it was concluded that there was no significant deterioration in hormone activities in patients with PBS or TBS; however, there may be a negative correlation between sella dimensions and cortisol, ACTH, progesterone, testosterone, TSH and free T4 levels and the levels of these hormones may decrease in these patients when sella dimensions and/or the volume of the invaded subarachnoid space increase and therefore periodic follow-up of hormone levels and MR images of these patients would be appropriate.

Conflict of Interest
There is no "conflict of interest" among the authors. Furthermore, through any of the products used in this research, no financial engagement has been established with any company that makes and/or markets these products or with any corporation that produces and/or markets a competing product.

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Intradural versus Extradural Anterior Clinoidectomy: Comparison of Visual Loss in Patients with Paraclinoid Aneurysms

Série de casos: Comparação da perda visual em pacientes submetidos a clinoidectomia intra versus extradural para abordagem de aneurismas paraclinoideos

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Arq Bras Neurocir 2024;43(4):e278–e285.

Abstract

Introduction Visual deficit after surgical treatment for paraclinoid aneurysms is a problem faced by many neurosurgeons. Anterior clinoidectomy, performed to access the aneurysm, is one the most important steps of the surgery. However, it is also the step related the most with lesions to the optic nerve. The aim of this study was to compare the rate of visual loss between extradural versus intradural clinoidectomy in patients harboring paraclinoid aneurysms which underwent open surgery.

Methods Analysis of 36 patients harboring paraclinoid aneurysms operated by the senior authors between 2020–2022. We compared our results to other series published previously.

Results Fifteen patients underwent intradural clinoidectomy (41.6%), twenty patients extradural clinoidectomy (55.5%) and one patient intra and extradural clinoidectomy (2.7%). The incidence of postoperative visual deterioration was 11.1% (4 patients), all of them were from the extradural clinoidectomy group. Other complications found were cerebrospinal fluid leak (1 patient) and vasospasm followed

Keywords
- vascular
- paraclinoid
- aneurysm
- visual loss
- internal carothid artery

received
December 17, 2023
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1795070.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

by diffuse ischemia (1 patient). Visual evoked potential was used in 6 patients (16.6%). In two cases VEP was normal during surgery, however they developed visual deterioration in the postoperative period.

Conclusion Both techniques have advantages and disadvantages, however extradural clinoidectomy showed higher rates of visual deterioration than intradural clinoidectomy. Regardless of the chosen procedure, precise surgical technique is mandatory when dealing with paraclinoid aneurysms.

Resumo

Introdução Déficit visual após abordagem microcirúrgica de aneurismas paraclinoideos é um problema encontrado por diversos neurocirurgiões. Clinoidectomia anterior, realizada para obter acesso aos aneurismas paraclinoideos, é um dos passos fundamentais da abordagem cirúrgica, entretanto pode levar a lesões do nervo óptico. O objetivo deste estudo foi comparar a incidência de déficit visual em pacientes submetidos a clinoidectomia intradural versus aqueles submetidos a técnica extradural.

Métodos Análise de 36 casos operados no servico durante o período de 2020–2022. Os resultados foram comparados com outras séries previamente publicadas.

Resultados Clinoidectomia intradural foi realizada em 15 pacientes (41.6%), clinoidectomia extradural em 20 pacientes (55.5%) e abordagem combinada em 1 paciente (2.7%). A incidência de deficit visual no período pós-operatório foi de 11.1% (4 pacientes), todos do grupo extradural. Outras complicações encontradas foram: fístula liquórica (1 paciente) e vasoespasmo difuso (1 paciente). Potencial evocado visual foi utilizado em 6 pacientes (16.6%). Em dois casos, o potencial permaneceu inalterado durante a cirurgia, entretanto houve deterioração visual no período pós-operatório.

Conclusão Ambas técnicas possuem vantagens e desvantagens, entretanto, a clinoidectomia extradural apresentou maior incidência de deficit visual nesse estudo. Independente da abordagem escolhida, uma técnica cirúrgica exímia é mandatória no manejo desses aneurismas.

Palavras-chave
- vascular
- aneurisma
- paraclinóide
- perda visual
- artéria carótida interna

Introduction

Blindness after surgery for aneurysms in the paraclinoid region may be greater than described.

The major obstacle to these aneurysms at the level of the distal dural annulus was the anterior clinoid process (ACP) that partially or totally concealed the neck *(►**Fig. 1**)*, leading to partial clipping or even untimely rupture during clip placement.[1]

In the 1980s, techniques for clipping paraclinoid aneurysms were described involving the section of the ACP to better identify the aneurysmal neck.[2]

In anatomical studies Dolenc showed that by extradural route it is possible to open the falciform ligament and remove the orbital roof, sphenoid wing, optic pillar and anterior clinoid. That allows an adequate view of the aneurysmal neck and ophthalmic artery outlet. If we open the distal dural ring it facilitates the location of the clip even more.[1,3]

On the other hand, other authors have supported the use of intradural clinoidectomy for paraclinoid aneurysms surgery. This technique showed good results and few descriptions of intraoperative visual loss.[2,4,5]

There is still doubt regarding which approach should be used to decrease visual loss in the postoperative period. We reviewed paraclinoid aneurysm cases operated in our service that underwent intradural or extradural clinoidectomy and investigated the incidence and the factors related to visual loss in those patients.

Materials and Methods

Thirty-six patients harboring paraclinoid aneurysms were included in this review. They were operated by the senior authors during the period of 2020 to 2022.

Localization and number of aneurysms, age, gender, intra or extradural clinoidectomy, visual deterioration, complications and use of visual evoked potential were the parameters evaluated.

A literature review was also done to compare our results with previously published series.

Results

Thirty-six patients were included in our series. All of them harbored carotid-ophthalmic aneurysms. One case also had a

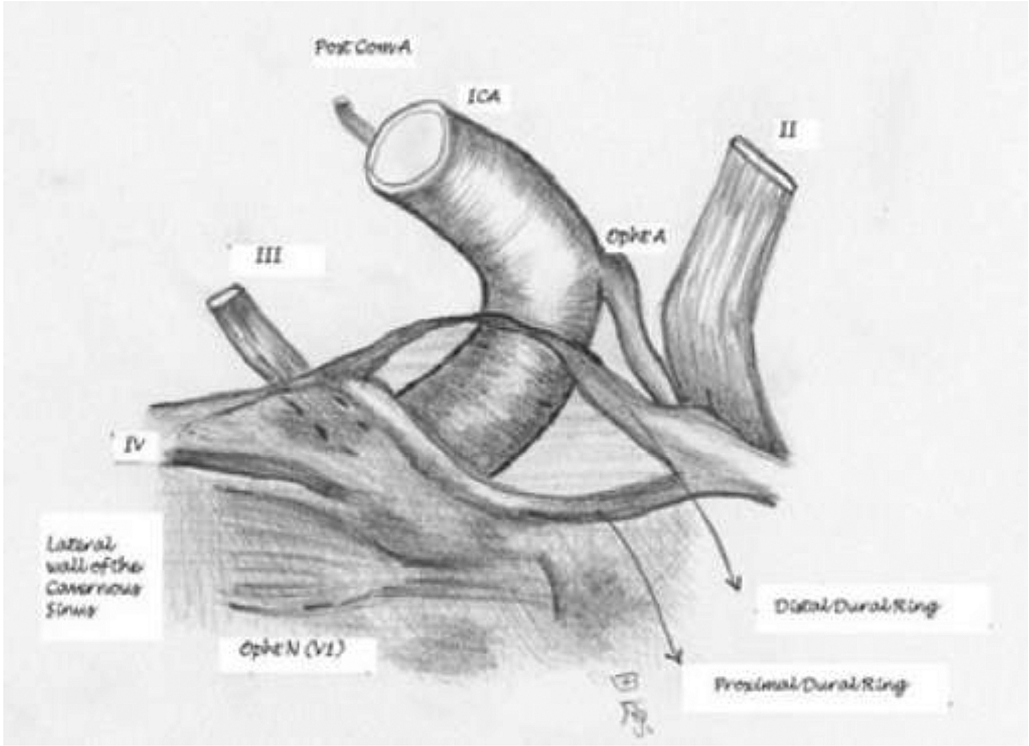


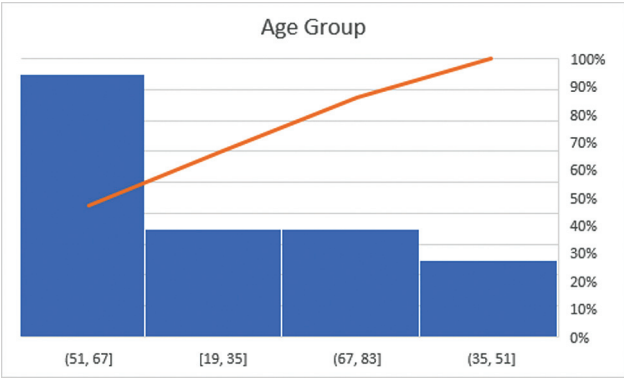
Fig. 1 Anatomical Scheme of the Paraclinoid Region. The scheme shows proximal dural ring, distal dural ring and lateral wall of the cavernous sinus.PostCom A- posterior communicating artery; ICA-Intern carotid artery; Oph A-ophthalmic artery; V1 ophtalmic branch of trigeminal nerve, III-oculomotor nerve and IV -Throclear nerve.

posterior communicating artery aneurysm and another one a hypophyseal artery aneurysm.

We noticed a female predominance (58%). Medium age was 52.5 years-old (range: 19–72). Fifteen patients (41.6%) had multiple aneurysms. Three patients (8.3%) had ruptured aneurysms. *(►**Graph 1–3**)*

The incidence of multiple aneurysms was almost five times higher in women *(►**Graph 2**)*. Right sided aneurysms were four times more frequent than left sided ones in the male group *(►**Graph 3**)*.

Fifteen patients underwent intradural clinoidectomy (41.6%), twenty patients extradural clinoidectomy (55.5%) and one patient intra and extradural clinoidectomy (2.7%). One of the extradural cases also had a pituitary tumor.



Graph 1 Age at presentation.

The incidence of postoperative visual deterioration was 11.1% (4 patients), all of them were from the extradural clinoidectomy group. The intradural clinoidectomy group had no visual deterioration after surgery. Other complications found were cerebrospinal fluid leak (1 patient) and vasospasm followed by diffuse ischemia (1 patient). *(►**Graph 4**)*

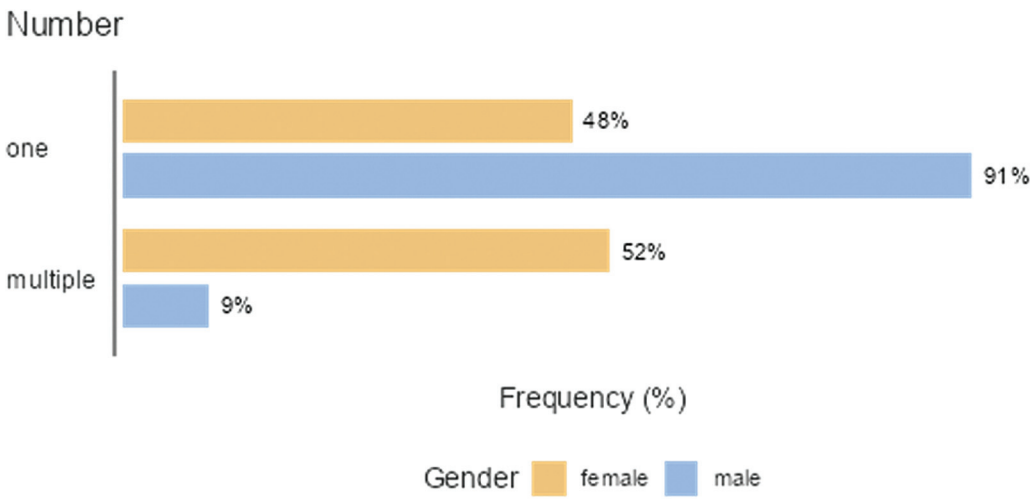
Visual evoked potential was used in 6 patients (16.6%). In two cases VEP was normal during surgery, however they developed visual deterioration in the postoperative period.

Discussion

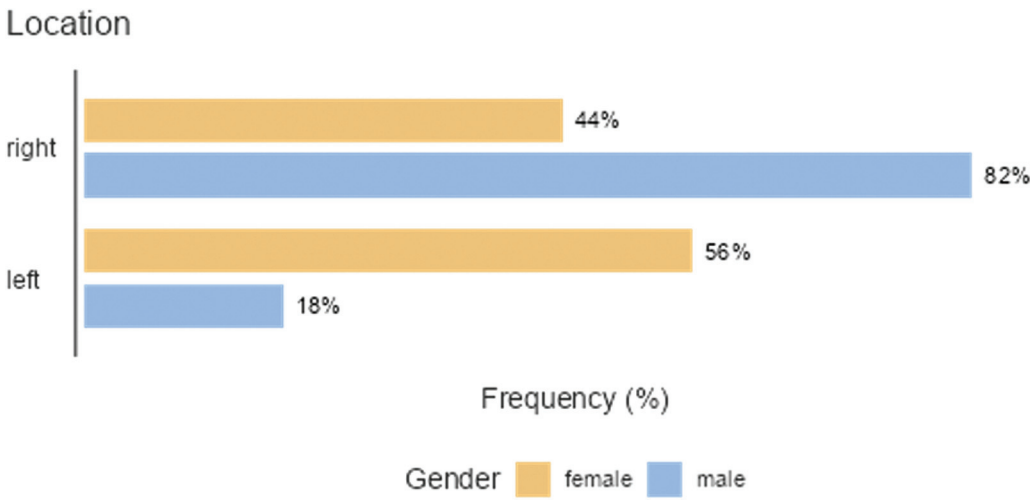
Intradural Clinoidectomy

The intradural clinoidectomy described by Khrist and Fukushima has been frequently used in the last decade. A deeper knowledge of the anatomy of this region is mandatory when performing this technique *(►**Figs. 1–3**)*.[6]

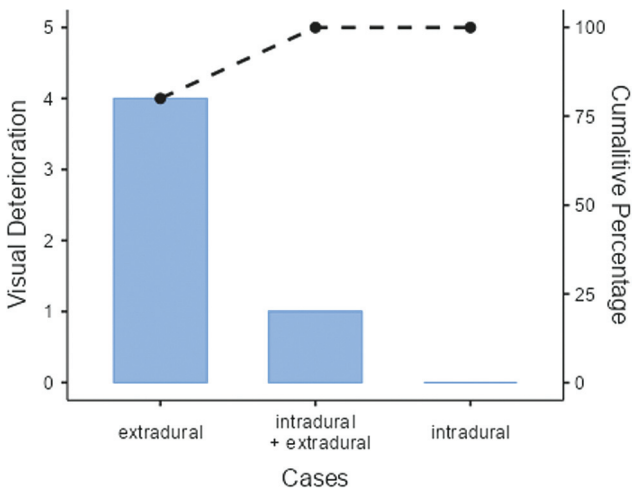
Intradural clinoidectomy can be performed from the dura mater opening, with visualization of the clinoid covered by a thin dura mater mat. We cut out this dural mat with a scalpel and then scissors. With a 3mm diamond drill, we drill the base of the clinoid up to the optic pillar with continuous irrigation so we could check the carotid artery and optic nerve posteriorly. We then remove the clinoid en bloc allowing the visualization of the aneurysm and its neck. The cavernous sinus may bleed soon after clinoid removal, hereby we performed hemostasis as soon as possible with Surgiflow Hemostatic matrix (Ethicon USA) or Floseal (Baxter, USA). *(►**Fig. 4**)*



Graph 2 Gender x Number of aneurysms.



Graph 3 Gender x laterality.



Graph 4 Visual Deterioration x Clinoidectomy.

Our case series and other studies published before showed that this technique has several advantages, especially for the management of paraclinoid aneurysms. The paraclinoid region contains several delicate structures that demand an extremely precise surgical approach, hereby an open view could make the procedure easier.

Intradural clinoidectomy allows the proper understanding of the relation between the anterior clinoid process and the other structures in the paraclinoid region as the internal carotid artery, the optic nerve, the optic struct and also aneurysms that might be present. All variations of ophthalmic artery aneurysms could be managed through this approach. Another advantage is the proximal control of the internal carothid artery (ICA). If an intrasurgical aneurysm rupture occurs, it could be managed swiftly.

The clinoidectomy extent is also a major concern when discussing surgical technique. Only intradural procedures allow the proper assessment of the anterior clinoid process volume that should be removed.[5] Surgeries may be less detrimental if an incomplete ACP removal is performed. The predictive value of three-dimensional computerised tomography angiography (3D-CTA) on the extent of anterior clinoidectomy still remains unsatisfactory; it is limited by

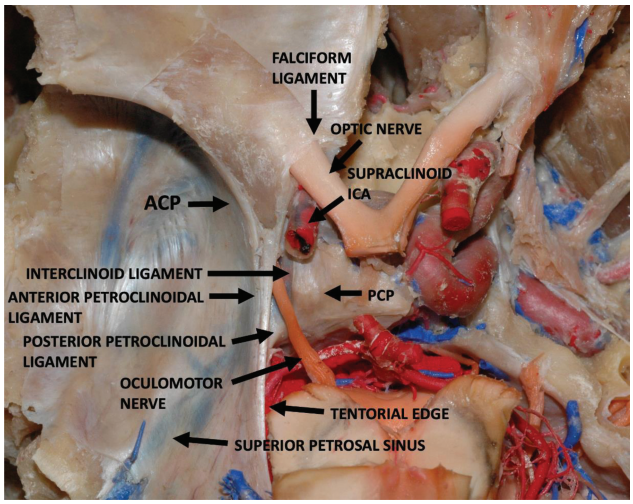


Fig. 2 Superior endocranial view of the skull base, highlighting the anatomical structures most relevant in the anterior clinoidectomy. ACP, anterior clinoid process; PCP, posterior clinoid process; ICA, internal carotid artery.

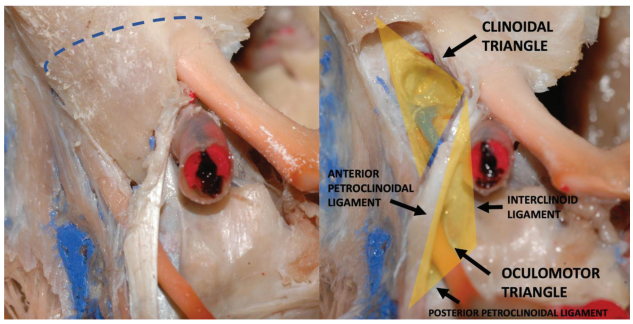


Fig. 3 Superior view of the anterior clinoid process. (**A**) Dotted line demonstrates the clinoidectomy trajectory. (**B**) Same specimen after clinoidectomy, highlighting the anatomical structures of the clinoidal and oculomotor triangles.

the individual variability of carotid-ophthalmic aneurysms (COA) and its surrounding structures.[7]

Possible disadvantages are injury to neurovascular structures durign drilling, lengthy procedure, technical difficulties and complications related to bone dust, such as chronic headache.[8,9]

The protection of the ICA and optic nerve with a dural flap or using gelfoam, as we usually do, minimizes the damage of the adjacent structures. Extensive surgical training allows faster surgeries, which can be as time consuming as the extradural clinoidectomy.[9]

Optic nerve injury is less common with the intradural technique, because of early visualization and drilling further away from the optic nerve. Oculomotor nerve injury is more common in the intradural approach.[7]

Extradural Clinoidectomy

The extradural clinoidectomy described by Dolenc and propagated by several authors[10,11] can be performed using a 3mm diamond drill, under microscopic view. Initially the roof of the orbit and the entire sphenoid wing are removed, followed by cutting the meningo orbital band, which separates the neurovascular structures and the venous plexus inside and meningo orbital artery, and then opening the superior orbital fissure to expose the junction between the dura propria of the temporal lobe and inner membrane of the cavernous sinus. We began to drill the clinoid and optic pillar, leaving the final bone fragment adhered to the carotid artery to be removed with a thin needle holder.

Cavernous sinus hemostasis should be performed with Surgiflo or Floseal, or packaged surgicel. After the epidural procedures, intradural procedures are also performed. The falciform ligament and the distal dural ring are incised to mobilize the optic nerve and the internal carotid artery.[1] Irrigation with cold serum must be constant and we can never fail to move the frontal with a spatula and whenever possible do it with microscopic magnification.

Dolenc's approach requires dividing the meningo-orbital band. Peeling of the dura propria from the inner membrane is continued until the anterior clinoid process is exposed epidurally. Extradural clinoidectomy and optic canal opening are then performed. After the epidural procedures, intradural procedures are also performed. The falciform ligament and the distal dural ring are incised to mobilize the optic nerve and the internal carotid artery.[3,7,9]

We opened the dura mater in an inverted T and moved it aside with prolene stitches as if we were opening a book,[1] then we opened the distal dural ring with microscissors so we could see the aneurysmal neck in all extension.

The extradural approach protects the paraclinoid structures during drilling, which is its greatest advantage. It can also be helpful for removal of medial sphenoid wing meningiomas, pituitary adenomas and craniopharyngiomas. Extradural bone removal increases the devascularization of the tumor and enhances gross tumor resection.[12]

Extradural clinoidectomy is not indicated for ruptured aneurysms or aneurysms in direct contact with the ACP. For those cases, some authors indicate extradural drilling with intradural surveillance and removal of the final portion of the ACP intradurally.[7]

Hybrid Clinoidectomy

Tayebi Meybodi et al. developed a technique that combined extra and intradural steps. Their aim was to avoid the most common disadvantages of both techniques.[13]

Their procedure consists of a standard pterional craniotomy, followed by a 2-step ACP removal. They divided the ACP into anterior and posterior based on the localization of the optic strut. The anterior segment was removed extradurally while the posterior one intradurally, under direct view of the adjacent neurovascular structures.[13]

They concluded that this modified technique allows early decompression of the optic nerve, decreasing visual loss in the postoperative period, while preserving the neurovascular structures. No complications occurred.[13]

Visual Loss

Visual deterioration is one the most discussed complications after clinoidectomy. Several series showed an incidence of

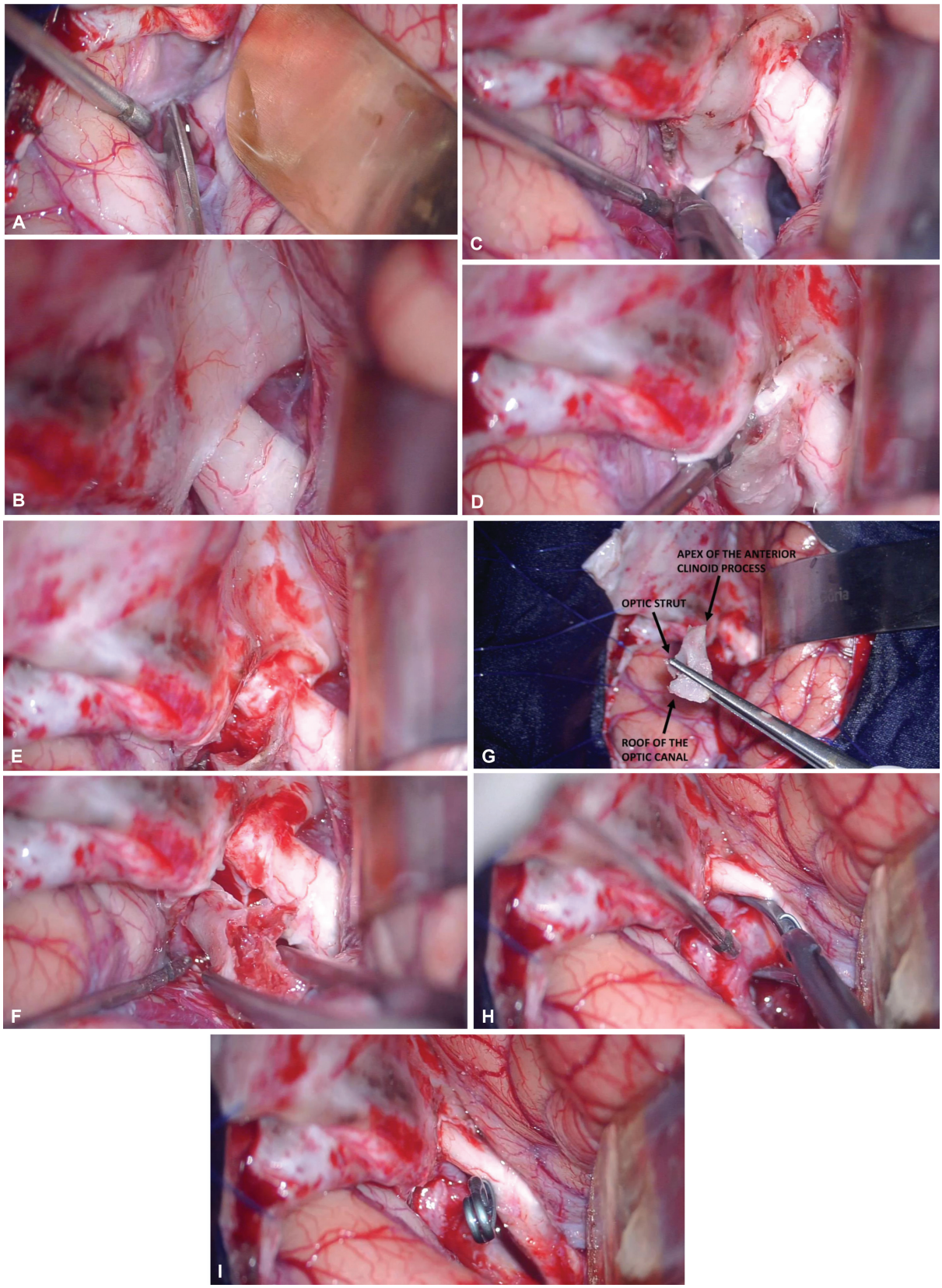


Fig. 4 (**A**) After pterional craniotomy, the Sylvian fissure must be opened with a sharp opening. (**B**) The neck of the aneurysm is hindered by anterior clinoid process. (**C**) The dural surface is cut and removed over the clinoid process exposing the bone surface to be drilled. (**D**) The clinoid process is drilled from the lateral border of the falciform ligament to the lateral border of the clinoid process. (**E**) The optic strut which connects the body of sphenoid bone to anterior clinoid process. (**F**) The optic strut must be removed in bloc by drilling its basal portion. (**G**) Anatomy of clinoid process. (**H**) Clip placement. (**I**) After clipping with total occlusion of the aneurysm while preserving the ophthalmic artery. Intradural removal of anterior clinoid process allowing the view of the aneurysm neck.

visual loss of 0–10% after surgery for COA.[7,14–16] Rates of postoperative visual morbidity in patients with normal vision who underwent elective repair of paraclinoid aneurysms were higher following microsurgical (10.8%; 95% confidence interval [CI] 8.5–13.7) than endovascular (2.0%; 95% CI 1.2–3.2) interventions, $p < 0.001$.[8] Postoperative transient oculomotor palsy also occurred considerably more often in patients undergoing direct clipping and anterior clinoidectomy.

Our series had an incidence of 11.1% of visual loss, discreetly higher than others found in the literature.[3,7,15,16] Yamada et al. had an incidence of 6.2% of visual deterioration in 33 patients operated through the extradural approach.[3]

Several causes could lead to blindness after clinoidectomy, including direct trauma to the optic nerve, heat from drilling without proper cooling by irrigation, devascularization of the ophthalmic artery during dissection and mechanical compression of the clip.

Drill temperature is a point of concern. Drilling close to the optic nerve can lead to several damages to its structure. Nerve tissue can suffer permanent damage around 47°C, the bone temperature around the drill can be up to 70°C.[5]

Direct traumatic injuries are also a problem. Neurovascular structures can suffer mechanical injury during inadvertent drilling. Cottonoids can also get entangled to the rotating drill, injuring the surrounding structures.[7]

Some authors proposed the use of micro-rongeurs instead of a drill for superior projecting paraclinoid ICA aneurysms; they obtained excellent results.[17,18] The 'no drill' technique offers a more conservative approach to anterior clinoidectomy and optic canal unroofing by eliminating the risks of thermal injury and ultrasound-associated cranial neuropathies.[19]

Several procedures during surgery could minimize the risk of visual deterioration. The use of dura mater and gelfoam for protection of ICA and optic nerve are mentioned in almost all surgical reviews. Statistical analysis also showed that piecemeal anterior clinoidectomy was significantly safer than en bloc removal in preserving visual function.[20] Tsukahara showed that postoperative visual complications occurred significantly more often in en bloc clinoidectomy with high-speed drills than in piecemeal clinoidectomy with an ultrasonic bone curette and microrongeurs.[19]

Excess dissection of carotid oculomotor membrane causes postoperative delayed visual worsening. Ota et al. avocated that for small aneurysms, the membrane should not be opened. They also mentioned that microsurgical clipping of asymptomatic medial projecting aneurysms should be avoided; the endovascular approach seems to be more appropriated for those cases.[18]

Intraoperative visual evoked potential is a current trend, however controversial. It may not be effective in cases of aneurysm surgeries with optic nerve compression or optic juxta position. Some authors concluded that it might be useful for preventing postoperative worsening of visual function.[20] Our series did not show this relation. In 2 cases the VEP showed preservation of visual system, although we noticed postoperative visual loss. Tsukahara et al. also found similar results as ours.

Recent studies suggest the use of ultrasonic bone removal instead of the tradicional power-drilling clinoidectomy. However, what we noticed so far is that it could lead to ultrasound-related cranial neuropathies. The cost of the device also decreases its routine use.[19]

Barrenechea et al. evaluated the results of optic nerve mobilization instead of anterior clinoidectomy. They unroofed the optic canal with a diamond drill, made an incision in the falciform ligament and optic sheath and then gently mobilized the optic nerve with a dissector. As a result, they facilitated the aneurysmal neck exposure without the use of clinoidectomy. Patients did not develop any added visual loss. They concluded that this technique permitted not only early decompression of the optic nerve, but also dissection of the arachnoid between the inferior surface of the optic nerve and the superior surface of the ophthalmic-carotid artery and aneurysm dome.[21]

Conclusion

Visual loss is a relevant and relatively common complication after clinoidectomy. Our series showed a higher incidence of visual loss in the extradural clinoidectomy. Regardless of the approach used, careful use of the drill around neurovascular structures is mandatory. Piecemeal clinoid removal and even partial clinoid removal are recommended.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest
None.

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An Algorithm for the Multimodality Treatment of Cerebral Arteriovenous Malformations

Um algoritmo para o tratamento multimodal de Malformações Arteriovenosas Cerebrais

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Arq Bras Neurocir 2024;43(4):e286–e295.

Abstract

Introduction: The algorithm of multimodal treatment (MMT) of arteriovenous malformations (AVMs) combined with intent-to-cure and presurgery embolization benefits was developed. **The aim** was to analyze the effectiveness of the MMT compared with unimodal intent-to-cure embolization in patient groups matched concerning clinical and angiographic characteristics.

Methods: A prospective cohort study of MMT effectiveness and safety was performed. To estimate differences in the total occlusion rate and complication rate of MMT compared to unimodal embolization, a 1:1 matched patient group was identified from the Russian Endovascular Neuro Society (RENS) AVM registry using the propensity score matching (EMB group). The treatment outcomes were assessed by the rate of achieving 100% AVM obliteration on follow-up angiography, morbidity, mortality, and the perioperative complication rate.

Results: Complete AVM occlusion was achieved in 93.7% of patients in the MMT group vs 76.2% of patients in the EMB group ($p < 0.001$). A favorable clinical outcome (mRS = 0–1 at the end of follow-up) was observed in significantly more patients in the MMT group compared with the EMB group (88.9% vs 71.4%, $p = 0.024$). In the MMT group, the rates of intraoperative and postoperative ischemic complications were comparable to those in the EMB group, and there was a significantly lower rate of postoperative hemorrhagic complications (6.3% vs 20.6%, $p = 0.035$).

Conclusions: Embolization as the main curative technique of the multimodal algorithm timely followed by microsurgery and radiosurgery ensures the highest clinical

Keyword
► malformation

received
November 7, 2023
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1795069.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

and angiographic efficacy of treatment and reduces the rate of disabling postoperative complications.

Resumo

Introdução: O algoritmo de tratamento multimodal (MMT) de malformações arteriovenosas (MAVs) combinado com os benefícios da embolização com intenção de cura e pré-cirurgia foi desenvolvido. O objetivo era analisar a eficácia da MMT em comparação com a embolização com intenção de cura unimodal em grupos de pacientes pareados em relação às características clínicas e angiográficas.

Métodos: Um estudo de coorte prospectivo da eficácia e segurança da MMT foi realizado. Para estimar as diferenças na taxa total de oclusão e na taxa de complicação da MMT em comparação com a embolização unimodal, um grupo de pacientes pareado 1:1 foi identificado no registro de MAV da Russian Endovascular Neuro Society (RENS) usando a correspondência de pontuação de propensão (grupo EMB). Os resultados do tratamento foram avaliados pela taxa de obtenção de 100% de obliteração da MAV na angiografia de acompanhamento, morbidade, mortalidade e taxa de complicação perioperatória.

Resultados: A oclusão completa da MAV foi alcançada em 93,7% dos pacientes no grupo MMT vs 76,2% dos pacientes no grupo EMB ($p < 0,001$). Um resultado clínico favorável (mRS = 0–1 no final do acompanhamento) foi observado em significativamente mais pacientes no grupo MMT em comparação com o grupo EMB (88,9% vs 71,4%, $p = 0,024$). No grupo MMT, as taxas de complicações isquêmicas intraoperatórias e pós-operatórias foram comparáveis às do grupo EMB, e houve uma taxa significativamente menor de complicações hemorrágicas pós-operatórias (6,3% vs 20,6%, $p = 0,035$).

Conclusões: A embolização como a principal técnica curativa do algoritmo multimodal seguida oportunamente por microcirurgia e radiocirurgia garante a mais alta eficácia clínica e angiográfica do tratamento e reduz a taxa de complicações pós-operatórias incapacitantes.

Palavras-chave
► malformação

Introduction

Arteriovenous malformations (AVMs) of the brain are complex lesions characterized by a tortuous vascular bundle located between one or more feeding arteries and one or more draining veins.[1] The incidence rate of newly diagnosed AVMs ranges from 1[2] to 1.34 (3) per 100,000 population per year, of which about half are malformations with hemorrhagic presentation.[3,4] Only a small number of intact AVMs result in neurological deficits; however, after rupture, neurological deficits of varying severity are present in 30–50% of cases,[5] which necessitates timely diagnosis and treatment of AVMs to reduce the risk of disability. Despite the rapid development of endovascular techniques, which improves the clinical and angiographic outcomes of treatment each year, there are still some disputes about their applicability for certain groups of patients[6] and about correct combinations of modalities to achieve the maximum efficacy and safety of surgical treatment.[7–10]

The first and most important problem is the management of patients with unruptured AVMs. Surgical treatment is considered conditionally mandatory for patients with ruptured AVMs[11] due to a significantly increased risk of rerupture and mortality.[12] However, the management of unruptured AVMs (especially asymptomatic) is still contradictory.[13,14] This is largely related to the inability to assess real risks of a natural course of the disease because a high number of patients are unaware of their AVMs (in this group, both silent AVMs and, on the contrary, the most severe AVMs in which the first rupture leads to immediate death) and because disparate groups are often compared. In this case, most neurosurgical centers are required to offer treatment to AVM patients, which consistently updates statistics on the treatment of different AVMs.

The second important problem is the choice of optimal surgical management. Currently, there are three surgical options: microsurgery, endovascular embolization, and radiosurgery.[1] Each of them has its own advantages and disadvantages, so their combinations, i.e. multimodal treatment,[15] are usually used, depending on characteristics of the patient and AVM. However, there are different approaches to multimodal treatment, which vary depending on the surgeon's preferences, current clinical guidelines, and protocols.[16,17] The question of how to combine them correctly and, most importantly at the moment, how embolization should be optimally used remains unresolved.[18] In this regard, there

are two extreme opinions: consider embolization primarily as an adjuvant option to reduce the AVM size and facilitate subsequent microsurgery or radiosurgery[19,20] or consider it as a stand-alone and main option with intent to cure and to embolize up to the maximum occlusion.[12,19,21] At the start of the AVM registry of the Russian Endovascular Neuro Society (RENS), the second option was initially adopted. The 6-year experience in treating more than 500 AVMs, a gradual modification of the surgical approach, and increasing competence in radiosurgery and microsurgery have prompted us to conclude that embolization should be considered as the main curative modality combined with microsurgery or radiosurgery to improve safety and long-term clinical outcomes, which provides a third option for its use, rarely considered in the literature. Based on this option, we developed and implemented an algorithm for multimodal management of AVM patients, which accounts for the main advantages and limitations of each of the modalities. The aim of this study was to analyze the efficiency of the implemented algorithm for multimodal treatment of cerebral AVMs compared with that of the monomodal intent to cure use of embolization in groups of patients comparable in clinical and anatomical characteristics of AVMs, who were selected using the propensity score matching (PSM) method.

Methods

Study Design and Patient Selection

We performed a prospective cohort study of multimodal treatment with a comparison group selected from the RENS AVM registry. The study included 562 patients with intracranial AVMs who received endovascular treatment at the Centre for Angioneurology and Neurosurgery of the Meshalkin National Medical Research Center in the period between 2009 and 2019 and at the Federal Center of Brain Research and Neurotechnologies of the FMBA in the period between 2021 and 2022. Starting in 2011, multimodal treatment of AVM patients, with continuous efficiency evaluation, was introduced. All patients who agreed to participate in the study were included in the multimodal treatment group (MMT group, n = 75).

The criteria for inclusion in the MMT group were as follows:

- age below 75 years;
- technical feasibility of endovascular treatment;
- impossibility of complete one-stage AVM embolization;
- signed informed consent to participate in the study.

The exclusion criteria were:

- history of AVM rupture within the last 30 days;
- clinical and neurological instability of the patient within 24 hours before surgery;
- indications for palliative treatment (subtentorial AVM, Spetzler–Martin grade 5 AVM);
- severe comorbidity.

The comparison group (endovascular embolization (EMB) alone) was selected from 220 patients who underwent endovascular embolization alone, completed treatment, and followed up for at least 6 months with control angiography. After excluding patients with 100% occlusion after the first stage of embolization as not comparable with patients of the MMT group, 127 patients of the embolization group were allocated to the comparison group and included in the analysis. To eliminate differences between the groups and potential bias in the selection of patients, comparable groups were selected using the PSM method. The final groups included 63 patients each (►**Table 1**).

Principles of Endovascular Embolization

Based on our previous studies of hemodynamic models of AVM embolization and clinical experience, we set up the following embolization principles which have been adhered to regardless of whether the patient belongs to the MMT or embolization group:

- AVM closure is performed using intranidal embolization and is not limited to the closure of feeding arteries;
- Use of a catheter with a distal detachable tip;
- Treatment begins with elimination of a fistula component;
- Along with fistula components, AVM compartments with intranidal aneurysms, as potential sources of hemorrhagic complications, are first eliminated;
- Tendency for radicality without increasing the risk of complications;
- Multistage embolization with no more than 60% occlusion in one stage is preferable to decrease the risk of sudden changes in AVM hemodynamics;
- Feeding arteries should be closed starting from large to small vessels.

Treatment Protocol and Ethics

For patients included in the MMT group, the individual treatment approach was defined based on monitoring the patient's condition after each of the surgical stages with additional, if necessary, radiosurgery or microsurgery after one or more stages of embolization. Embolization included 1 to 11 stages to comply with the identified principles of curative embolization while minimizing the risk of procedures. The study was conducted according to good clinical practice, which ensures that the design, implementation, and communication of data are reliable, that patient's rights are protected, and that the integrity of subjects is maintained by the confidentiality of their data. The study was approved by the Local Ethics Committee of the Meshalkin National Medical Research Center (number of protocols 15, September 3, 2009). All patients provided written informed consent by the Declaration of Helsinki, which included their consent for using their data in analyses and for it to be presented.

Data Collection

At enrollment, information on disease history, characteristics, and severity was collected for each patient. Data about the disease onset, clinical course, and complete preoperative neurological status were considered. Preoperative non-

Table 1 Comparative characteristics of patients with multimodal treatment and embolization before and after selection of comparable groups using the PSM method

Parameter	Before PSM			After PSM		
	EMB (n = 127)	MMT (n = 75)	P value	EMB (n = 63)	MMT (n = 63)	P value
Gender: female, n [%]	62 [48.82%]	41 [54.67%]	0.511	34 [53.97%]	32 [50.79%]	0.858
Age of onset, Me (IQR)	28 (21 : 40)	27 (17 : 42)	0.668	28 (20.5 : 42)	25 (16 : 40)	0.393
Age at treatment, Me (IQR)	35 (24.5 : 45.5)	36 (24 : 47.5)	0.996	35 (25 : 47)	32 (22 : 45)	0.481
Disease duration, Me (IQR)	1 (0 : 5.5)	2 (0.5 : 6)	0.214	1 (0 : 6.5)	2 (1 : 5.5)	0.294
Primary symptom, n [%]			0.624			0.495
Asymptomatic	4 [6.35%]	3 [4.76%]		11 [8.66%]	5 [6.67%]	
Headache	11 [17.46%]	6 [9.52%]		20 [15.75%]	9 [12%]	
Neurological deficit	2 [3.17%]	1 [1.59%]		6 [4.72%]	1 [1.33%]	
Seizure	22 [34.92%]	23 [36.51%]		43 [33.86%]	24 [32%]	
Intracranial hemorrhage	24 [38.1%]	30 [47.62%]		47 [37.01%]	36 [48%]	
mRS score, n [%]			0.317			0.516
0	106 [83.46%]	59 [78.67%]		49 [77.78%]	50 [79.37%]	
1	15 [11.81%]	9 [12%]		11 [17.46%]	7 [11.11%]	
2	3 [2.36%]	3 [4%]		1 [1.59%]	3 [4.76%]	
3	3 [2.36%]	1 [1.33%]		2 [3.17%]	1 [1.59%]	
4	0 [0%]	2 [2.67%]		0 [0%]	1 [1.59%]	
5	0 [0%]	1 [1.33%]		0 [0%]	1 [1.59%]	
Spetzler–Martin grade, n [%]			0.72			0.975
I	5 [3.94%]	5 [6.67%]		3 [4.76%]	2 [3.17%]	
II	39 [30.71%]	20 [26.67%]		18 [28.57%]	18 [28.57%]	
III	62 [48.82%]	35 [46.67%]		29 [46.03%]	30 [47.62%]	
IV	21 [16.54%]	15 [20%]		13 [20.63%]	13 [20.63%]	
Localization: involvement of two or more brain areas, n [%]	25 [19.69%]	18 [24%]	0.585	17 [26.98%]	16 [25.4%]	>0.999
Localization: eloquent brain area, n [%]	22 [57.89%]	13 [61.9%]	0.981	12 [54.55%]	11 [64.71%]	0.755
Cysts associated with AVM, n [%]	25 [19.69%]	20 [26.67%]	0.328	12 [19.05%]	18 [28.57%]	0.296
Presence of a fistula component, n [%]	50 [39.37%]	25 [33.33%]	0.479	22 [34.92%]	20 [31.75%]	0.85
Aneurysms associated with AVM, n [%]	35 [55.6%]	14 [22.2%]	**0.002**	17 [26.98%]	14 [22.22%]	0.679
Transient afferents, n [%]	30 [26.79%]	36 [50.7%]	**0.002**	18 [30.51%]	28 [47.46%]	0.089
Caliber of AVM vessels, n [%]			**0.035**			0.882
Small	13 [14.94%]	20 [33.9%]		11 [22.92%]	11 [23.4%]	
Mixed	32 [36.78%]	15 [25.42%]		17 [35.42%]	14 [29.79%]	
Medium	6 [6.9%]	6 [10.17%]		6 [12.5%]	5 [10.64%]	
Large	36 [41.38%]	18 [30.51%]		14 [29.17%]	17 [36.17%]	
Venous drainage, n [%]		43 [57.33%]	0.078			0.135
Superficial	75 [59.06%]			32 [42.67%]	26 [41.27%]	
Mixed	19 [14.96%]			15 [20%]	11 [17.46%]	
Deep	33 [25.98%]			28 [37.33%]	26 [41.27%]	
Maximum AVM size, cm, Me (IQR)	36 (29 : 44)	35 (28 : 45)	0.581	35.5 (30 : 43.5)	35 (29 : 46)	0.895

invasive neuroimaging (CT, MRI) was used to assess the AVM size and localization, eloquence of the brain area, and Spetzler–Martin grade.[22] If there were signs of previous hemorrhage (posthemorrhagic cysts, hemosiderin deposits), the type of disease course was assessed as hemorrhagic. Preoperative panangiography was performed, which involved selective angiography of both carotid territories (internal carotid arteries (ICAs) and external carotid arteries (ECAs) separately) and the vertebrobasilar territory (both vertebral arteries). Angiography data were used to evaluate malformation vascular territories, the number, type (terminal, transient), and diameter of feeding arteries, the presence of flow-related or unrelated aneurysms, their type, location, number, and size, the presence of a fistula component, the caliber of AVM nidus vessels, the number of veins, the type (deep, superficial) of venous drainage, and the presence of varices.

Endpoint Definition

The primary endpoint of the study was 100% AVM obliteration on follow-up angiography scans after the last surgical stage.

The secondary endpoints of the study were:

- 90% or more (subtotal) malformation occlusion according to follow-up angiography;
- neurological outcomes in patients: the number of patients with different dynamics of neurological deficit (achievement or maintenance of the mRS; an increase in the mRS by 1 or more points; achievement of the mRS = 2 or more; an increase in the mRS by 2 or more points);
- development of complications associated with AVM surgery during postoperative hospital stay: the total number of complications (any technical complication) and the number of complications leading to deterioration in the patient's condition (a persistent decrease in the mRS by at least 1 point, which was not compensated until discharge from the hospital);
- mortality in the early postoperative period.

Statistical Analysis

The STATISTICA 7.0 software (StatSoft, USA) and RStudio software version 1.0.136 (Free Software Foundation, Inc., USA) with R packages version 3.3.1 (R Foundation for Statistical Computing, Austria) were used for analyses.

Descriptive statistics were shown as absolute frequencies or medians with interquartile range. The Mann-Whitney U-test, ANOVA, Pearson's χ^2 test, Fisher's exact test, and nonparametric Kruskal–Wallis test by rank and median multiple comparisons were used depending on the type of analyzed data. Statistically significant predictors were identified by univariate logistic regression analysis. All reported *p*-values were based on two-tailed tests of significance; *p*-values < 0.05 were regarded as statistically significant.

To form comparable surgical groups of intervention and minimize the risk of bias, patients were selected using the propensity score matching (PSM) method. PSM statistical model included the gender, age, and type of AVM presentation, age at surgery, vascular territory, caliber of AVM vessels, size of feeding vessels, presence of fistulas and aneurysms, and Spetzler–Martin AVM grade.

Results

Baseline Characteristics of Study Groups

PSM enabled balancing the groups on baseline characteristics, which made the groups comparable not only in demographic indicators but also in disease severity, onset, and course as well as in AVM angiographic characteristics (►**Table 1**). The number of patients with a history of at least one AVM rupture was 27 (42.9%) in the embolization group and 31 (49.2%) in the MMT group ($p = 0.592$), with some patients presenting with a history of multiple bleeding episodes (6.35 and 12.7%, respectively, $p = 0.363$). Approximately 2/3 of patients in each group had AVM treatment initiated within the first three years after AVM symptom onset or MRI findings (65.1 and 68.25%, respectively, $p = 0.850$).

Approximately 2/3 of patients in each group had a complex vascular territory (69.8% and 68.3%, respectively, $p > 0.999$). The number of feeding arteries amenable to catheterization was 5 (3: 7) and 6.5 (4: 7), respectively, ($p = 0.313$), and the number of draining veins was 2 (1: 3) and 2 (1: 3), respectively, ($p = 0.093$).

Characterization of Treatment

Depending on the baseline patient's condition, AVM size, and characteristics, and by the principles of embolization, each patient underwent 1 to 11 successive stages of surgical treatment. ►**Figure 1** shows the overall study design and surgical options for enrolled patients. In the multimodal treatment group, the embolization series was followed by microsurgery in 30 (47.6%) patients, radiosurgery in 32 (50.8%) patients, and a combination of microsurgery and radiosurgery in 1 (1.6%) patient.

In total, patients of the EMB and MMT groups underwent 193 and 214 embolization stages, respectively, and 193 and 278 stages of all types of treatment. Most embolization stages were performed through the transarterial approach (177 (92.2%) and 202 (94.4%) stages, respectively, $p = 0.330$). The most common agents used for embolization were Onyx and its analogs (151 (78.6%) stages in the EMB group and 178 (83.2%) stages in the MMT group, $p = 0.210$); also, sulfacrylates (48 (25%) and 54 (25.2%), respectively, $p > 0.999$), coils (15 (7.8%) and 10 (4.7%), respectively, $p = 0.218$), PHIL (2 (1%) and 3 (1.4%), respectively, $p > 0.999$), and their combinations were used in one-stage procedures.

Efficacy of AVM Occlusion

After the last surgical stage, all patients underwent a follow-up examination at 6 and 12 months. The multimodal approach compared with monomodal embolization was slightly less effective regarding the number of patients with 100% occlusion immediately after treatment (30 (47.6%) vs 34 (54%), $p = 0.593$), but showed a significant advantage at the end of follow-up (59 (93.7%) vs 42 (66.7%), $p = 0.0002$). In this case, 3 (4.8%) patients in the EMB group had recanalization at the follow-up examination; there was no recanalization in patients of the MMT group ($p = 0.244$). The number of patients with subtotal occlusion ($\geq$ 90%) at the end of follow-up was 62 (98.4%) in the multimodal treatment group and 48 (76.2%) in the endovascular treatment group ($p < 0.001$). The median number of stages required for complete AVM occlusion, confirmed by follow-up angiography at 12 months after treatment, was 2 (2: 4) stages in the EMB group and 4 (3: 5) stages in the MMT group ($p = 0.310$).

Clinical Efficacy of Treatment

Both treatment approaches demonstrated a high clinical efficacy, with over 60% of patients lacking neurological symptoms at the end of follow-up. The key neurological outcomes of treatment and changes in the patient's condition at the end of follow-up are presented in ►**Table 2** and ►**Figure 2**. In this case, the MMT group showed better clinical outcomes in the number of patients with worsening of the baseline condition: 20 (31.7%) patients in the EMB group had worsening of the

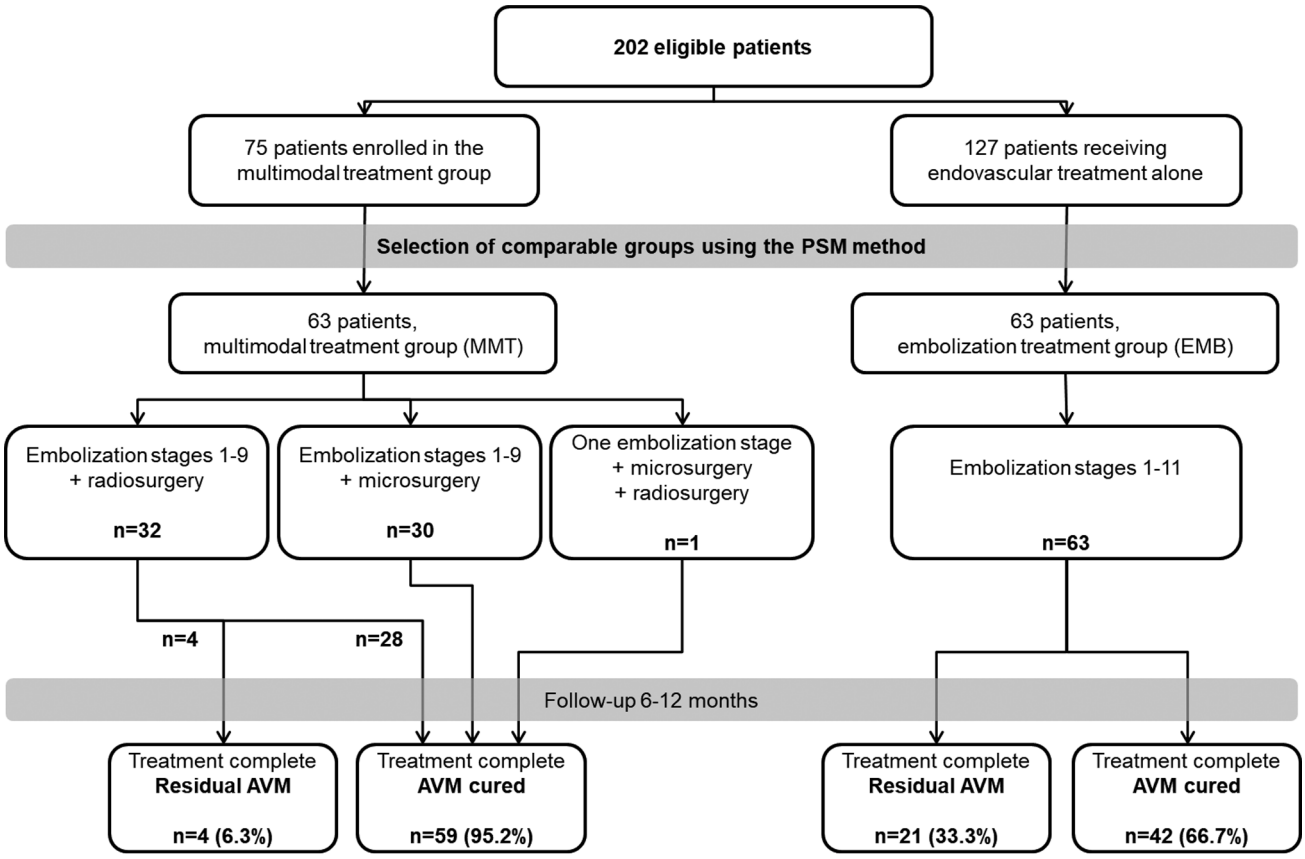

Fig. 1 Distribution of patients by surgical modality in the endovascular and multimodal treatment groups.

Table 2 Clinical outcomes in the compared groups

Clinical outcome	EMB (n = 63)	MMT (n = 63)	p value
Mortality	1 (1.6%)	0 (0%)	>0.999
Morbidity (the number of patients with mRS≥2 at the end of follow-up)	16 (25.4%)	8 (12.7%)	0.111
Full recovery of function (mRS = 0 at the end of follow-up)	39 (61.9%)	45 (71.4%)	0.349
Patients with a mRS score of 0–1 at the end of follow-up	45 (71.4%)	56 (88.9%)	**0.024**
Patients without worsening (preservation of mRS = 0 or any improvement in the condition)	39 (61.9%)	48 (76.2%)	0.123
Patients without improvement (retaining or worsening of preoperative deficit)	24 (38.1%)	15 (23.8%)	0.123
Patients with a decrease in the mRS by 1 or more points	20 (31.7%)	9 (14.3%)	**0.033**
Patients with a decrease in the mRS by 2 or more points	13 (20.6%)	3 (4.8%)	**0.015**

baseline condition by 1 or more mRS points compared with only 9 (14.3%) patients in the MMT group (p = 0.033); worsening by 2 or more points was detected in 13 (20.6%) and 3 (4.8%) patients, respectively (p = 0.015). A lethal outcome occurred in one patient of the EMB group, whereas there were no deaths in the MMT group (p > 0.999).

Perioperative Complications of Treatment

At each stage of the treatment, all technical complications, intraoperative bleeding, intraoperative thromboembolic complications, and any complications in the postoperative period were recorded. The groups demonstrated comparable results regarding the safety of surgery (►**Table 3**). Intraoperative complications at least at one stage occurred in 14 (22.2%) patients in the EMB group and 11 (17.5%) patients in the MMT group (p = 0.656); in this case, less than one-third of the complications led to persistent neurological deficit: 2 (3.2%) in the EMB group and 4 (6.3%) in the MMT group (p = 0.680). Postoperative complications at least at one stage occurred in 24 (38.1%) patients in the EMB group and 18 (28.6%) patients in the MMT group (p = 0.345); they led to persistent neurological deficit in 18 (28.6%) patients in the EMB group and 10 (15.9%) patients in the MMT group (p = 0.133). Endovascular treatment alone significantly

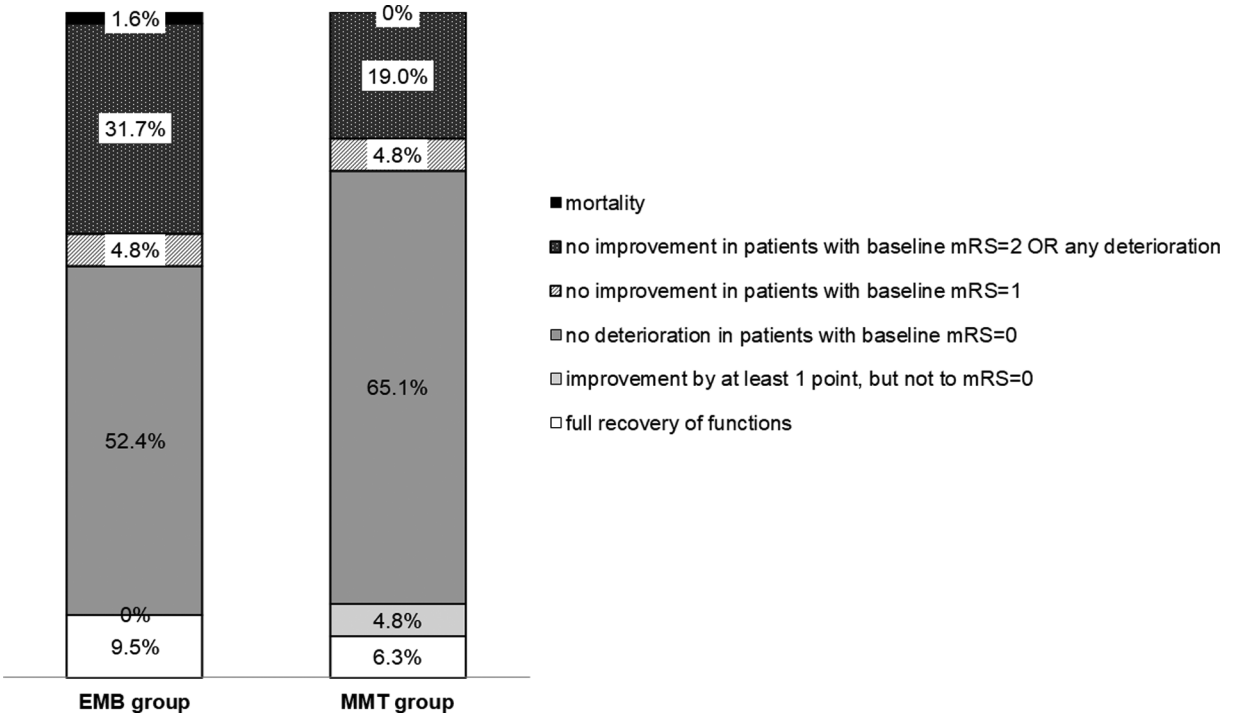

Fig. 2 Dynamics of neurological deficit in the compared groups.

Table 3 Intraoperative and postoperative complications in the groups

Complication	Number of patients		
	EMB (n = 63)	MMT (n = 63)	p value
Complications not associated with deterioration of the patient's condition			
Intraoperative complications			
Hemorrhagic	9 (14.3%)	9 (14.3%)	>0.999
Thromboembolic	5 (7.9%)	2 (3.2%)	0.273
Postoperative complications			
Hemorrhagic	13 (20.6%)	4 (6.3%)	**0.035**
Ischemic	11 (17.4%)	14 (22.2%)	0.656
Complications associated with deterioration of the patient's condition			
Intraoperative complications			
Hemorrhagic	1 (1.6%)	4 (6.3%)	0.365
Thromboembolic	1 (1.6%)	0 (0%)	>0.999
Postoperative complications			
Hemorrhagic	8 (12.7%)	1 (1.6%)	**0.033**
Ischemic	10 (15.9%)	9 (14.3%)	>0.999

increased the risk of postoperative hemorrhagic complications with a rate of 8 (12.7%) in the EMB group and 1 (1.6%) in the MMT group ($p = 0.033$). In this case, most of these complications of the endovascular approach occurred after one of the first 3 stages, whereas risks of postoperative bleeding upon multimodal treatment increased only after the 5th stage ($p = 0.011$). Emergent surgery due to a postoperative complication was required in 21 cases in 15 patients (23.9% of patients, 10.9% of stages) in the EMB group and 2 cases in 2 patients (3.2% of patients, 0.7% of stages) in the MMT group, ($p = 0.001$ for patients, $p < 0.001$ for stages).

Discussion

A comparison of two surgical strategies (endovascular embolization vs multimodal management) demonstrated that

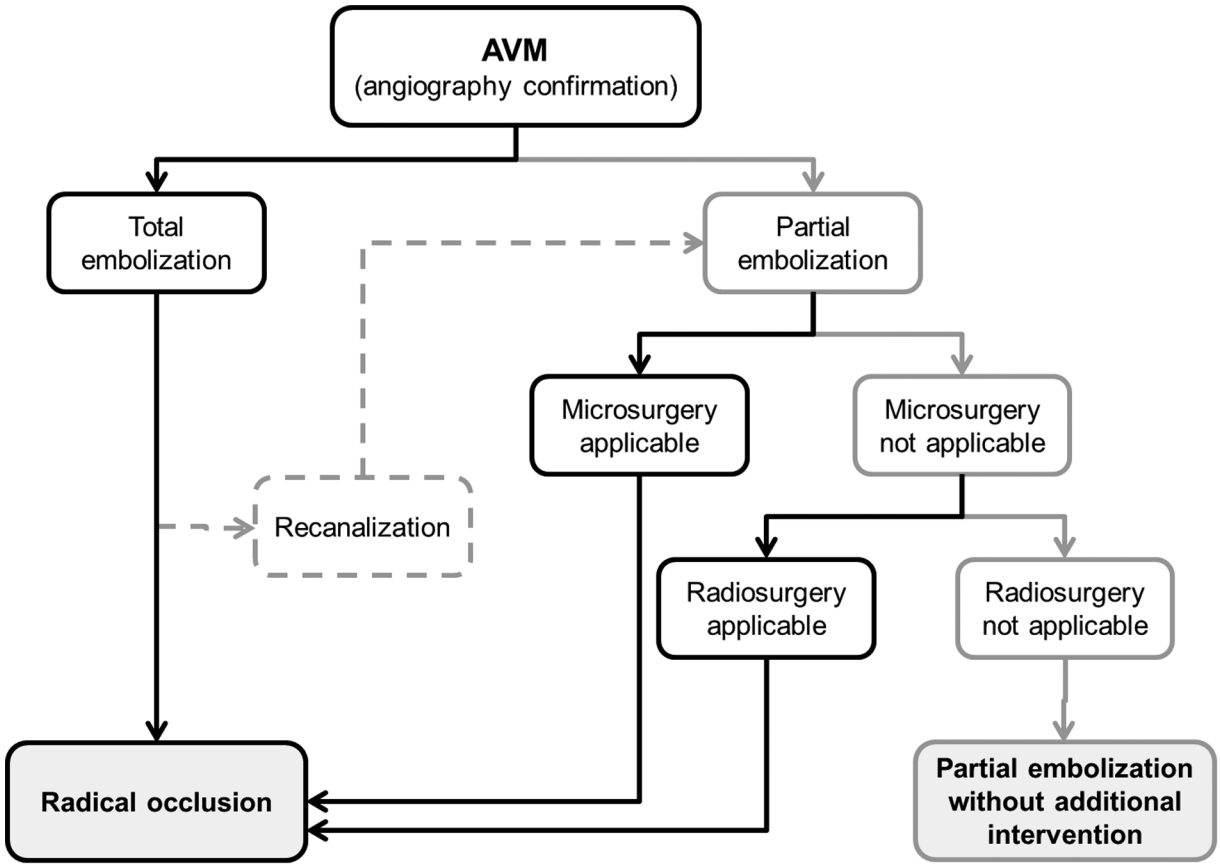

Fig. 3 Algorithm for multimodal AVM treatment.

embolization timely combined with other surgical options not only significantly enhanced the overall radicality of AVM treatment but also increased the safety of surgery and provided better clinical outcomes in patients. Comparison of clinical outcomes and dynamics of neurological deficit in patients after treatment showed that, in the groups comparable in baseline clinical conditions, the multimodal management provided complete AVM occlusion in 93.7% of patients and preserved or improved clinical parameters in a significantly larger number of patients compared with those in the group of endovascular treatment alone.

Because cerebral AVMs differ in size, location, and complexity of treatment, treatment methods also vary. To date, there are three AVM treatment modalities: microsurgery, endovascular embolization, and radiosurgery.[12] Each of them has its own advantages for certain subgroups of patients.[16] All of them are aimed at preventing hemorrhages, which require complete AVM occlusion.[23] At present, there is no ideal versatile treatment option, and their combination is optimal, depending on the patient characteristics and the AVM parameters, i.e. multimodal treatment. In this case, there are different approaches to multimodal treatment, which vary depending on the surgeon's preferences, current clinical guidelines, and protocols.[24,25] In some cases, microsurgery or radiosurgery can be the major option, with embolization being used only as a pretreatment stage to reduce the AVM size and mitigate the risks of the main surgical modality.[26,27] In other situations, embolization can be used as the main curative modality, switching to microsurgery or radiosurgery only if safe embolization of the malformation nidus is impossible.[21,27]

In this study, we demonstrated that the use of embolization alone, as the only surgical option, has high efficacy and safety rates comparable to data of other major centers.[15,28] However, the best angiographic and clinical results can be achieved if other treatment options may be timely supplemented, which allowed us to formulate a decision-making algorithm for multimodal AVM treatment (►**Fig. 3**). Endovascular embolization should be used as a curative option in strict accordance with the principles of safe embolization unless the risks of the next stage exceed the appropriate risks of microsurgery and radiosurgery. When achieving subtotal AVM occlusion, it is necessary to complete embolization; if the endovascular technique cannot provide complete AVM exclusion, microsurgical removal or radiosurgical treatment should be used as soon as possible. The latter is less preferable because of the delayed effect and should be considered on a residual basis.

An important factor affecting the choice of a treatment option is the degree of modality development in each medical center. Often, the authors focus on only one modality because they do not have the technical capacity or sufficient experience to implement other intervention types. This limits the surgical approach and prevents the surgeon from switching to another type of intervention to reduce the risk of complications and leads to unsatisfactory

treatment outcomes. In this study, we demonstrated that the use of one modality alone significantly increased the risks of short-term and long-term treatment complications associated with the deterioration of the patient's condition. For this reason, clinical efficacy indicators in the group of embolization alone were comparable to those in the ARUBA study.[10] However, the addition of microsurgical and radiosurgical modalities reduces the number of postoperative complications associated with the development or worsening of neurological deficit in patients and increases the number of patients with an mRS score of 0–1 to 88.9% at the end of follow-up. This result is comparable to 87.1% obtained in one of the largest studies in 142 ARUBA-eligible patients who underwent multimodal treatment[15] and demonstrates a significant expansion of the opportunities for surgical treatment if the surgeon has the technical capability and experience in using different modalities.

Until now, the unresolved issue of surgical management of AVMs is the need for intervention, and disputes about whether AVM removal reduces the risks of a natural course do not subside. The most famous study that aimed to answer this question, ARUBA,[29] was prematurely terminated; later, its results received much criticism.[14,30] In the present study, we showed that the use of even one modality in modern conditions provided total occlusion in 66.7% of patients (which is significantly higher compared with 44.3% in ARUBA, $p = 0.007$) without deterioration of the health condition in 58.4% of patients; addition of other surgical options increases these indicators to 93.7% and 78.1%, respectively, which is significantly higher than those demonstrated in ARUBA and is comparable with data from other studies conducted in comparable groups of patients.[1,12,15,19,25]

This study has some limitations. First, the impossibility of ethical and legal reasons to organize a randomized prospective study led to the need to use the PSM method to eliminate the potential selection error, which, nevertheless, allowed the selection of comparable groups. Another limitation was exclusion of patients with 100% one-stage embolization because this option is valid only for Spitzler–Martin grades I–II malformations without additional hemodynamically significant features and small deeply located class B AVMs and is not suitable either for staged embolization or for multimodal management. The last limitation was the small size of each group, which prevented separate evaluation of patients with and without rupture history without a significant loss of study power but enabled the identification of some statistically significant differences between the approaches used.

Conclusions

Curative embolization should be considered as the main option of the multimodal algorithm and supplemented, if necessary, with radiosurgery and microsurgery. The technical capability and surgeon's experience, which enable the use of all three modalities and their combinations, can significantly increase the radicality of AVM cure and enhance treatment safety, even in patients with rupture history or preoperative neurological deficit.

Authors' Contribution
All authors contributed equally to this work.

Disclosure of Funding
None.

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

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Cellular Regulation and Oncogenesis of Primary Tumors in the Central Nervous System

Regulação celular e oncogênese de tumores primários no sistema nervoso central

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Arq Bras Neurocir 2024;43(4):e296–e307.

Abstract

The World Health Organization's system for classifying and grading primary tumors of the Central Nervous System conjectures the clinical-biological course of the oncogenic process based on morphological, genetic, histological, and immunohistochemical parameters. These principles are fundamental for a progression in the classification of these tumors, to guarantee the promotion of a more precise diagnosis. In this sense, it is important to understand the process of oncotic cell formation, which is the result of mutations in intra and extracellular control pathways. In this way, genes that act to induce the cell cycle, under normal conditions, when mutated, can result in a dysregulation of the progress of the cycle, causing alterations in the control factors and, consequently, phenotypic transformations in the cell. Thus, to understand the role of genes in modulating primary tumors in the Central Nervous System, mutations in the genes most prevalently related to Gliomas, Meningiomas, and Medulloblastomas were addressed highlighting their influences on the development of these tumors.

Keywords
- Carcinogenesis
- cell cycle
- phenotype
- genes
- central nervous system neoplasms

Resumo

O sistema de classificação e graduação dos tumores primários do Sistema Nervoso Central da Organização Mundial da Saúde conjectura os cursos clínico-biológicos do processo oncogênico com base em parâmetros morfológicos, genéticos, histológicos e imuno-histoquímicos. Tais princípios são fundamentais para uma progressão na classificação desses tumores, a fim de garantir a promoção de um diagnóstico mais preciso. Nesse sentido, mostra-se relevante o entendimento do processo de formação de uma célula oncótica, resultado de mutações em vias de controle intra e extracelular. Dessa forma, genes que em condições normais atuam induzindo o ciclo celular, quando sofrem mutações, podem resultar em uma desregulação do progresso do ciclo,

Palavras-chave
- Carcinogênese
- ciclo celular
- fenótipo
- genes
- neoplasias do sistema nervoso central

received
February 28, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1796653.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

causando alterações nos fatores de controle e, consequentemente, transformações fenotípicas na célula. Assim, para o entendimento da atuação dos genes na modulação de tumores primários no Sistema Nervoso Central, foram abordadas as mutações nos genes mais prevalentes relacionados com Gliomas, Meningiomas e Meduloblastomas, destacando as suas influências no desenvolvimento desses tumores.

Introduction

The cell division process can be understood as a sequence of phases, essentially resulting in the duplication of genetic material and cell division, steps that are essential to the cell's activities.[1]

To these operations to take place, there is the need for various means of regulating internal control, such as growth, protein synthesis, nutrients, and cell adhesion; and of external control, as the activation of external cell membranes and activation or inhibition of genes; which, jointly, are essential to the occurrence of the cell cycle sequencing.[1,2]

Therefore, the entirety of the cellular factors mentioned contribute to the regulation of the cell cycle, which is fundamental for the functioning of the cell. Thus, specific mutations in the genes that transcribe proteins that control cellular physiology, contribute to the development of defects in protein expression, providing a possibility for the advent of oncogenesis.

Within this reasoning, Gliomas, Meningiomas and Medulloblastomas are the primary tumors of the Central Nervous System that present a greater expression of mutant genes.[3]

In this context, the tumor is a condition in which there is a change in cellular phenotype, resulting in a genetic modification transmitted in the process of cell division. For this change in the cell to occur, it is necessary, for the tumor structure, to remodel several compensatory mechanisms, to avoid any means of cell destruction, such as apoptosis.[1]

This article has the purpose to describe the physiology of cell division control, relating it to possible mutations in genes most relevant to the development of oncogenic cells in the most prevalent primary tumors of the Central Nervous System.

Material and Methods

This article is an integrative review of various other scientific projects that have contributed to the enrichment of neuroscience. To execute this work, several other articles were selected through the scientific research platforms: Medline, PubMed, SciELO and Google Scholar, with emphasis on those in English and Portuguese, to provide a better foundation on the subject. The following keywords filtered in the "Descritores em Ciências da Saúde" (DeCS) and "Medical Subject Headings" (MeSH) systems were used as search parameters: Carcinogenesis; Cell Cycle; Phenotype; Genes; Central Nervous System Neoplasms. The articles obtained had, as a selection criterion, data related to the theme: Cellular Regulation and Oncogenesis of Primary Tumors in the Central Nervous System, and those that did not conform to the theme presented were discarded.

Regarding primary tumors of the Central Nervous System, only three were selected for a systemic approach: Gliomas, Meningiomas and Medulloblastomas. This decision was based on a comparison of the primary tumors in relation to the mutant gene expression expressed in each type, with a greater expression of mutant genes in the tumors. This analysis was carried out using the 5th Edition, Volume 6 of the classification of primary tumors of the Central Nervous System elaborated by the World Health Organization in 2021.[3]

Regarding genes, the following genes were selected for systemic identification of the impact of their mutations: Tumor Protein p53 (*TP53*), Isocitrate Dehydrogenase (*IDH*) and Telomerase Reverse Transcriptase (*TERT*). They were chosen due to their prevalence in the tumors and their respective impacts on modulation of the primary oncogenesis process in the Central Nervous System. The 5th Edition, Volume 6 of the classification of primary tumors of the Central Nervous System elaborated by the World Health Organization in 2021 was also used for this selection.

There was no restriction in relation to data from other works for the preparation of this article, therefore, articles were selected that were relevant to the subject from different periods.

Results

Cellular Regulation

The process of cell division can be understood through a sequential progression of four phases: G1 → S → G2 → M. In this way, the G1, S and G2 phases are the period of Cell Interphase, which can be understood as a interval of intense growth in the cell's activities; while the M phase is characterized by the stages of Mitosis and Cytokinesis, in which the cell division actually happens. Furthermore, it is important to notice that between these periods of cell division there is the cell cycle control system, taking place in three regulation points, so that only in this way it is possible for the cell to progress to the next phase of cell division.[1]

In this sense, the cell cycle control system can be interpreted in three checkpoints. Firstly, the Start or Restriction Point, which is at the end of the G1 phase, is responsible for

the occurrence of cell consolidation so that there is, consequently, chromosome duplication and, only then, is the cell allowed to enter the cell cycle. Secondly, the transition from G2 to M is verified, resulting in chromosomal alignment to the mitotic axis in the Metaphase phase. Finally, the cycle of checks ends with the third stage of the transition from Metaphase to Anaphase, consolidating in the separation of the sister chromatids, thus concluding Mitosis and Cytokinesis.[1] (►**Fig. 1**)

In regard to the regulation of the checkpoints stages, this control is positively regulated through extracellular and intracellular response pathways that contribute to the modification of target proteins in the cellular environment to process the progression of cell cycle phases. The main protein complexes responsible for these activities are cell surface receptors, retinoblastoma proteins, Bax proteins and, fundamentally, a series of protein-enzymatic complexes called cyclin-dependent kinases.

Cyclin-CDK Complex

Therefore, worth mentioning the main structure responsible for the cell cycle control system, the cyclin-dependent kinases (CDKs) enzymes. These structures perform their regulatory functions by varying their activity as the cell progresses through its cycle, and these oscillations are regulated by the activity of a family of proteins, the cyclins. The cyclins are regulatory proteins that are associated with kinase enzymes, promoting, by binding to these enzymes, the activation of the cyclin-CDK complex so that, only in this way, can the development of the cell cycle be made possible.[1]

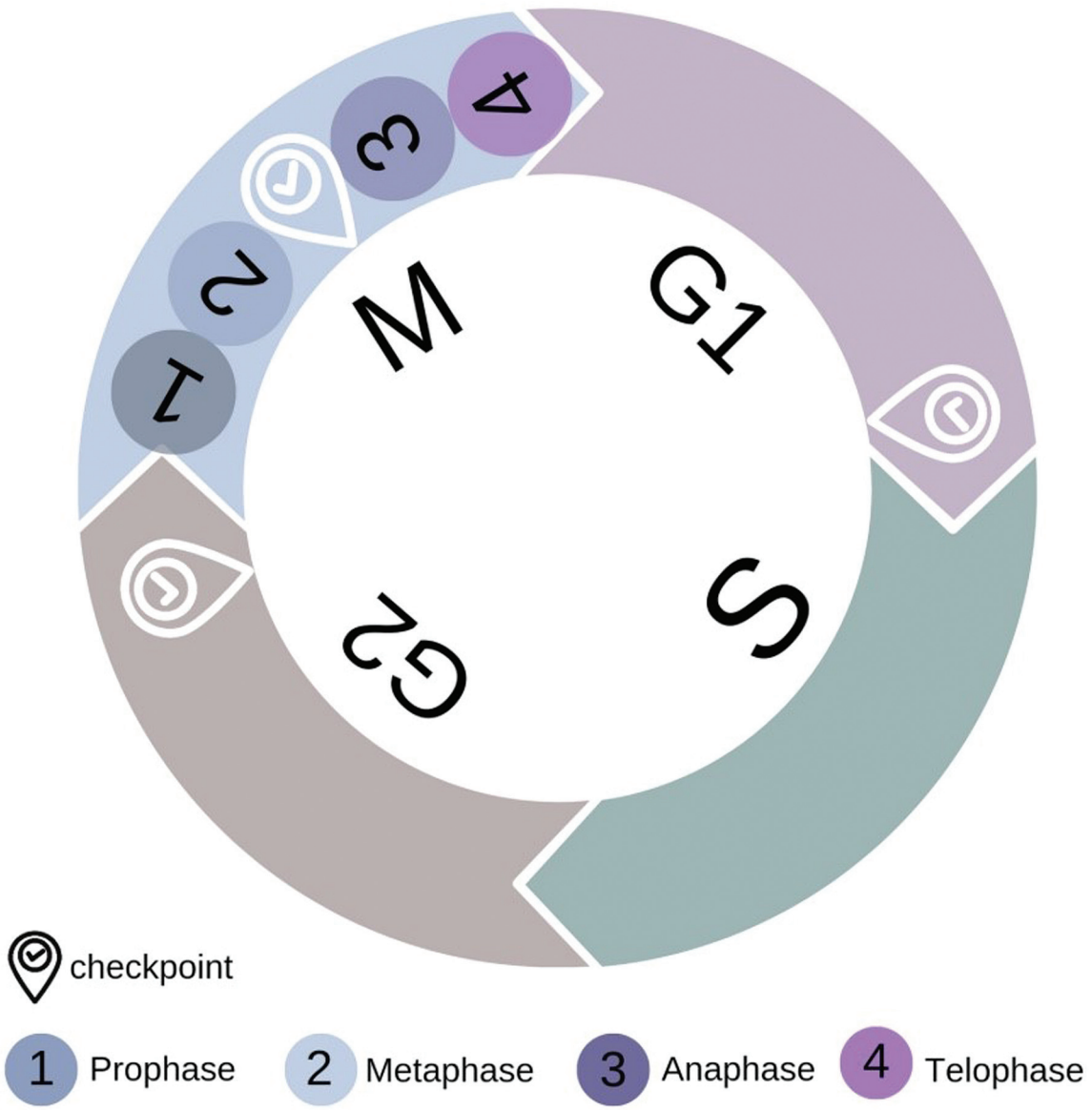

Fig. 1 Illustrative representation of the stages of the cell cycle. The symbol was used to represent the checkpoints present in the G1, G2 and M phases. The arabic numbers in the M phase represent the stages of Mitosis, dividing it neatly into 1-Prophase; 2-Metaphase; 3-Anaphase and 4-Telophase.

In this context, the formation of the cyclin-CDK complex, initially, occurs in the active site of the CDK enzyme, which exhibits, in this location, an inhibitory control protein loop that, upon binding to the cyclin, stimulates its withdrawal. Thus, with the displacement of this protein loop, there is the possibility of partial activation of CDK and, consequently, of the cyclin-CDK complex. Therefore, the full activation of this complex will only occur when there is a process of phosphorylation of the CDK active site, this activity being carried out by the cyclin-CDK activating kinase (CAK) enzyme, which will promote the phosphorylation of an amino acid close to this active site. This process causes a structural change to occur in CDK, ensuring, for both it and cyclin, more efficient ways to synthesize their target proteins to induce cell cycle progression.[1]

Furthermore, cyclin-CDK complexes have the relevance of synthesizing different sets of substrate proteins at each stage of the cell cycle, and for this reason there is a need to have specific cyclin-CDK complexes for each phase of this process, namely: G1-CDK → G1/S-CDK → S-CDK → M-CDK.[1]

Thus, according to the order of the cell cycle phases, the G1-CDK complex, which is associated with cyclin D, is active in cells from the start of the G1 phase as a regulator of its successive complex. Sequentially, the G1/S-CDK complex, together with cyclin E, acts to regulate target proteins to help process the transition from G1 to S phase. In addition, the S-CDK complex, which is linked to cyclin A, incites chromosome duplication after entry into the cycle, helping to control the replication of genetic material during the S phase and preparing the cell for the Mitotic phase. Finally, the M-CDK complex, together with cyclin B, stimulates the passage of the cell from the end of the G2 phase to the beginning of the Mitosis phase, acting in various stages to promote this process, such as inducing the formation of the mitotic spindle, disintegration of the nuclear envelope and rearrangement of the cytoskeleton; there is a progressive decrease in its concentrations halfway through this stage of the cell cycle.[1] (►**Fig. 2)**

Regulation of the Cyclin-CDK Complex

Once the cyclin-CDK complex was explained, its regulated both by the different levels of cyclin throughout the cell cycle and by other physiological processes, such as the suppression of this complex by inhibitory phosphorylation and the action of the cyclin-dependent kinase inhibitor (CKI) protein. In this way, the process of inhibitory phosphorylation occurs from a kinase enzyme called Wee1, which adds a phosphate group to the cavity of the active site of the CDKs, inhibiting their activity and, conversely, their dephosphorylation is succeeded by a dephosphorylation protein known as Cdc25, which increases the action of the CDKs by removing the phosphate group. Thus, this phosphorylation and dephosphorylation mechanism is extremely important, especially in the regulation of M-CDKs, given the need to synthesize various substrate proteins to help promote the cell phase of mitosis. Furthermore, in relation to the CKI protein, it acts to inactivate CDKs by stimulating the structural rearrangement of its active site, consequently suppressing cyclin-CDK complexes.[1]

Rb Protein

In parallel to the cyclin-CDK complex, the retinoblastoma protein (Rb protein) is a protein transcribed by the *Rb* gene that is present in most of the body's cells.[1] This structure is responsible for the intrinsic regulation of the cell cycle through the activation of a transcription factor that acts as a signal transducer, allowing control of the expression of genes that mediate cell progression during the replication of genetic material in the S phase, and therefore, it is involved in tumor suppression.[2]

Therefore, the physiological activity of the Rb protein must be presented in two states of action, acting in the presence and absence of stimuli for the Mitosis phase. Therefore, when the cell receives mitogen stimulation, through cell surface receptors, there is the activation of a main intracellular signaling pathway that is conducted through the monomeric Ras GTPase enzyme, leading to the activation of the mitogen-activated protein kinase (MAPK) which, in turn, increases the production of proteins that regulate cellular transcription, notably Myc.[1]

In this context, among the Myc mechanisms that promote entry into the cell cycle, there is an increase in the expression of genes that encode cyclins present in the G1-cyclin phase, cyclins D, which, as a result, also increase the activity of G1-CDK. Thus, the main function of the G1-CDK complex is to promote the activation of a group of gene regulatory factors called E2F proteins. Thus, the E2F protein is responsible for binding to various gene promoter regions in the DNA that encode proteins, such as G1/S-cyclin and S-cyclin, which are necessary for progression to the S phase of the cell cycle.[1]

Based on this, it is possible to understand the action of the Rb protein, since in the absence of mitogenic stimulus, it interacts with the E2F protein, inhibiting its gene expression and, consequently, preventing the progression of the cell cycle. On the other hand, when there is a mitogenic stimulus, the G1-CDK complex promotes phosphorylation of the Rb protein, reducing its binding to E2F and thus allowing expression of the protein's target genes.[1]

Bax Protein

In the context of cell cycle control, the Bax protein plays an important role, being a pro-apoptotic function in the intrinsic pathway and one of the main effectors of the BCL2 family of proteins. This structure acts in conjunction with another BCL2 family protein, Bak, since at least one of these proteins must function for the intrinsic apoptosis pathway to develop.[1]

In terms of their functionality, Bax proteins are inactive in the form of monomers or dimers and are predominantly concentrated in the cytosol due to their constant translocation from the mitochondria to the cytoplasm. On the other hand, following apoptotic stimuli in cells under oxidative stress, Bax accumulates in the mitochondrial outer membrane (MOM) to be activated by interaction with the pro-apoptosis BH3-only proteins, which allow both the insertion

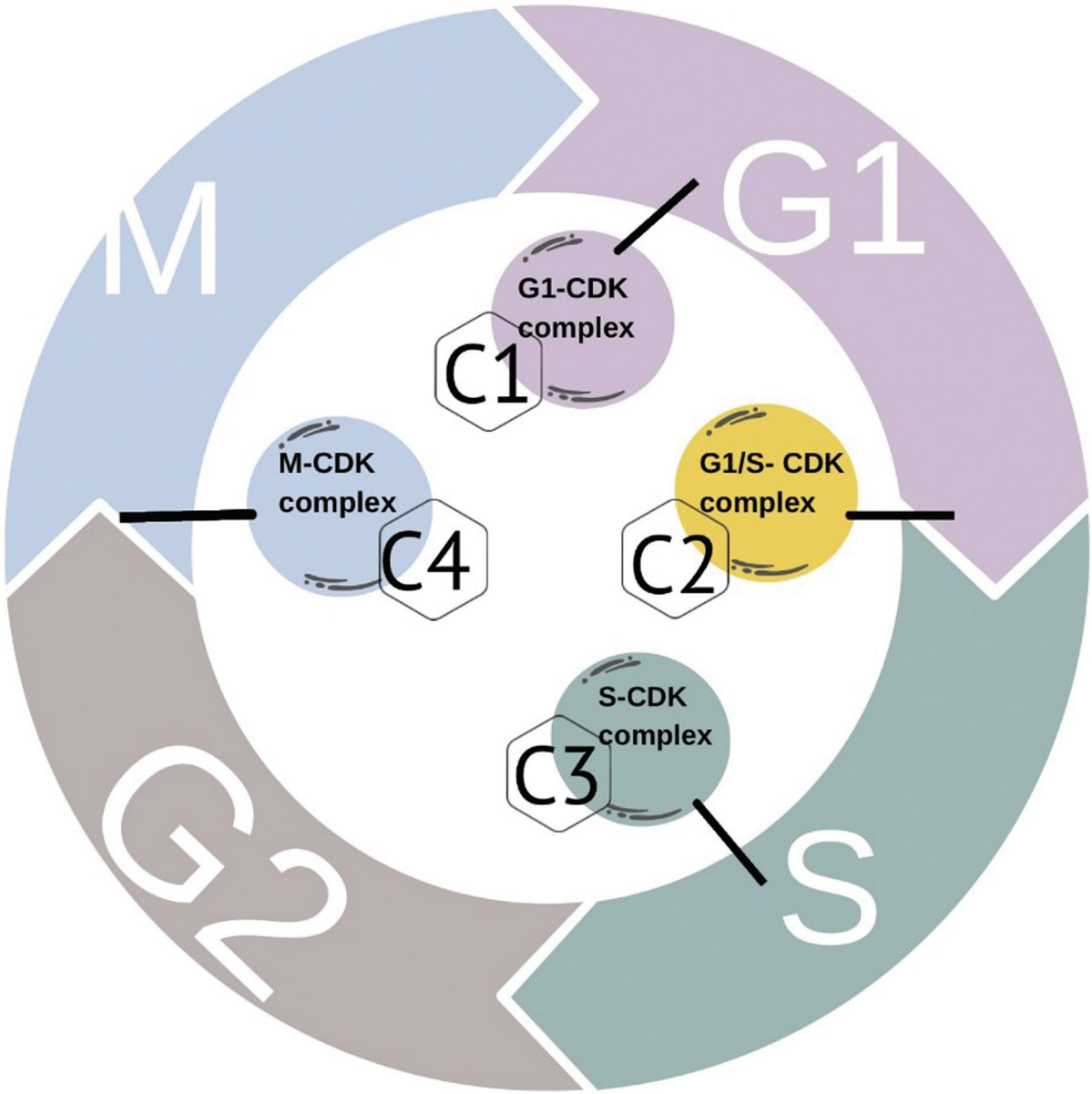

Fig. 2 Illustrative representation of the action of cyclin-CDK complexes present in the cell cycle. In the G1 phase, there is the G1-CDK complex associated with cyclin D (C1). At the transition from G1 to S phase, the G1/S-CDK complex is found associated with cyclin E (C2). In the S phase, the S-CDK complex is associated with cyclin A (C3). At the transition from G2 to M phase, the M-CDK complex is found associated with cyclin B (C4).

of Bax into the MOM and the transient exposure of the BH3-binding domain of the Bax protein. Following this logic, the Bax protein aggregates to the outer mitochondrial lipid bilayer in the form of oligomers so that it is possible to promote an accumulation of proteins in the leaflet of this membrane, increasing its stress and tension, thus, resulting in the opening of pores that allow the permeabilization of the MOM and the release of cytochrome C from the mitochondria into the cytosol.[4]

Thus, during apoptosis, this release occurs through the action of a protein called "dynamin-related protein 1", which contributes to the formation of essential platforms for calcium transfer. As a result of this calcium mobilization, cytochrome C is released from the mitochondria into the cytosol.[4]

In this way, cytochrome C is responsible for transporting electrons from Mitochondrial Complex III to IV during the process of oxidative phosphorylation, promoting, as a result, the synthesis of adenosine triphosphate (ATP). Due to the relevance of ATP for promoting the metabolism of several cell pathways, occasional inadequate transcriptions of the Bax protein by the *BCL2* gene can impede the synthesis of this compound, causing cell death due to hypoxia and acidification of the environment. This process is due, respectively, to the absence of electrons for the bond with oxygen and the formation of H^+ in the intracellular environment; both adversities are caused by the absence of cytochrome C and ATP molecules in the cell.[1]

Therefore, once the importance of cellular control to guarantee successive cell division is understood, there is a need to address oncogenic factors to understand the successive manifestation of tumors in the Central Nervous System (CNS).

Oncogenic Factors

Modifications in genes that stimulate cell division can affect the cell due to intense and/or deregulated regulatory signals, which come from intrinsic and extrinsic sources, such as, respectively, results from the metabolism of deoxyribonucleic acid (DNA) and irradiation, thus configuring in mutations in the genes responsible for the transcription of proteins acting in the "checkpoints" stages.[5] Furthermore, this mutant process it may result from a resistance on the part of these mutant cells to the apoptosis process, which contributes to causing oncogenic cellular products, giving the cell growth advantages and phenotypic transformations in relation to other functional units.[2,6] However, under normal physiological conditions, the genes that act positively in inducing the cell cycle are called proto-oncogenes, because, if they present mutations, there is the possibility of becoming oncogenic; while the genes influential in protecting and blocking the cell cycle are called tumor suppressor genes.[2]

In this sense, to systematize an explanation about the impact of these types of genes on oncogenic modulation in primary CNS tumors, the following stand out: Tumor Protein p53 (*TP53*), Isocitrate Dehydrogenase (*IDH*) and Telomerase Reverse Transcriptase (*TERT*).

TP53 Gene

The *TP53* gene is a tumor suppressor gene that is predominantly associated with Gliomas, but can also be associated with Medulloblastoma.[7] It can be understood as a great detector of damage to genetic material, as its transcription factor coordinates the expression of several genes that act in different cellular responses to conditions of oxidative stress in the cell.[8] Like these cellular control factor pathways, there is predominantly DNA repair through the association between the *TP53* gene and the p21 protein. This repair occurs through the elevation of *TP53* levels because of the perception of any cellular stress, inducing the transcription of p21. This activation contributes to the promotion of DNA repair, since, when activated, p21 performs its function of preventing the cyclin-CDK bond from being made, which, consequently, inhibits the phosphorylation of the Rb protein, thus allowing, a repair of genetic material.[2]

Therefore, due to its important reparative role, abnormalities in the *TP53* gene can compromise cellular repair and can induce the cell to synthesize proteins related to negative control of the cell cycle. Thus, this mutant process can be understood by the acetylation of *TP53* in response to possible cellular stress, which results in a selective induction of the inhibition of pro-apoptotic genes, such as the *BCL2* gene, with the possibility of preventing apoptosis of the mutant cell, which can result in a change in the cellular phenotype, establishing the primary tumor.[9]

IDH Gene

The *IDH* gene is a proto-oncogene that is predominantly found in its mutant form in Gliomas, which are one of the main types of primary tumors of the CNS.[7] In this context, the role of this gene is in the transcriptional synthesis of the isocitrate dehydrogenase (IDH) enzymes, which are divided into three types according to the transcription of their respective genes, namely: "IDH1" enzyme - transcribed by the *IDH1* gene, is located in the cytoplasm and in the peroxidase; "IDH2" enzyme - transcribed by the *IDH2* gene, is located in the mitochondria; and "IDH3" enzyme - transcribed by the *IDH3A*, *IDH3B* and *IDH3G* genes, also located in the mitochondria.[10] Thus, these enzymes are responsible for catalyzing, in the third stage of the citric acid/tricarboxylic acid cycle, the oxidative decarboxylation of isocitrate into α-ketoglutarate and carbon dioxide, synthesizing, at the end of this process, Nicotinamide Adenine Dinucleotide Phosphate (NADPH).[10–12]

In this sense, of the three enzymes mentioned, the IDH1 enzyme stands out, as it can be a factor in preventing cellular damage because of its regulation of epigenetic modifications and the stabilization of demethylated histones that result from oxidative stress to the cell, thus promoting control of cell proliferation.[12]

Thus, a mutation in the IDH1 enzyme by the *IDH1* gene can compromise the synthesis of NADPH, preventing the restoration of glutathione, which is a tripeptide with important antioxidant action in the cell. This effect of inhibiting glutathione synthesis is the advent of an accumulation of free radicals in the cell, due to the decrease in antioxidant agents and the increase in the generation of oxidizing substances, reflecting, in the structure, a state of oxidative stress that can favoring lesions at the levels of DNA bases, which may lead to the establishment of a primary tumor.[12]

In this way, in addition to the aforementioned adversities, specific mutations in the *IDH1* gene contribute to a modification in its active site, resulting in the loss of the ability of its transcribed enzymes to decarboxylate isocitrate and the synthesis of an onco-metabolite product called 2-hydroxyglutarate (2-HG).[13] This mutant metabolite is involved in several tumor biological changes, notably blocking the histone demethylase enzyme, resulting in DNA hypermethylation and, consequently, changes in gene expression.[14,15] Furthermore, another important factor to be highlighted is that 2-HG can affect the function of non-tumor cells that are around this tumor, thus emphasizing neurons and immune cells, given, again, the prevalence of this gene mutant in the Gliomas.[16]

TERT Gene

The *TERT* gene is a proto-oncogenic gene that is, predominantly, associated with Gliomas and Meningiomas.[7] Thus, this gene acts in the transcription of the telomerase reverse transcriptase enzyme or, simply, telomerase; which has the function of acting in the maintenance of telomere length, which is an extremely relevant factor for the cell, since telomeric length correlates with the process of cellular

senescence, which is characterized by the arrest of cell division due to the absence of telomerase enzyme.[17]

Furthermore, the eventual shortening of these structures is promoted at the end of the entire cell cycle, impacting the cell in a stage of aging so that, only then, it is possible to enter the senescence phase. This process occurs through the continuity of Mitosis cycles, since for each of these phases there is a progressive loss of telomeres. Thus, when telomeres reach their critical shortening stages, the cell loses its replicative capacity and undergoes apoptosis, this phenomenon being called the Hayflick Limit.[18]

Thereby, tumor cells can avoid their Hayflick Limit due to the fact that there is a mutation in the *TERT* gene that leads to overexpression of telomerase.[19] This increase in expression is due to mutations in certain locations of this gene that result in new binding sites for a family of proteins called E-twenty-six (ETS). Therefore, with the possibility of greater connections between *TERT* and ETS, there is, as a result, a maintenance of positive regulation of the gene in its mutant state, contributing to the conservation of telomere length in tumor cells.[18]

In this sense, even in a state of senescence, cancerous structures can reactivate their telomerases, giving them cellular dysregulation, making it possible to impede the apoptosis process and, consequently, the continuation of mutant cell division.[19]

Classification of CNS Tumors

Tumors in the CNS can be classified according to their grades of clinical-biological behavior, being idealized by histological, immunohistochemical, cytogenetic patterns and, recently, by molecular biomarkers.[20] These standards contribute to evaluating and classifying the grades of tumor variation, which can range from 1 to 4.

In that regard, to exemplify these grades of classification, a subdivision of Gliomas, Astrocytomas, was used as a representation, given their best definition in terms of the presence of biological indicators, such as necrosis and cell proliferation.

Thereby, grade 1 tumors have lesions with low proliferative potential with a high possibility of cure after treatment. The grade 2 proliferates slowly and may or may not invade adjacent brain tissue. The grade 3 has a high rate of proliferation and invasion of normal tissue, with a high rate of recurrence. Finally, grade 4 tumors correspond to tumors with higher rates of mitotic activity, with a tendency to form necrosis and/or microvascular proliferation, with the possibility of infiltration into the surrounding tissues and craniospinal metastasis.[21]

This structuring in grades of variation was designed, mainly, to provide greater flexibility of use in relation to the type of tumor, highlight biological similarities and adapt CNS tumors to other tumors that did not belong to that location.[7]

Failures in cellular control processes result in conditions favorable to a greater expression of primary tumors in the CNS. Among primary CNS tumors, Gliomas, Meningiomas and Medulloblastomas are the most prevalent and stand out for the highest expression of mutant genes.

Gliomas

Gliomas can be understood as tumors that affect Glial cells, ranging from grade 1 to grade 4. This group of tumors includes oligodendrocytes (oligodendrogliomas), ependymal cells (ependymomas) and, predominantly, astrocytes (astrocytomas). Its epidemiology is predominantly composed of adult men, with, due to the presence of 4 types of grades, a wide rate of variation in the survival of this sample space.[22] Thus, such cellular structures, together with clinical-biological behaviors, contributes to the recognition of the division of Gliomas into 6 defined Molecular types, namely: Adult-type diffuse gliomas, Pediatric-type diffuse low-grade gliomas, Pediatric-type diffuse high-grade gliomas, Circumscribed astrocytic gliomas, Glioneuronal and neuronal tumors; and Ependymomas.[7]

Adult-type Diffuse Gliomas

Adult-type diffuse gliomas are subdivided into 3 types: Astrocytoma, *IDH*-mutant; Oligodendroglioma, *IDH*-mutant, and 1p/19q-codeleted; and Glioblastoma, *IDH*-wildtype.[7] (►**Fig. 3**)

Pediatric type Diffuse Low-Grade Gliomas

In reference to Pediatric-type diffuse low-grade gliomas, they are subclassified into 4 types: Diffuse astrocytoma, *MYB*-altered or *MYBL1*-altered; Angiocentric glioma; Polymorphous low-grade neuroepithelial tumor of the young; and Diffuse low-grade glioma, MAPK pathway-altered.[7] (►**Fig. 3**)

Pediatric type Diffuse High-Grade Gliomas

Pediatric-type diffuse high-grade gliomas are sub-related into 4 types: Diffuse midline glioma due to histone 3 (H3) alteration in the *K27* gene (Diffuse midline glioma, H3 *K27*-altered); Diffuse hemispherical glioma due to H3 mutation in the *G34* gene (Diffuse hemispheric glioma, H3 *G34*-mutant); Diffuse pediatric-type high-grade glioma, H3-wildtype and *IDH*-wildtype; and Infant-type hemispheric glioma.[7] (►**Fig. 3**)

Circumscribed Astrocytic Gliomas

Circumscribed astrocytic gliomas are segmented into 6 types: Pilocytic astrocytoma; High-grade astrocytoma with piloid features; Pleomorphic xanthoastrocytoma; Subependymal giant cell astrocytoma; Chordoid glioma; and Astroblastoma, *MN1*-altered.[7] (►**Fig. 4**)

Glioneuronal and Neuronal Tumors

Glioneuronal and neuronal tumors are fragmented into 14 types: Ganglioglioma; Desmoplastic infantile ganglioglioma/Desmoplastic infantile astrocytoma; Dysembryoplastic neuroepithelial tumor; Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters; Papillary glioneuronal tumor; Rosette-forming glioneuronal tumor; Myxoid glioneuronal tumor; Diffuse leptomeningeal glioneuronal tumor; Gangliocytoma; Multinodular and

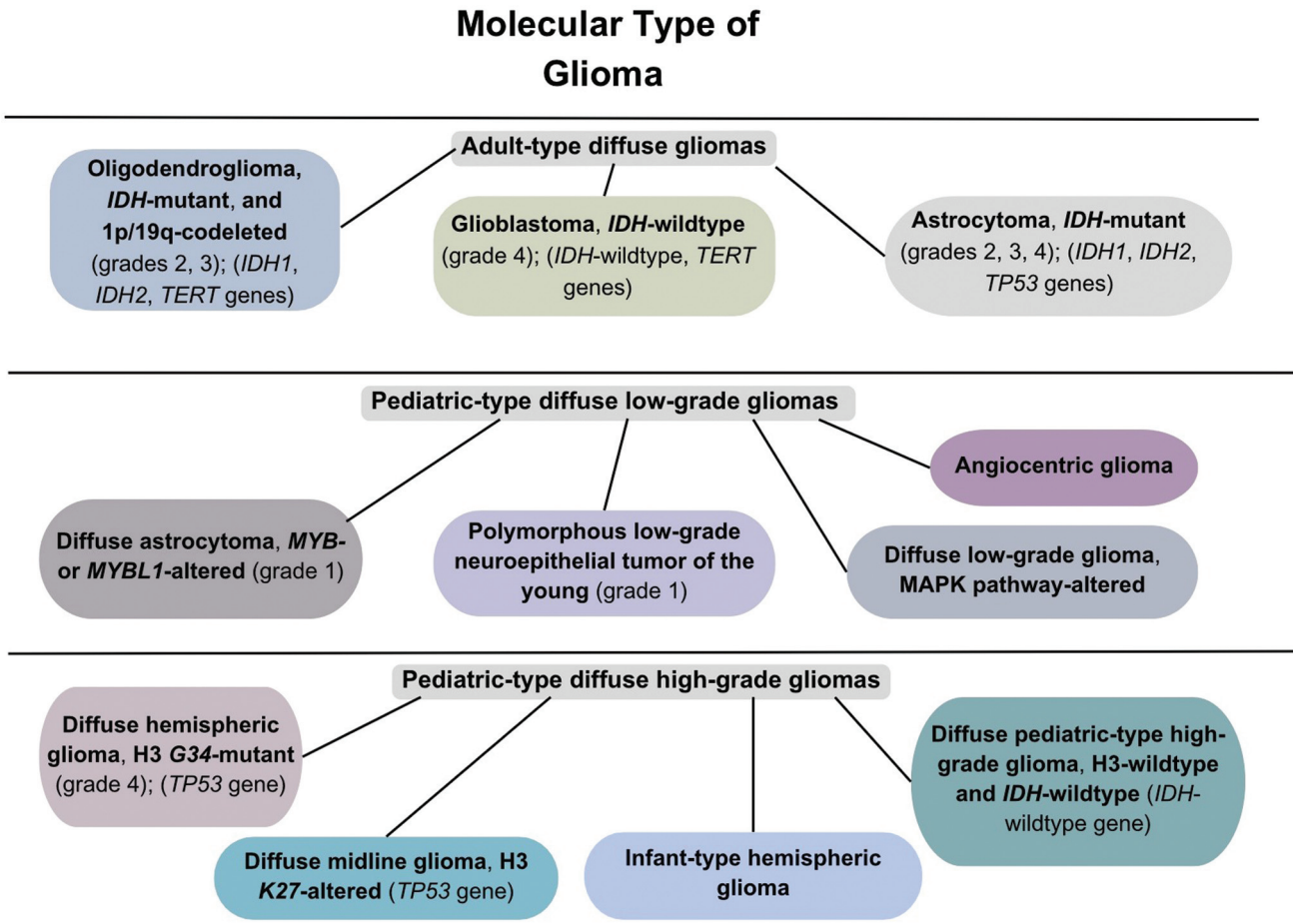

Fig. 3 Illustrative representation of the Molecular type of Glioma: Adult-type diffuse glioma, Pediatric-type diffuse low-grade glioma, Pediatric-type diffuse high-grade glioma. For certain types of gliomas, there are still no definitive grade classification criteria. Tumors that mention the *TP53*, *IDH* and *TERT* genes have a direct mutation relationship with them.

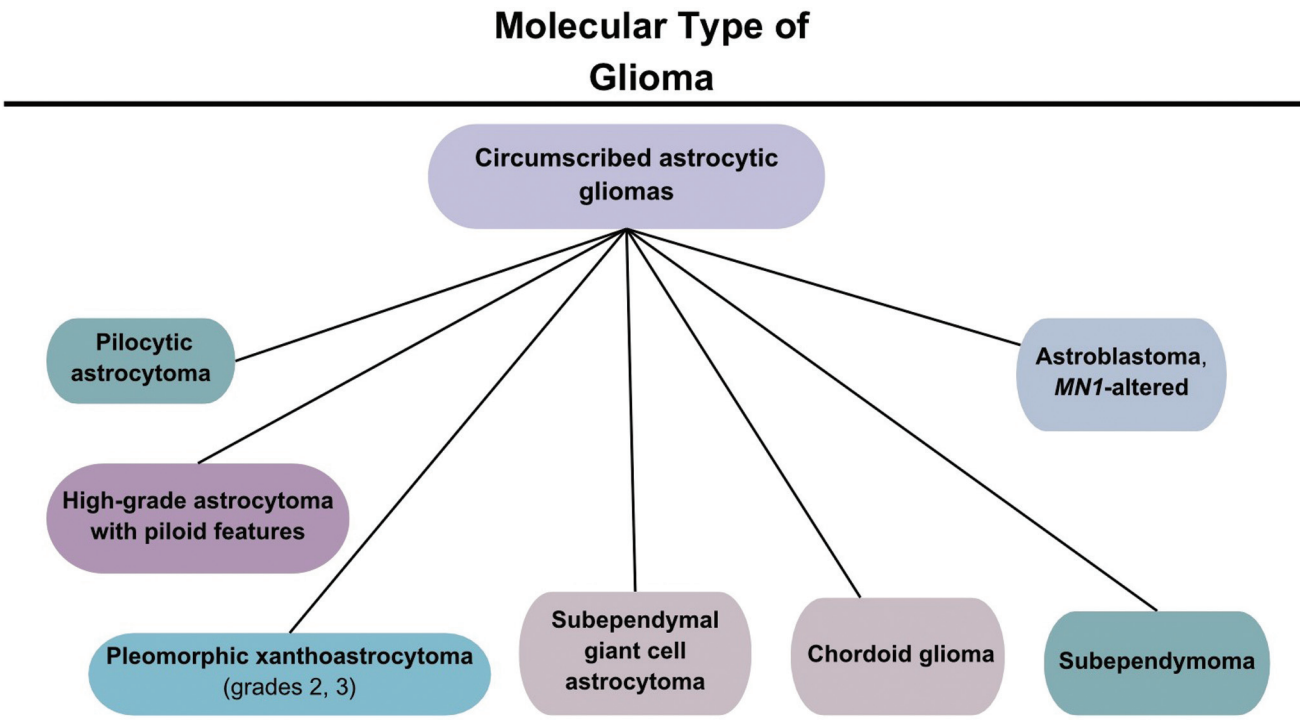

Fig. 4 Illustrative representation of the Molecular type of Glioma: Circumscribed astrocytic glioma. For certain types of gliomas, there are still no definitive grade classification criteria.

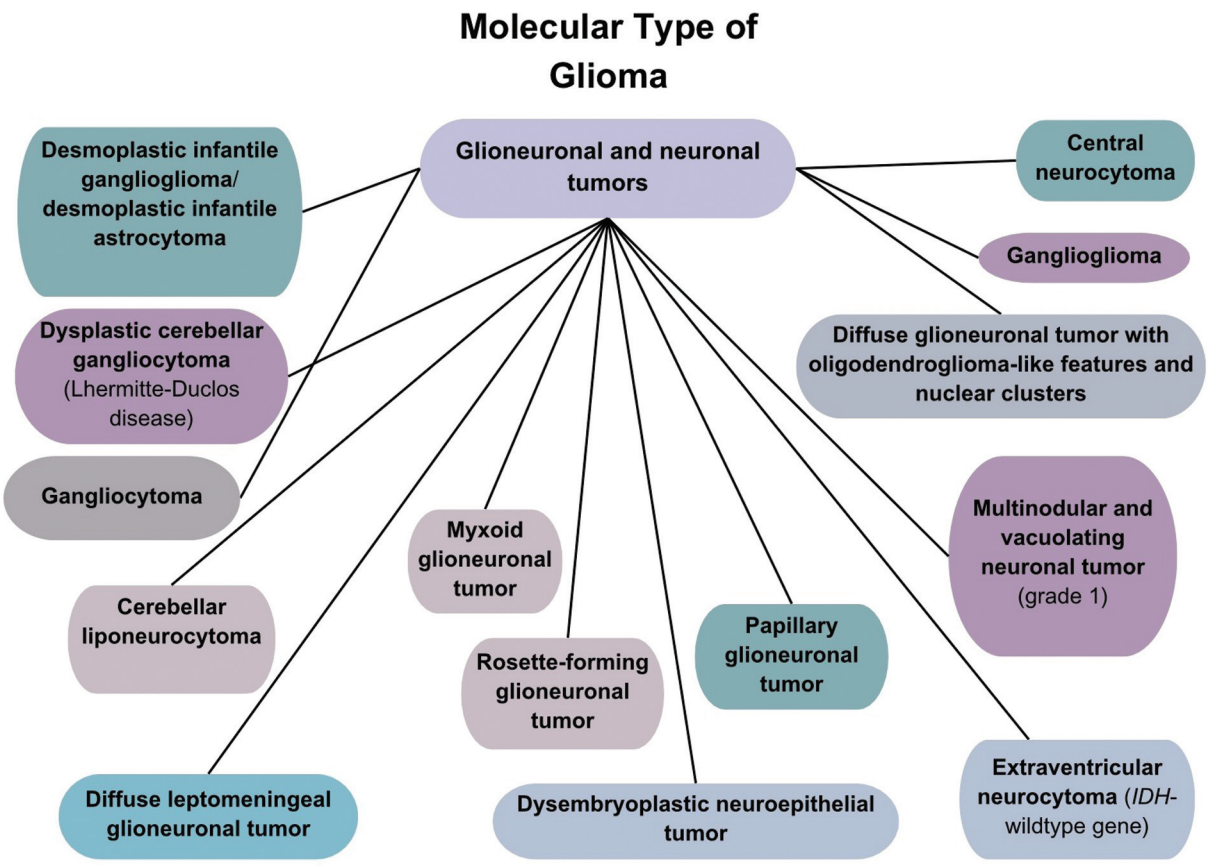

Fig. 5 Illustrative representation of the Molecular type of Glioma: Glioneuronal and neuronal tumors. For certain types of gliomas, there are still no definitive grade classification criteria. Tumors that mention the *IDH* gene have a direct mutation relationship with it.

vacuolating neuronal tumor; Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease); Central neurocytoma; Extraventricular neurocytoma; and Cerebellar liponeurocytoma.[7] (►**Fig. 5**)

Ependymomas

In reference to Ependymomas, they are sub-fractionated into 10 types: Supratentorial ependymoma; Supratentorial ependymoma, *ZFTA* fusion-positive; Supratentorial ependymoma, *YAP1* fusion-positive; Posterior fossa ependymoma; Posterior fossa ependymoma, group *PFA*; Posterior fossa ependymoma, group *PFB*; Spinal ependymoma; Spinal ependymoma, *MYCN*-amplified; Myxopapillary ependymoma; and Subependymoma.[7] (►**Fig. 6**)

Meningiomas

Meningiomas are the most prevalent representatives of primary CNS tumors. Its epidemiology is mainly composed of adults over 65 years of age, being twice as common in womans.[20] Thus, Meningiomas can only classify their grades of variation from 1 to 3; therefore, they are interpreted as tumors that affect the meninges, encompassing Dura mater, Arachnoid mater and Pia mater.[7]

Such tumors are classified according to their clinical-biological characteristics into just one Molecular type, which is the Meningioma itself, which has a direct mutation relationship with the *TP53* gene; however, due to its broad morphological spectrum, it is reflected in several Histological subtypes, notably Meningiomas: Meningothelial, Fibrous, Transitional, Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich, Atypical, Chordoid, Clear cell; and Anaplastic. Of these histological subtypes mentioned, the only one considered malignant is Anaplastic, as it has a grade of variation of 3.[23] (►**Fig. 7**)

Medulloblastomas

Medulloblastomas are the most prevalent primary malignant tumors in pediatric cases, representing around 20% of tumors for this sample space; being predominantly located in the cerebellar region.[24]

In this context, Medulloblastomas, as well as the other tumors mentioned, can be classified according to their clinical-biological behavior into 4 defined Molecular types, namely: Medulloblastoma, Wntless (WNT) protein-activated (Medulloblastoma, WNT-activated); Medulloblastoma, Sonic Hedgehog (SHH) protein-activated and *TP53*-wildtype (Medulloblastoma, SHH-activated and *TP53*-wildtype); Medulloblastoma, SHH-activated and *TP53*-mutant; and Medulloblastoma, non-WNT/non-SHH. Furthermore, in relation to its histological classification, it can be presented as "Histologically defined Medulloblastoma", encompassing 4 subtypes: Classic; Desmoplastic; Medulloblastoma with extensive nodularity (MBEN); and Anaplastic. It is worth mentioning that all these Medulloblastomas mentioned have

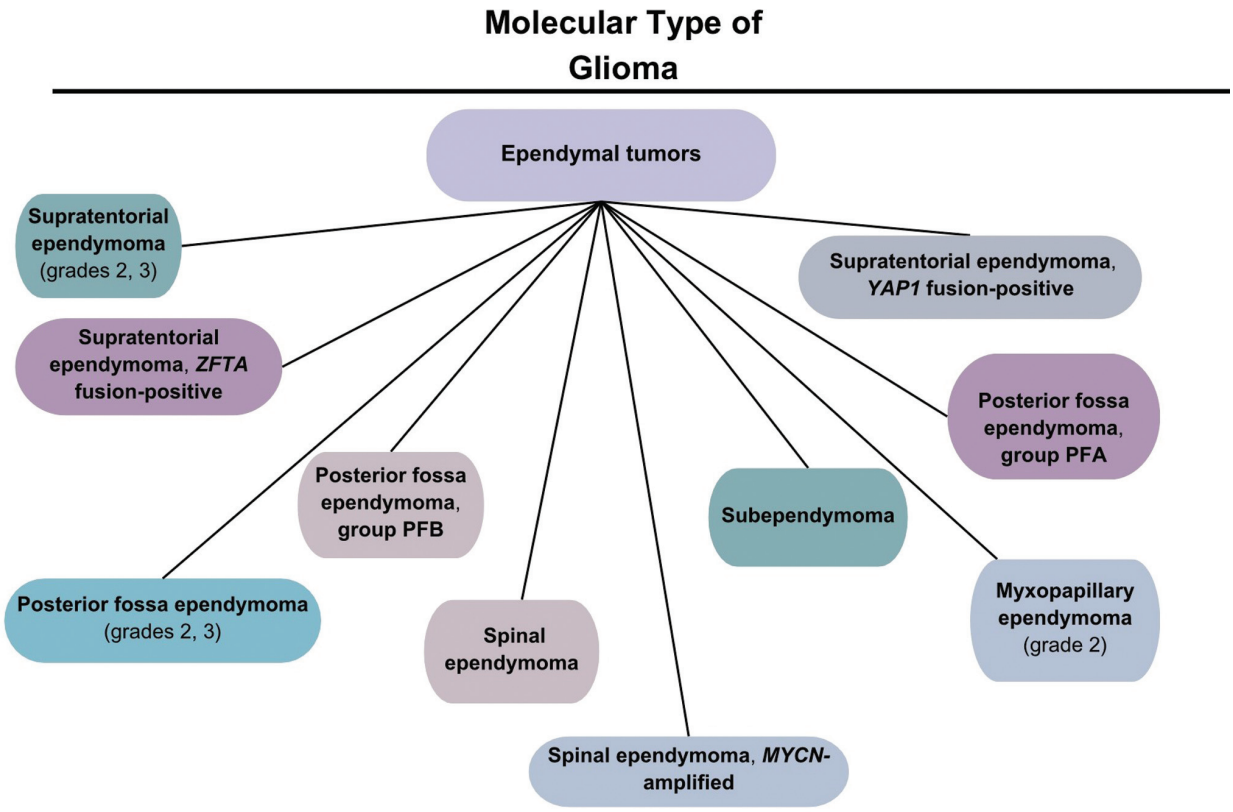

Fig. 6 Illustrative representation of the Molecular type of Glioma: Ependymomas. For certain types of gliomas, there are still no definitive grade classification criteria.

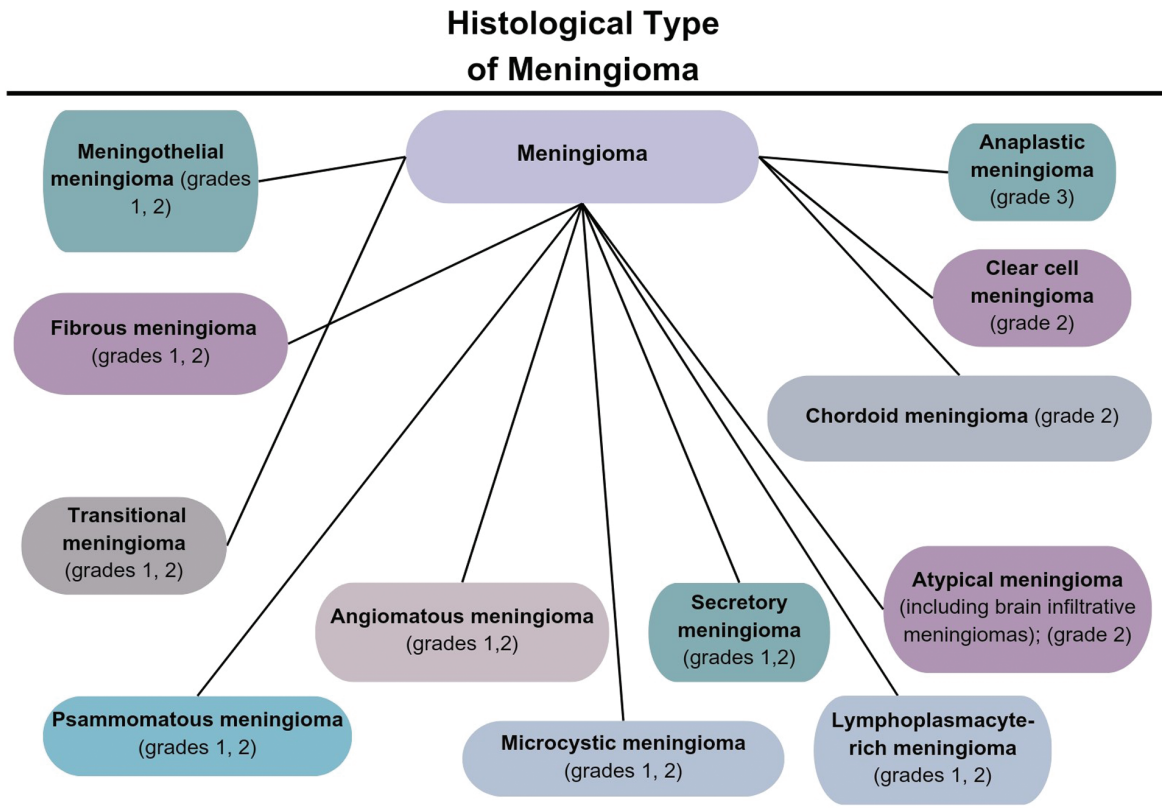

Fig. 7 Illustrative representation of the Histological type of Meningioma: Meningothelial, Fibrous, Transitional, Psammomatous, Angiomatous, Microcystic, Secretory, Lymphoplasmacyte-rich, Atypical, Chordoid, Clear cell and Anaplastic. All types of Meningiomas have a direct mutation relationship to the *TERT* gene.

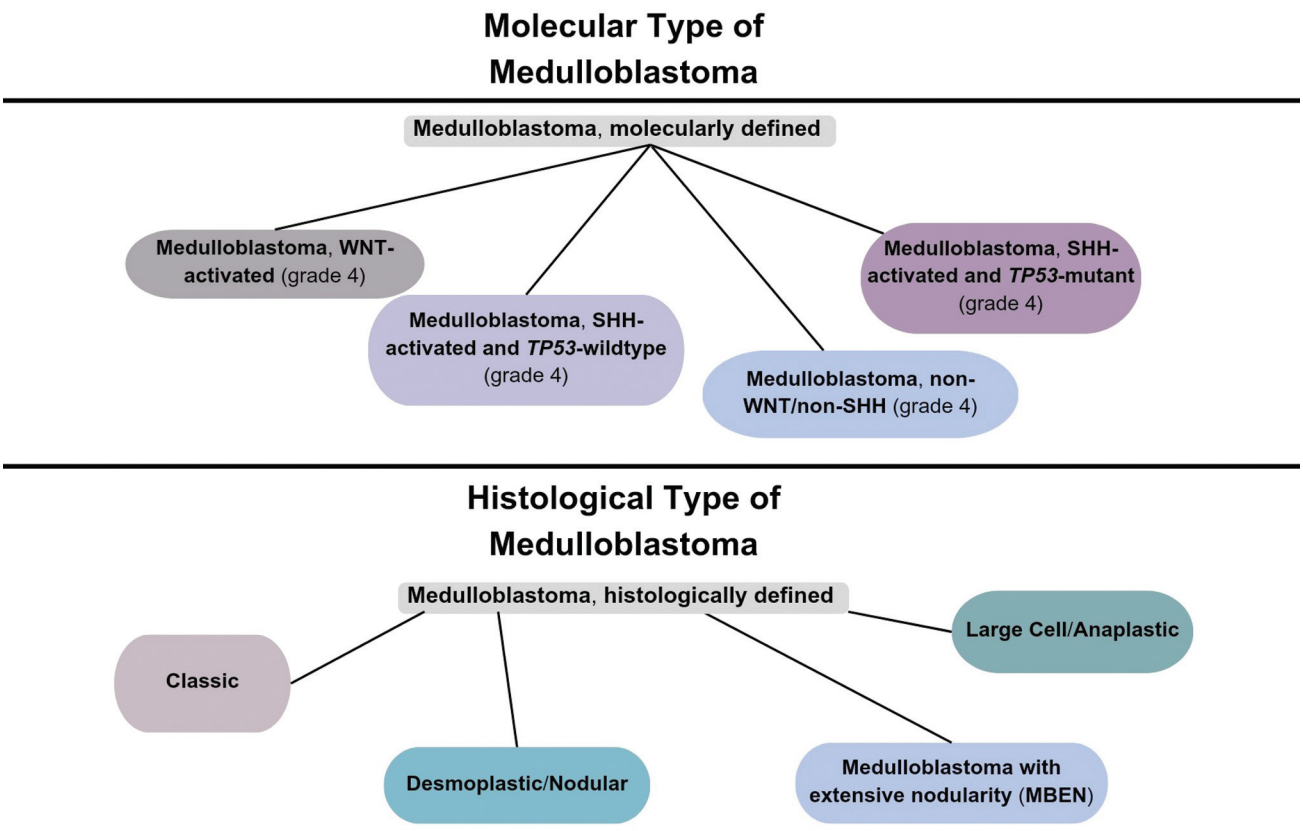

Fig. 8 Illustrative representation of the Molecular and Histological types of Medulloblastoma. For the Molecular type there are: Medulloblastoma, WNT-activated; Medulloblastoma, SHH-activated and *TP53*-wildtype; Medulloblastoma, SHH-activated and *TP53*-mutant; and Medulloblastoma, non-WNT/non-SHH. For the Histological type there are: Classic, Desmoplastic, Medulloblastoma with extensive nodularity (MBEN) and Anaplastic. Tumors that mention the *TP53* gene have a direct mutation relationship with it.

a grade 4 variation, making them extremely susceptible to the oncogenic process of metastasis.[7] (►**Fig. 8**)

Discussion

Furthermore, in relation to the types of Gliomas mentioned, these 7 types stand out: Astrocytoma, *IDH*-mutant; Oligodendroglioma, *IDH*-mutant, and 1p/19q-codeleted; Glioblastoma, *IDH*-wildtype; Diffuse midline glioma, H3 *K27*-altered; Diffuse hemispheric glioma, H3 *G34*-mutant; Diffuse pediatric-type high-grade glioma, H3-wildtype and *IDH*-wildtype; and Extraventricular neurocytoma. Such caveats were recommended, since these tumors are directly related to the mutant genes, such as the *IDH*, *TERT* and *TP53* genes. Given this reasoning, it is possible to relate the mutations occurring in these genes to the types of primary tumors mentioned, which thus develops the respective carcinogenic mechanisms of these structures. For example, there is the "Diffuse midline glioma, H3 *K27*-altered" and the "Diffuse hemispheric glioma, H3 *G34*-mutant", due to the fact that these present mutations in the *TP53* gene.[7] Thus, as already discussed, mutations in this gene can compromise cellular repair, inducing the cell to synthesize proteins related to negative control of the cell cycle, such as inhibition of the apoptosis process.[8]

In this sense, Meningiomas have a prevalent mutation in the *TERT* gene, since the increase in the frequency of mutations in this gene is directly proportional to the increase in the degree of variation in the tumor.[25] This fact can serve as an impact to result in the carcinogenic mechanisms mentioned, such as preventing the action of the telomerase enzyme in the shortening of telomeres, preventing the cell from entering the state of senescence, which, consequently, allows the continuation of the process of cellular replication of the mutant structure.[17] Furthermore, another adversity that has been recognized in Meningiomas that can cause an increase in expression in the *TERT* gene is hypermethylation in the DNA site called cytosine-phosphate-guanine (CpG). Thus, CpG hypermethylation may be associated with the inactivation of several tumor suppressor genes, such as *TP53*, which is a possible explanation for why there is an increase in the expression of the proto-oncogenic genes, like *TERT*.[26] Therefore, the presence of mutations in the *TERT* gene can be considered as biomarkers for therapeutic interventions, since these genetic changes are associated with greater risks of tumor recurrence and progression.[27]

Thereby, it is observed that Medulloblastomas are more susceptible to mutations in the TP53 gene, with the following molecular types standing out for this condition: Medulloblastoma, SHH-activated and *TP53*-wildtype; and Medulloblastoma, SHH-activated and *TP53*-mutant.[7] Thus, these mutant adversities may be associated with the epidemiology of Medulloblastomas, since the mutant state in the *TP53* gene is commonly observed in pediatric cases and, rarely, in adult

cases. Furthermore, because of this relationship between the *TP53* mutation and Medulloblastoma, there is, for pediatric cases, a frequent association of "Medulloblastoma, SHH-activated" with Li-Fraumeni syndrome, conferring a worse prognosis for carcinogenesis.[28]

Conclusion

Therefore, it is concluded that the process of carcinogenesis in the CNS is determined by the advent of failures in cell cycle control processes, with mutations in genetic factors being a direct result of this process. Such genetic mutations, evidencing those of the *TP53*, *IDH* and *TERT* genes, are dominant conditions for the development of Gliomas, Meningiomas and Medulloblastomas, causing, due to the phenotypic alteration of the affected cells in the locations of these primary tumors, the modification of cellular parameters morphological, genetic, histological and immunohistochemical; thus, demonstrating a deregulation of the clinical-biological behavior of the cellular structures.

Conflict of Interests

The authors have no conflict of interests to declare.

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Treatment Options for Intracranial Epidural Hematoma - An Integrative Review of the Past Three Decades

Opções de tratamento para hematoma epidural intracraniano - Uma revisão integrativa das últimas três décadas

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Arq Bras Neurocir 2024;43(4):e308–e314.

Abstract

Introduction Acute epidural intracranial hematoma (IEH) has been considered one of the most relevant neurosurgical emergencies in recent decades due to its high potential for morbidity and mortality. Early diagnosis followed by appropriate treatment results in a more favorable prognosis considering its rapid progression.

Objective To describe the various treatment modalities for IEH in the last three decades and their updates.

Methods Integrative literature review on therapeutic options in IEH treatment. The terms "Epidural hematoma," "Traumatic brain injury," and "treatment" were used in the Medline/PubMed, Google Scholar, and SciELO platforms, resulting in 90 articles.

Results Appropriate treatment for IEH depends directly on the Glasgow Coma Scale score obtained during admission, bleeding location, lesion size, presence of associated intracranial injuries, and the neurosurgeon's experience.

Conclusion Initial treatment for IEH is predominantly surgical, with conservative treatment indicated in selected cases. Both neurosurgeons and clinicians must identify characteristic signs and symptoms promptly to avoid treatment delay. Moreover, minimally invasive approaches have gained prominence in recent decades, associated with image-guided procedures, and when well-indicated, result in rapid recovery and lower morbidity.

Keywords
- acute intracranial epidural hematoma
- head trauma
- treatment
- craniotomy
- conservative treatment
- endovascular embolization

Resumo

Introdução O hematoma epidural intracraniano agudo (HEIA) tem sido considerado uma das emergências neurocirúrgicas de maior relevância das últimas décadas devido ao seu alto potencial de morbimortalidade. O diagnóstico precoce seguido de

received
February 15, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1796652.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

tratamento adequado resulta em prognóstico mais favorável, tendo em vista sua progressão galopante.

Objetivo Descrever as diversas modalidades de tratamento do HEIA nas últimas três décadas e suas atualizações.

Métodos Revisão integrativa de literatura sobre as opções terapêuticas no tratamento do HEIA. Foram utilizados os termos: "Hematoma epidural", "Traumatismo cranioencefálico" e "tratamento" nas plataformas Medline/PubMed, Google Scholar e SciELO, resultando em 90 artigos.

Resultados O tratamento adequado para o HEIA, depende diretamente do escore na escala de coma de Glasgow obtido durante a admissão, localização do sangramento, tamanho da lesão, presença de lesões intracranianas associadas e da experiência do neurocirurgião.

Conclusão O tratamento inicial para o HEIA é eminentemente cirúrgico. Sendo o tratamento conservador indicado em casos selecionados. É de suma importância que tanto neurocirurgiões quanto clínicos devam saber identificar os sinais e sintomas característicos para não retardar o tratamento. Além disso, a abordagem minimamente invasiva vem ganhando notoriedade nas últimas décadas, associada aos procedimentos guiados por imagem, e, quando bem indicadas, resultam numa rápida recuperação e menor morbidade.

Palavras-chave
- hematoma epidural agudo intracraniano
- traumatismo cranioencefálico
- tratamento
- craniotomia
- tratamento conservador

Introduction

Intracranial epidural hematoma is defined as a collection of blood located between the dura mater and the cranial bones.[1,2] Acute intracranial epidural hematoma (IEH) accounts for 0.2% to 6% of all traumatic brain injuries (TBIs) and 9% to 12% of severe TBIs.[2–6] It predominantly affects the second and third decades of life.[3,7–9] In 70% to 90% of cases, it is due to motor vehicle accidents and accidental falls.[3,7,9,10] Its location is supratentorial in 90% and infratentorial in 10% of cases. Approximately 95% are unilateral and 5% are bilateral.[9,11]

The classic clinical picture of loss of consciousness after TBI followed by a lucid interval, accompanied by homolateral mydriasis to the hematoma and contralateral hemiparesis, with a decreased level of consciousness, occurs in only 20% of cases.[2] CT is the method of choice for initial diagnosis and treatment.[2] Treatment varies according to the size, location, evolution, neurological status of the patient, and findings on neuroimaging exams. The authors discuss the various means of invasive and non-invasive treatment of IEH.

Methods

Justification: IEH has been frequent in cases of traumatic brain injury (TBI). Various procedures have been performed with excellent results. **Objective:** To describe the various modalities of IEH treatment. **Methods:** Integrative literature review on therapeutic options in the treatment of IEH. The terms "Epidural hematoma," "Traumatic brain injury," and "treatment" were used in the Medline/PubMed, Google Scholar, and SciELO platforms, resulting in 90 articles selected based on inclusion and exclusion criteria, as well as their respective citation impact and content. **Inclusion criteria:** Articles written in Portuguese, English, and Spanish, published in the last three decades (1980-2023), absence of tangential discussion of the topic. **Exclusion criteria:** Articles published in languages other than Portuguese, English, and Spanish, publications outside the specified time frame, and tangential discussions of the topic. **Conclusion:** The treatment of IEH depends on a series of factors such as Glasgow Coma Scale score on admission, size, location, presence of associated intracranial lesions, findings of neuroimaging exams, and the experience of the neurosurgical team.

Discussion

IEH is a lesion that requires neurosurgical intervention in most cases. When it reaches a certain volume, it can cause elevated intracranial pressure (ICP) and lead the patient to a state of coma or cerebral herniation, and in some cases, death. Craniotomy has been the most indicated procedure for cerebral decompression.[1] The treatment of IEH ranges from conservative treatment to endovascular therapy, depending on the clinical picture and findings in neuroimaging exams. The main treatment options for IEH include conservative management, immediate surgery, exploratory craniotomy, conventional surgery, decompressive craniectomy, arterial embolization, ultrasound or computed tomography (CT) guided aspiration, and endoscopic drainage.[2,12–22]

Conservative Treatment

Several factors are reported to influence the strategic approach to IEH treatment. Selection criteria for conservative versus surgical treatment remain controversial.[12,23] The decision for conservative treatment and the timing for delayed intervention can be made on an individual basis

and depend on parameters such as patient age, size and location of the hematoma, neurological status of the patient upon admission, and case evolution.[2,24] Shahid et al.[25] observed that young patients who underwent early surgery with no or minimal associated brain injury recovered better than those who underwent surgery late.

Conservative treatment is indicated in patients with a preserved level of consciousness, without focal neurological deficit, absence of associated intracranial lesion, and CT showing IEH volume below <30 ml, thickness below 15 mm, and midline shift below 5 mm six hours or more after trauma, but with constant clinical observation and CT monitoring; in case of neurological decompensation, immediate surgery is indicated. Bullock et al.[13] demonstrated that a volume between 12-38 ml was suitable for conservative treatment, but Chen et al.[12] suggest that hematoma larger than 30 ml, thickness greater than 15 mm, and midline shift greater than 5 mm constitute a strong indication for surgical drainage. There is still disagreement regarding the management of IEH located in the posterior fossa; several authors indicate surgical treatment in all cases due to the potential for a considerable mass effect in a small space. Wong[26] reported that IEH located in the posterior fossa, with a volume smaller than 10 ml, can undergo conservative treatment. In cases with associated intracranial lesions, it indicates greater severity of trauma, and conservative treatment is contraindicated.[8,27,28] Samadi-Motlagh et al.[29] used tranexamic acid in selected IEH patients for conservative treatment and observed a decrease in hematoma volume expansion compared to the control group that did not use the medication, concluding that tranexamic acid plays an important role in bleeding control in IEH patients and improves their prognosis.

An important consideration should be made regarding the timing of repeat CT scans in cases of conservative treatment. Hematoma volume increases in 23% of cases, beginning eight hours after trauma and completing within 36 hours.[30–32] Spontaneous resolution rarely occurs in cases undergoing conservative treatment.[33–35]

Conventional Surgery

Surgical treatment is indicated based on neurological status and head CT findings (►**Table 1**):

Surgical treatment is performed through osteoplastic craniotomy above the site of the hematoma, with coagulation of the lacerated vessel always necessary. Dura mater suturing at the edges of the craniotomy and in the center of the bone flap to prevent its recurrence. In cases of bleeding from venous sinuses, control is achieved through tamponade using gelfoam or surgicel, and the patient's head is elevated in bed to prevent air embolism.[10,13,36,37] It is important to emphasize that drains should not be placed in postoperative cases of IEH, as they may lead to local infection and have not been effective in cases of IEH recurrence.

Table 1 Indications for urgent surgery in cases of intracranial epidural hematoma

1. Coma with anisocoria and CT demonstrating IEH necessitate urgent surgery.
2. Coma and worsening neurological status in IEH with a volume > 25 ml.
3. Volume of IEH > 30 ml, even in the absence of symptoms.
4. Volume of IEH > 25 ml, located in the posterior fossa or temporal region.
5. Midline shift > 4 mm, with worsening neurological status.
6. Increase in volume of the IEH.

Immediate Surgery and Exploratory Trepanation

In cases where a patient presents in the emergency room with unilateral pupillary dilation, decerebrate posture, and signs of elevated intracranial pressure, emergency action may involve making a small incision in the suspected area above the hematoma. A quick trephine hole is made, allowing for partial drainage of the hematoma to relieve intracranial hypertension, followed by craniotomy, definitive hematoma drainage, and coagulation of the injured vessel.[14,38–40] In the presence of associated intracranial lesions (subdural hematoma, brain contusion, intracerebral hematoma) seen on CT scan, if necessary, surgical drainage is performed. Intraoperative ultrasound may sometimes be useful to identify deep lesions. In cases of decompressive craniectomy (DC) where the bone flap cannot be immediately repositioned, it should be preserved in the freezer or the fatty layer of the abdominal wall for later repositioning. This occurs when there is cerebral edema or an existing lesion seen on CT observed during surgery, or in cases of refractory intracranial hypertension developed perioperatively. A new CT scan is indicated to determine the extent of hematoma drainage and to identify late-evolving hematomas.

Decompressive Craniectomy

Considerable controversy exists regarding the initial treatment of IEH, especially the optimal surgical treatment option, particularly in patients with cerebral herniation. The recommended treatment for IEH is osteoplastic craniotomy and hematoma drainage with replacement of the bone flap. Experiences with decompressive craniectomies (DC) in IEH have been sparsely reported in the literature.[41–43] Korde et al.[15] reported their experience in ten cases of IEH with admission Glasgow Coma Scale (GCS) scores below 5, who underwent DC initially, and concluded that these patients showed better outcomes.

Other authors[2,44,45] recommend DC as the first choice in cases of massive hematoma and low GCS, and it has been beneficial. In some cases, hematoma drainage with additional DC may effectively prevent and/or alleviate postoperative cerebral infarction; however, further investigation through randomized clinical trials is needed for confirmation. Korde et al.[15] suggest DC in patients with admission GCS scores below 5, with anisocoria for more than two hours from the time of the first neurological examination, or bilateral mydriasis at presentation, as they independently contribute to massive cerebral infarction and diffuse cerebral edema.

Predictive imaging factors for DC indication include hematoma volume above 100 ml or the presence of the swirl sign. Evidence of infarction in the middle cerebral artery or posterior cerebral artery territory also serves as an indicator for DC, as

does midline structure deviation, indicating elevated intracranial pressure. The incidence of post-traumatic cerebral infarction secondary to IEH is 18.2%, even higher in patients with risk factors such as transtemporal location, preoperative hypovolemic shock for more than 30 minutes, bilateral mydriasis, and preoperative cerebral herniation.[13,46,47]

DC plays a crucial role in controlling elevated intracranial pressure and is recommended when feasible in severe cases of post-traumatic cerebral infarction secondary to IEH.[46–50] According to Vilcinis et al,[16] DC may effectively reduce intracranial pressure, but its effects on outcomes remain unknown. However, DC associated with IEH drainage in patients with profound coma appears to have inferior outcomes compared to osteoplastic craniotomy. Therefore, DC associated with initial IEH drainage may represent the best surgical option in well-selected cases, although more prospective studies are needed for conclusive evidence.

Inappropriately indicated DC as initial hematoma drainage may lead to inevitable complications, such as cerebral hemodynamic abnormalities, subsequent cerebral necrosis, and infarction, as well as the need for cranioplasty. The decision to drain the hematoma with or without DC, especially in patients with cerebral herniation, remains controversial.[46,51]

Arterial Embolization

Recent technological advancements have enabled endovascular treatment in a variety of cerebrovascular lesions, including IEH.[18,52–55] Middle meningeal artery embolization plays a crucial role as an alternative treatment, particularly in certain coexisting disease scenarios where conventional surgical treatment of IEH is precluded.[55,56] For other authors, endovascular treatment has proven useful in cases of small IEH, serving as an effective treatment option.[17,18,54,57]

Endovascular treatment of the middle meningeal artery was initially described in 2004 by Suzuki et al,[18] and subsequent studies have reinforced its indication.[17,18,53,58] Endovascular intervention is a method that can be effective in treating IEH without hematoma progression compared to traditional craniotomy.[59,60] According to Madison et al,[59] treatment decisions depend on the severity of the patient's injury and their neurological conditions. Ye et al[61] reported that endovascular intervention yields good results in treating IEH complicated by oronasal hemorrhage due to skull base fracture. Other authors recommend endovascular intervention in the treatment of IEH or its progression.[18,62] Peres et al[17] treated 80 patients with IEH, primarily in temporal locations, with excellent results. Suzuki et al[18] used endovascular embolization in nine patients during the acute phase of IEH and achieved excellent outcomes. The potential role of endovascular embolization in the treatment of IEH in carefully selected patients has been beneficial.

Ultrasound and/or CT-Guided Aspiration

In cases of neonates, needle aspiration guided by transcranial ultrasound can be performed with excellent results.[63,64] Spontaneous resolution without the need for neurosurgical intervention may also occur, but in cases of voluminous IEH with mass effect, surgical treatment is indicated to prevent neurological deterioration and IEH ossification.[65]

Zhao et al[19] used traumatic IEH drainage in 33 selected patients, with puncture guided by CT and instillation of urokinase during drainage, concluding that this procedure is safe, simple, rapid, and accurate, as reported by other authors as well.[1,14,66]

In cases associated with cephalohematoma, aspiration can be performed due to the common finding of communication between these hematomas.[67–71] It has been described that between 61% to 70% of IEH in young children coexist with cephalohematoma, and half of these have communication between them.[68] Smets and Vanhanwaert[72] suggest that in the absence of neurological signs and symptoms, aspiration of the cephalohematoma to drain the communicating IEH in newborns can avoid a more aggressive surgical intervention.

Endoscopic Drainage and Minimally Invasive Surgery

Endoscopic treatment for IEH drainage has been rare. This procedure has been performed in cases of acute spinal epidural hematoma and subdural and intraparenchymal hematomas.[22,46,73] Oshima et al[55] performed a combined approach (endoscopy and embolization of the middle meningeal artery), under local anesthesia for IEH drainage, in an elderly patient with poor clinical conditions, with excellent results.

Minimally Invasive Surgery (MIS) has been increasingly performed in patients with intracranial hematoma. It has the advantage of better-preserving brain tissue compared to more invasive procedures. According to Huang et al,[74] MIS is suitable for uncomplicated IEH, while for IEH involving the temporal base or major venous sinuses, craniotomy is the preferred initial choice. Wang et al[46] reported good results in 59 cases of IEH treated with aspiration and drainage through MIS, using urokinase in eight cases with excellent results.

Tseng et al[21] concluded in their study that MIS assisted with an endoscope in traumatic hemorrhage are efficient and effective in carefully selected cases. According to Tseng et al,[21] its advantages include early decompression, reduced surgical time, less blood loss, small incisions, early recovery, short hospital stays, and lower operational costs. Lu et al[75] performed aspiration and drainage through MIS, being effective in treating 58 patients with IEH involving the transverse sinus. Other authors performed trepanation followed by urokinase instillation and concluded it to be an efficient, easily performed technique effective in IEH treatment in selected cases.[14,76,77] With the evolution of new devices and techniques, it will be a procedure to be successfully performed in experienced hands in the future.[55]

Prognosis

IEH is an important cause of morbidity and mortality in patients with TBI.[4] Factors that significantly influence prognosis include age, low GCS score on admission, presence of associated intradural injury, time elapsed between trauma and symptom onset, hematoma size, and location.[3,49,78,79] Mortality from IEH varies from 0% to 21%.[12,80–84] Stephanov[85]

demonstrated that pre-CT era mortality ranged from 16% to 52%, while post-CT era mortality ranged from 8% to 14%. This author concluded that rapid patient transport to a neurosurgical referral center was the most important factor in reducing mortality. Jones et al[86] reported a decrease in mortality from 29% to 8% over the last 35 years. Other authors have shown that the absence of an early diagnosis, anisocoria, preoperative GCS score, time between injury and surgery, and presence of associated intradural injuries contribute to high morbidity and mortality.[87–90]

Conclusion

The treatment of IEH is considered one of the most rewarding neurosurgical interventions for the neurosurgeon because when treated early and appropriately, the patient transitions from a severe neurological state to a normal one. Therefore, it is of utmost importance that both neurosurgeons and clinicians be able to identify the characteristic signs and symptoms to avoid treatment delay. Furthermore, it is concluded that treatment is invariably surgical in many cases. Additionally, it is worth noting that minimally invasive approaches have gained prominence in recent decades, associated with image-guided procedures, and when well-indicated, result in rapid recovery and lower morbidity.

Conflict of Interest
The authors report no conflicts of interest.

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Sellar Neurocysticercosis: A Literature Review

Neurocisticercose Selar: Uma revisão de literatura

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Arq Bras Neurocir 2024;43(4):e315–e318.

Abstract

The objective of this study was to carry out a literature review on neurocysticercosis. In this sense, a literature review was performed based on articles published on Bireme and Pubmed in the period 2018–2024. The descriptor was used: "intrasellar cysticercosis." Five studies met the eligibility criteria. Headache was the main symptom observed. The prevalence of the disease by age profile occurred mainly in young adults. The lack of general knowledge and the lack of resources for prevention, diagnosis, and early treatment may be factors that contribute to the persistence of the disease in the population. Furthermore, the lack of resources, such as neuroimaging exams and neurological care, makes it difficult to diagnose and treat the disease; thus, delaying diagnosis contributes to the spread of the infection.

Keywords

- neurocysticercosis
- sellar
- intraventricular cyst
- racemose
- subarachnoid space

Resumo

O objetivo deste estudo foi realizar uma revisão de literatura sobre neurocisticercose. Nesse sentido, foi realizada uma revisão de literatura baseada nos artigos publicados na Bireme e Pubmed no período de 2018–2024. Foi utilizado o descritor: "Intrasellar cysticercosis." Cinco estudos preencheram os critérios de elegibilidade. Cefaleia foi o principal sintoma observado. A prevalência da doença por perfil etário se deu principalmente em adultos jovens. A falta de conhecimento geral e carência de recursos para prevenção, diagnóstico e tratamento precoce podem ser fatores que corroboram para a permanência da doença na população. Ademais, a falta de recursos, como exames de neuroimagem e cuidados neurológicos dificultam o diagnóstico e tratamento da doença, com isso, a demora no diagnóstico contribui para disseminação da infecção.

Palavras-chaves

- neurocisticercose
- selar
- cisto intraventricular
- racemose
- espaço subaracnóide

received
February 10, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1795073.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Introduction

Worms are caused by worms that parasitize the host's body. In this context, human cysticercosis is a clinically relevant verminosis with a high incidence, especially in underdeveloped countries.[1] According to the World Health Organization (WHO), Taenia solium is a zoonotic parasite with global distribution but high transmission and is hyperendemic in parts of Latin America, South and Southeast Asia, and sub-Saharan Africa.[2]

The main risk factors for neurocysticercosis are poor environmental conditions, a lack of basic sanitation, and hygienic dietary habits. It is believed that contamination is transmitted via the oral-fecal route, either through food contaminated with parasite eggs or through ingestion of raw or undercooked pork meat.[3] After ingesting T. solium eggs, the cysticerci reach the adult stage in the small intestine. In the muscles, skin, and eyes, the resulting larvae form cysts. In the Central Nervous System (CNS), this same differentiation occurs; however, infection in this system refers to neurocysticercosis.[4]

Patients with neurocysticercosis may present symptoms associated with increased intracranial pressure, seizures, chronic headaches, focal neurological deficits, hydrocephalus, and focal epilepsy.[4] For diagnosis, neuroimaging tests, such as magnetic resonance imaging (MRI) and computed tomography (CT), are considered essential for the diagnosis of neurocysticercosis.[5,6] Thus, the management of this patient varies according to the severity of the clinical condition, with the use of drug therapy and/or surgical intervention in severe cases.[7]

The present study aims to carry out a literature review on neurocysticercosis.

Methods

This is a literature review on neurocysticercosis. The databases consulted were Bireme and Pubmed, using the following descriptor: "intrasellar cysticercosis." The inclusion criteria adopted were: i) studies performed in the last six years (2018–2024); ii) original articles. Studies were excluded: i) literature review. The inclusion criteria were: (i) studies performed in the last six years (2018–2024); (ii) original articles.

Results

Based on the chosen descriptors, in BIREME, 9 articles were initially identified. However, only 1 article met the eligibility criteria. In the Pubmed database, 30 articles were identified, but only 7 articles met the eligibility criteria. The sum of articles from BIREME and Pubmed totaled 8 articles. After excluding duplicates ($n = 1$)), 7 articles remained. With the exclusion of non-original articles ($n = 2$)), 5 articles were selected (►**Fig. 1**).

►**Table 1** presents the classification of the studies analyzed, according to year, symptoms, affected areas, and therapeutic approaches. It was observed that, in the cases analyzed, all the patients described presented with headaches. However, only a

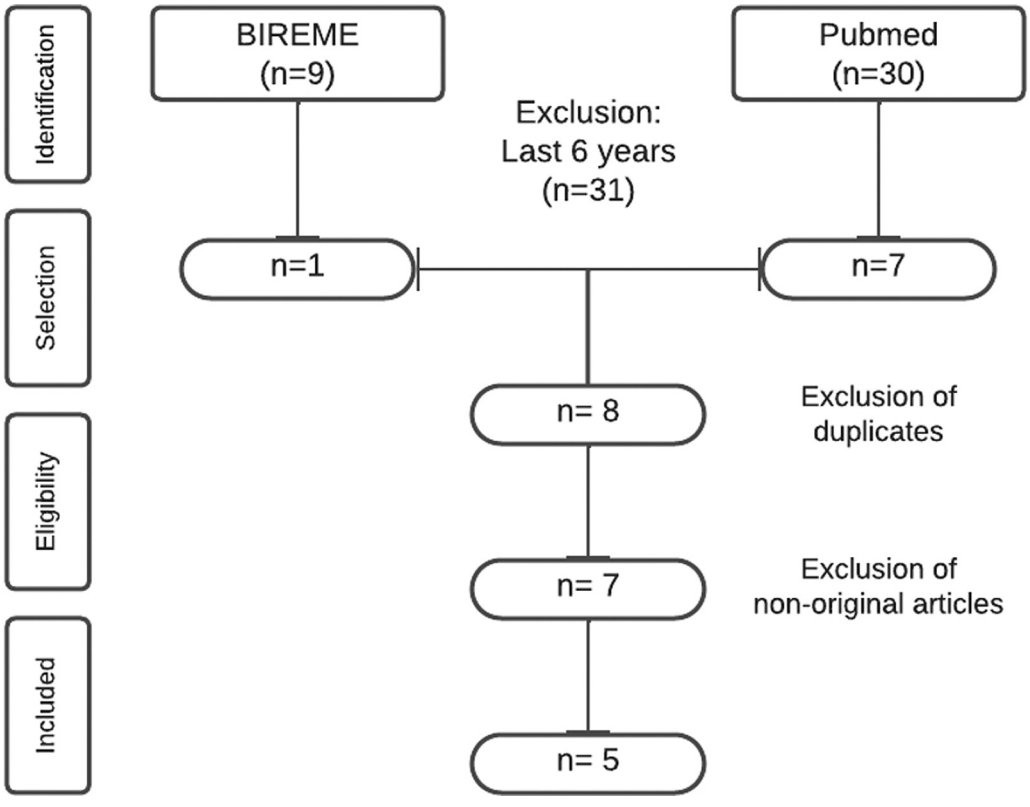

Fig. 1 Flowchart of selection of literature review citations.

Table 1 Characterization of selected studies, second year, symptoms, affected areas and approaches

Author	Yeah	Age	Symptomatology	Affected areas	Approaches
Goulart, et al.[10]	2022	26	Progressive frontal headache, dizziness episodes	Space subarachnoid	Endonasal endoscopic, medicated: dexamethasone (12 mg/day) and albendazole (30 mg/kg/day)
Zhang, et al.[12]	2022	20	Headache and nausea	Visual acuity of the left eye of 6/30 and temporal hemianopsia of the left eye	Medication (Albendazole and Praziquantel))
Shakya, et al.[14]	2021	28	Rapid progressive loss of vision and headache	Visual acuity of the left eye of 6/30 and temporal hemianopsia of the left eye	Medication and pterional craniotomy surgery
Hernandez, et al.[15]	2020	45	Intense chronic headache, progressive deterioration of visual acuity for 6 months and bitemporal hemianopsia	Visual acuity in the right eye 20/60 and in the left eye 20/80 and bitemporal hemianopsia	Surgery transciliary supraorbital keyhole.

few presented vision impairments at different degrees of progression. Furthermore, 1 of the 4 patients had manifestations related to nausea or dizziness; in the same proportion, a manifestation of subarachnoid or disseminated neurocysticercosis was also observed. Concerning the other affected areas, 2 of the 4 patients presented impaired visual acuity, whether bilateral or not. The approach varied, according to the severity and location affected, that is, there were surgical and/or pharmacological interventions.

Discussion

The present study verified the scientific production regarding the time interval between 2018 and 2024 regarding the NCC. Among the 5 selected studies, the following aspects related to the disease were mainly evaluated: clinical manifestations, approach, treatment, and clinical outcome.

According to the results, it was observed that distribution of the infection may occur, affecting neurological and other tissues. This is because the parasite has a tropism for the blood-brain barrier (BBB) and the blood-ocular barrier, which triggers the manifestations of the cases. These manifestations of neurocysticercosis depend on the location where the parasite settles in the human CNS. When the cysts are outside the brain parenchyma (extra parenchymal NCC), they grow and spread, causing conditions related to mass effect, hydrocephalus, chronic arachnoiditis, and vasculitis. Thus, it is the cause of the greatest morbidity and mortality.[8]

Parenchymal cysts rarely grow beyond 2 cm in diameter and establish themselves as small cysts, presenting a more positive prognosis. In this sense, the most common symptoms are headache and seizures, which are commonly of the same type, and their location is related to a parasitic lesion. The occurrence of the manifestations and affected areas described in the literature was observed in the clinical cases of the selected studies.[8]

Neurological symptoms lead patients to seek specialist care, and medical management is defined based on the presentation of symptoms. For symptomatic patients, such as those in the cases described, therapy is based on surgical intervention and/or the use of drugs to minimize symptoms and prevent the development of the parasite.[9]

Before starting treatment with antiparasitic drugs, it is important to establish pharmacological therapy to manage symptoms. The indication of mannitol, steroids, analgesics, and antiepileptics is generally necessary. The use of antiparasitics aims to eliminate cysticerci, although improvement is not immediate. In addition to the possibility of developing inflammation around the lesion, this can lead to the emergence or progression of neurological manifestations. To regulate these unwanted symptoms, the simultaneous administration of steroids is valid.[9]

The NCC of the patient described by Goulart et al.[10] affected the subarachnoid space, the most common site of infection. In these cases, antiparasitic medications are also used to resolve the lesions. Albendazole (ABZ) is the first option due to the drug's potential to reach higher levels in the subarachnoid space.[11]

In the approach chosen in the clinical case of disseminated cysticercosis described by Zhang et al.,[12] a combination of ABZ and praziquantel (PZQ) was chosen. Antiparasitics have different mechanisms of action but are used in combination due to evidence of parasiticidal superiority when compared with monotherapy.[13]

Furthermore, some cases require surgical approaches, among which the most common is the insertion of a ventriculoperitoneal shunt to treat hydrocephalus. Diagnosis and surgery must be performed as soon as possible to minimize the risk of sequelae or death. Others suggest that removing the cysts through surgery is a viable alternative only in situations where the patient has intracranial hypertension. In general, for most patients with neurocysticercosis with giant subarachnoid cysts, surgical procedures, and their potential complications can be avoided.[11]

Therefore, community health and education interventions are important to reduce cases of cysticercosis caused

by T. solium, as it is still a neglected disease, according to the WHO. The lack of information regarding the correct hygiene of food and the forms of contamination are the main factors in the spread of the parasite.

Conclusion

The lack of general knowledge and the lack of resources for prevention, diagnosis, and early treatment may be factors that contribute to the persistence of the disease in the population. Furthermore, the lack of resources, such as neuroimaging exams and neurological care, makes it difficult to diagnose and treat the disease; thus, delaying diagnosis contributes to the spread of the infection.

Conflict of Interest

None.

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Perspective on the Influence of Biopsy on the Survival of Pediatric Patients with Diffuse Brainstem Gliomas: A Literature Review

Perspectiva da influência da biópsia na sobrevida de pacientes pediátricos com Gliomas Difusos do Tronco: Uma revisão de literatura

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Arq Bras Neurocir 2024;43(4):e319–e324.

Abstract

Introduction Diffuse brainstem gliomas (DBG) represent the most common subtype of pediatric brainstem tumors, characterized by a systematically grim prognosis with a median survival rate of 10% two years post-diagnosis. Unlike other brain tumors, diffuse brainstem gliomas have traditionally relied on cranial magnetic resonance imaging (MRI) as a sufficient diagnostic tool, rendering surgical biopsies deemed unnecessary.

Objectives To conduct a literature review aiming to assess whether the performance of surgical biopsies has influenced the survival outcomes of children with diffuse brainstem gliomas.

Materials and Methods A comprehensive literature review was conducted using electronic databases PubMed, Embase, and LILACS. The search terms included "glioma" or "diffuse glioma" in conjunction with "pediatric" or "childhood," combined with "biopsy" or "stereotactic," and further combined with "brainstem," "pons," "pontine," or "mesencephalon," along with "survival." The searches were limited to studies involving pediatric patients (age <18 years) published between 1980 and 2021.

Results The analysis of the presented data revealed morbidity ranging from 0% to 33.3% and mortality from 0% to 2.2%. Transfrontal access was predominantly favored

Keywords
- brain stem neoplasms
- gliomas
- midline
- diffuse
- childhood
- biopsy

received
February 2, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1795072.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

by most authors, followed by transcerebellar approaches. The rate of inconclusive biopsies varied from 0% to 30%.

Conclusion Given the infiltrative nature of diffuse brainstem gliomas; surgical resection is generally deemed impractical. Radiation therapy remains the standard treatment, providing a marginal survival benefit of ~3 months. There is currently no established chemotherapy protocol for this pathology.

Resumo

Introdução Gliomas difusos do tronco (GDT) são o subtipo de tumor de tronco pediátrico mais comum, com prognóstico sistematicamente sombrio e sobrevida média de 10%, após 2 anos do diagnóstico. Diferentemente dos outros tumores cerebrais, a ressonância magnética de crânio é considerada suficiente para diagnóstico dos gliomas de tronco, fazendo com que a biópsia seja desnecessária.

Objetivos Realizar uma revisão de literatura buscando verificar se a realização de biópsias cirúrgicas impactou de alguma forma na sobrevida das crianças com GDT.

Materiais e Métodos Revisão bibliográfica nas bases de pesquisa de dados eletrônicos PubMed, Embase e LILACS; a partir dos termos: "glioma" ou "glioma difuso," em associação com "pediátrico" ou infância," em combinação com "biópsia" ou "estereotática," em combinação com "tronco cerebral," ou "ponte," ou "pontino," ou "mesencéfalo" em combinação com "sobrevida." As pesquisas foram limitadas a estudos em pacientes pediátricos (idade <18 anos), publicados entre 1980 2021.

Resultados Através da análise dos dados expostos foi possível observar que a morbidade variou de 0 a 33,3% e a mortalidade de 0 a 2,2%. A maioria dos autores preferiu a via de acesso transfrontal, seguida pela transcerebelar. A taxa de biópsias inconclusivas variou de 0 a 30%.

Conclusão Devido às características infiltrativas do tumor, a ressecção cirúrgica é desconsiderada. A radioterapia continua sendo o padrão de tratamento, conferindo benefício de sobrevida de cerca de 3 meses. Não há padrão de quimioterapia definido para essa patologia.

Palavras-chaves

- neoplasias do tronco encefálico
- gliomas
- linha média
- difusos
- infância
- biópsia

Introduction

Diffuse brainstem gliomas (DBGs) are the most common pediatric brainstem tumor subtype, accounting for 75% of tumors in this region in children, according to the CBTRUS published in 2020. It has a consistently poor prognosis and after 2 years of diagnosis, only 10% survive.[1,2] It mainly affects school-age children, with no predilection for sex. It is characterized by a rapid onset of symptoms in previously healthy patients.[3]

These tumors infiltrate both gray and white matter and their cells are often small and monomorphic but can be large and pleomorphic. They usually have astrocytic morphology but may sometimes be oligodendroglial.[4] Corresponds to grade IV glioma, regardless of histological grade.[5] In a recently revised 2021 World Health Organization (WHO) classification for central nervous system (CNS) tumors, most pediatric DBGs have been neuropathologically reclassified into a new tumor entity: diffuse midline glioma, H3-K27-altered.

The molecular profile of this entity is highly heterogeneous, with mutations such as histone H3, activin A receptor, type I (ACVR1), tumor protein p53 (TP53), platelet-derived growth factor receptor A (PDGFRA), phosphatidylinositol 3-kinase α catalytic subunit (PIK3CA) and Myc (MYC).[6] Some combinations of these genes are indicative of the behavior of the disease, for example, overlaps of Tp53 and H3K27M mutations have denoted a more aggressive course, in some series, as well as the loss of ATRX expression, which is an independent predictor of poor prognosis.[5]

Due to the tumor's infiltrative pattern, surgical resection is not considered. Currently, radiotherapy is the standard treatment, providing transient relief of symptoms, and without it, the median survival is 4 months.[2,3] Subsequent tumor progression is the rule and the median overall survival ranges from 8 to 11 months.[3] To date, there is no defined chemotherapy pattern.

Currently, the diagnosis of DBG does not require a biopsy, and is based on the following radiological criteria: a) intrinsic centrally located lesion, involving more than 50% of the axial diameter of the bridge; b) blurring of tumor margins; c) T1 hypointensity; d) T2 hyperintensity; e) irregular or absent contrast uptake; and f) absence of cystic or exophytic components.[7] The conviction of dismissing histopathological study for the diagnosis of DBG was influenced by some studies, among them one by Stroin et al.,[8] who published a

review of 49 children in which CT findings, pathological results, prognosis, and surgical efficacy were correlated. The authors concluded that the biopsy of diffuse lesions of the brainstem leads to a diagnostic yield and prognosis inferior to the radiological findings. Reinforcing the argument against performing biopsies, in 1987, Epstein et al.[9] published a series with 44 patients, in which he concluded that although biopsy can be performed with low morbidity/mortality, there was not enough useful information to justify it. Albright et al.,[10] in 1993, published more on the subject and after a retrospective review stated that performing a biopsy did not change the treatment instituted after the radiological diagnosis of DBG.

Until the end of the 1990s, physicians who cared for children with DBG did not routinely offer biopsy as part of the workup for handling these tumors.[3] This paradigm began to change slowly after some authors challenged this conduct. Among them, it is worth mentioning the work of Samadani et al.[11] (2003), a meta-analysis of 293 brainstem biopsies in adults and children, in which some diagnosis was made in 94% of patients after the first biopsy and in 96% after the second, with a mortality of 0.3% and the presence of persistent neurological deficit of 1%. Hamisch et al.[1] (2017) performed a meta-analysis with a systematic review of 735 pediatric patients with brainstem tumors, demonstrating not only the safety of performing a stereotactic biopsy in these patients but also its importance for identifying future treatments.

The present study aims to analyze the perspective of the influence of biopsy in pediatric DBG patients on the survival of these children.

Materials and Methods

We performed a bibliographic survey in the PubMed, Embase, and LILACS electronic databases; from the terms: "glioma" or "diffuse glioma," in association with "pediatric" or "childhood," in combination with "biopsy" or "stereotactic," in combination with "brainstem," or "bridge," or "pontine," or "midbrain" in combination with "survival." Research was limited to human studies, published in English, from 1980 to 2021. Reference lists of selected publications were also examined to identify additional studies.

Studies were eligible if they reported biopsy data from brainstem tumors (defined as tumors located in the midbrain, pons, or medulla oblongata) in pediatric patients (age <18 years), including details on procedure-related complications (morbidity and mortality).

Studies were excluded if they were descriptions of surgical technique, tumors that were not gliomas or dealt only with therapeutic measures.

Results

The search strategy found 772 results. The screening of titles and abstracts showed that 747 articles did not meet the study's inclusion criteria. Twenty-five complete articles were selected, and after the review, eight studies were eliminated for not meeting the inclusion criteria for the review.

Regarding the selected studies:

A. 2 meta-analyses with systematic review
B. 2 analysis of questionnaires for experts
C. 10 case series
D. 2 review articles

With the aim of better interpreting the results, comparative tables of studies of similar designs were prepared, including the number of patients, surgical access performed, diagnoses obtained, and outcome of the procedures (►**Tables 1** and **2**).

Through the analysis of this data, it was possible to observe that morbidity ranged from 0 to 33.3% and mortality from 0 to 2.2%. Most authors preferred the transfrontal access route, followed by the transcerebellar route. The rate of inconclusive biopsies ranged from 0 to 30%.

Discussion

For most CNS tumors, the first step of the workup includes performing the pathological analysis by performing the biopsy; the next steps are defined based on this result. DBGs are an exception to this pattern due to the correlation between radiological and pathological diagnosis, which provides enough confidence to indicate treatment without the need for confirmation of the lesion.[12]

Table 1 Meta-analysis studies

	Patients	Access	Diagnosis	Outcomes
Hamisch, C[1]	735	60% transfrontal	84.4% glial neoplasms	6.7% morbidity
		40% transcerebellar	7.4% other tumors	0.6% permanent morbidity
			4.5% non-neoplastic diseases	0.6% mortality
			3.5% inconclusive	
Kickingereder, P[2]	1480	64% transfrontal	76.23% glial neoplasms	7.8% morbidity
		36% transcerebellar	11.9% other tumors	1.7% permanent morbidity
			8.61% non-neoplastic diseases	0.9% mortality
			3.16% inconclusive	

Table 2 Case series studies

	Patients	Access	Diagnosis	Outcomes
Ogiwara, H.[17]	7	85% suboccipital	85% glial neoplasms	15% morbidity
		15% retrosigmoid	0% inconclusive	0% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			15% other tumors	
Morais, B.A.[18]	26	9.1% transfrontal	76.9% glial neoplasms	7.6% morbidity
		81.8% transcerebellar	15.4% inconclusive	0% permanent morbidity
		9.1% transoccipital	3.8% non-neoplastic diseases	0% mortality
			3.8% other tumors	
Dellaretti, M.[19]	44	95% transfrontal	88% glial neoplasms	9% morbidity
		4.5% transcerebellar	6.9% inconclusive	9% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			4.5% other tumors	
Quick-Weller, J.[20]	*5*	20% transcerebellar	80% glial neoplasms	0% morbidity
		40% transcerebellar	0% inconclusive	0% permanent morbidity
		40% unspecified	20% non-neoplastic diseases	0% mortality
			0% other tumors	100% unspecified
Albright, A.L.[10]	27	75% suboccipital	100% glial neoplasms	33.3% morbidity
		25% retromastoid	0% inconclusive	33.3% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			0% other tumors	
Manoj, N.[21]	41 (children)	92.7% transfrontal	82.9% glial neoplasms	2.4% morbidity
		7.3% transcerebellar	4.9% inconclusive	2.4% permanent morbidity
			12% non-neoplastic diseases	0% mortality
			2.4% other tumors	
Cage T.A.[12]	9	100% transcerebellar	100% glial neoplasms	11.1% morbidity
			0% inconclusive	0% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			0% other tumors	
Epstein, F.[9]	44	86% suboccipital	93% glial neoplasms	22.7% morbidity
		14% retromastoid	0% inconclusive	22.7% permanent morbidity
			0% non-neoplastic diseases	2.2% mortality
			7% other tumors	
Pérez-Gomes, J. L.[22]	20	100% transcerebellar	90% glial neoplasms	10% morbidity
			10% inconclusive	0% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			0% other tumors	
Pincus, D.W.[23]	10	60% transfrontal	70% glial neoplasms	10% morbidity
		40% transcerebellar	30% inconclusive	10% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			0% other tumors	
Wang, Z.J.[24]	15	100% transcerebellar	100% glial neoplasms	20% morbidity
			0% inconclusive	0% permanent morbidity
			0% non-neoplastic diseases	0% mortality
			0% other tumors	

In recent decades, research has been performed in search of the possibility of offering something more, besides radiotherapy, to these children. However, the targeted therapies offered so far were based on treatments for other pediatric and adult gliomas,[13] which possibly contributed to such poor responses in terms of survival. It is likely that this delay in the advancement of effective therapies is directly related to the low characterization of the individuality of this entity, a result of the choice to spare these patients from performing biopsies.

Fortunately, in the last twenty years, many authors began to challenge this paradigm, and several studies were published demonstrating the low rate of morbidity/mortality in performing biopsies, associated with a high rate of confirmed diagnoses.

Kickingereder et al.,[2] published, in 2013, a systematic review with a meta-analysis of 1480 cases of brainstem tumors, demonstrating that the diagnostic agreement between MR images and histology diverged widely, ranging from 42% to 100%. In addition, a high diagnostic success rate (96.2%) and low complication rates were found (permanent morbidity 1.7%; mortality 0.9%).

Hankinson et al.,[7] in 2011, conducted a survey, in which 86 pediatric neurosurgeons answered questionnaires in which, among other questions, one should classify MR images of brainstem lesions as typical or atypical for DBG. They showed that the agreement was greater than 75% in only 43.8% of the cases shown, which leads us once again to question the safety of the radiological diagnosis.

In the current oncological management, the performance of biopsies comes not only as a diagnostic determinant but also as an essential element for understanding the tumor entity, which allows safely for determining outcomes in relation to survival and offering a substrate for new effective target therapies.

In the recently revised WHO classification (2021) of CNS tumors, the majority of pediatric DBGs were neuropathologically reclassified into a new tumor entity: diffuse midline glioma, H3-K27-altered.[7]

Chen et al.[13] (2020) went further and classified DBGs according to the degree of methylation into four groups: "H3-Pons," "H3-Medulla," "IDH" and "Pilocytic-like Astrocytoma (PA-like), which have characteristics such as overall survival, oncogenic mechanisms, mutational profile, and distinct location. The PA-like group included grade II and III tumors according to the WHO classification, without identifiable IDH and histone H3 mutations, with a more benign clinical course and longer overall survival. The IDH cluster harbored IDH1, ATRX, and Tp53 mutations, being restricted to adult patients. The H3-Medulla group was in the medulla and dorsal medullary point junction. The H3-Pons cluster was present in the pons and cerebellar peduncle, encompassed grade II to IV tumors, and had worse overall survival.

Through works such as those mentioned above, we can glimpse a vision of a not-so-distant future, in which we will have effective targeted therapies in the management of DBGs, based on an understanding of the biology of this entity.

We can cite encouraging works from the discoveries of mutational and epigenetic profiles of these tumors. Among them, the research performed by Balakrishnan et al.,[14] in 2020, in which from the description of the increased expression of BMI1, an epigenetic chromatin modifier that regulates genomic complexes of stem cells and cancer cells, the effect of the H3K27M mutation; the authors were able to demonstrate that inhibition of BMI1 in vivo reduced tumor volume without detectable toxicity.

In 2015, Grasso et al.,[15] performed a multicenter preclinical study, in which the multi-HDAC *Panobinostat* inhibitor was identified, which works by restoring the methylation of H3K27 and normalizes oncogenic gene expression. In 2020, a phase I study of this drug was started, from which we await the results.

Park et al.[16] demonstrated that STAT3, a radioresistance-inducing oncogene present in some cancers such as lung, pancreas, and breast, is upregulated in DBG. This group showed a favorable response from the combination of STAT3 inhibition and radiotherapy, suggesting a potential route of treatment.

The studies cited are just a few examples of the potential offered by the collection of tumor material for analysis. We believe that the more researchers can have access to the materials offered by the biopsy, the closer we will be to the possibility of offering effective treatments to these children.

Conclusion

Biopsy for DBGs is feasible and presents very low complications. There is a tangible prospect of new therapeutic pathways for these children, based on the genetic and epigenetic individualization of these entities, which is only possible from the analysis of tumor tissue. Given the current oncological scenario of precision medicine, there is no possibility of adequately managing DBG patients without offering a biopsy.

Conflict of Interest
None.

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Precision in Neuronavigation Systems: A Systematic Review and Meta-analysis

Precisão em sistemas de neuronavegação: Uma revisão sistemática e meta-análise

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Arq Bras Neurocir 2024;43(4):e325–e336.

Abstract

Introduction To evaluate the accuracy of different neuronavigation systems and establish factors that influence their accuracy and their indications for use.

Methods This is a systematic review of the literature with meta-analysis based on the guiding question of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA): What is the accuracy of neuronavigation systems and the factors that influence it? For that, a search was performed in PubMed, LILACS, SciELO, Embase, Web of Science, and SCOPUS databases using descriptors combined with two Boolean operators. The articles found were submitted to eligibility criteria, and the reading was partial and complete. A total of 51 studies were selected, and 11 were included in the meta-analysis.

Results In total, 5,316 procedures were evaluated using neuronavigation systems and different types of procedures performed on the skull and spine. After meta-analysis, it was possible to establish the accuracy of the optical ($N = 297$) and AR ($N = 195$), with SBT of 2.34 mm and 2.09 mm, respectively. However, studies were evaluated regarding the influence of different recording methods, the use of associated technologies, and their indications for use.

Conclusions The accuracy of the systems was established through the TRE of 2.34 mm for the optical and 2.09 mm for the augmented reality, while it was not possible to establish the electromagnetic one. Thus, the ARN is the system with the best accuracy value, in addition to presenting advantages during the surgical period when compared with the others.

Keywords
- neuronavigation
- accuracy
- reliability
- neurosurgery
- neurosurgical procedures
- image-guided surgery

received
December 13, 2023
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1795095.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Introdução Avaliar a precisão de diferentes sistemas de neuronavegação e estabelecer fatores que influenciam sua precisão e suas indicações de uso.

Métodos Trata-se de uma revisão sistemática da literatura com meta-análise baseada na questão norteadora do *Preferred Reporting Items for Systematic* Review *and Meta-Analyses* (PRISMA): Qual a precisão dos sistemas de neuronavegação e os fatores que a influenciam? Para tanto foi realizada uma busca nas bases de dados PubMed, LILACS, SciELO, Embase, Web of Science e SCOPUS utilizando descritores combinados com dois operadores booleanos. Os artigos encontrados foram submetidos aos critérios de elegibilidade e a leitura foi parcial e completa. Foram selecionados 51 estudos e 11 foram incluídos na meta-análise.

Resultados No total foram avaliados 5.316 procedimentos utilizando sistemas de neuronavegação e diferentes tipos de procedimentos realizados no crânio e na coluna vertebral. Após a meta-análise foi possível estabelecer a precisão da óptica (N = 297) e da RA (N = 195) com SBT de 2 34 mm e 2.09 mm, respectivamente. No entanto foram avaliados estudos quanto à influência de diferentes métodos de registro ao uso de tecnologias associadas e suas indicações de uso.

Conclusões A precisão dos sistemas foi estabelecida por meio do TRE de 2.34 mm para a óptica e 2.09 mm para a realidade aumentada enquanto não foi possível estabelecer o eletromagnético. Dessa forma a ARN é o sistema com melhor valor de precisão além de apresentar vantagens durante o período cirúrgico quando comparado aos demais.

Palavras-chave

- neuronavegação
- precisão
- confiabilidade
- neurocirurgia
- procedimentos neurocirúrgicos
- cirurgia guiada por imagem

Introduction

Neurosurgery encompasses various image-guided surgical approaches, among which neuronavigation emerges as a principal tool. These devices exhibit millimetric precision and accuracy, significantly enhancing procedural safety and facilitating less invasive surgeries. Neuronavigation employs a Cartesian framework, enabling the monitoring of calibrated instruments within three-dimensional space while considering their orientation and position relative to cranial structures.[1] Consequently, these systems find utility in a wide array of applications, including intracranial biopsies, spinal pedicle screw placement, precise localization of minimally invasive craniotomies, planning and execution of microsurgery for intracranial tumors and arteriovenous malformations, among other procedures.

Currently, the market offers diverse navigation technologies, predominantly featuring two tracking systems: optical and electromagnetic. These systems are responsible for perceiving the intraoperative environment in three dimensions, thereby enhancing surgical accuracy and yielding improved clinical outcomes. Moreover, augmented reality systems are available, providing an enhanced user experience.

Therefore, the purpose of this study is to conduct a systematic review focusing on the accuracy of neuronavigation. It aims to explore different navigation systems and investigate the impact of application errors (AE) and associated imaging techniques on the overall accuracy of neurosurgical procedures.

Methodology

This study comprises a systematic literature review with a meta-analysis, adhering to the criteria and guidelines outlined in the Cochrane Manual[2] (The Cochrane Collaboration) for investigating current neuronavigation technologies. The primary objective is to determine the accuracy of neuronavigation systems. The research question is formulated based on the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)[3] guidelines.

Search Strategy

Comprehensive searches were conducted in multiple online databases, including PubMed, Latin American and Caribbean Literature in Health Sciences (LILACS), Online Scientific Electronic Library (SciELO), Embase, Web of Science, and SCOPUS. The descriptors "neuronavigation," "accuracy," "reliability," "neurosurgery," "neurosurgical procedures," and "image-guided surgery" were combined using Boolean operators. The search criteria employed were ("neurosurgery" OR "neurosurgical procedures") AND ("image-guided surgery" OR "neuronavigation") AND ("reliability" OR "accuracy"). The search spanned from 1993 to January 1, 2023.

Study Selection

Upon completing the initial search, two authors (E.R.S.S.; M. A.C.L.) independently assessed the identified articles. Discrepancies were resolved through discussion with a third author (B.F.O.S.) to achieve a consensus. The following inclusion criteria were applied: articles published in English; experimental, observational studies (including cross-sectional, cohort, and case-control) or clinical trials that

reported the accuracy of the neuronavigation system; articles published within the past 30 years; and availability of the full text. Articles that did not address the topic or lacked sufficient data to fulfill the objectives of this review were excluded (see ►**Fig. 1**).

Data Extraction

A single author conducted the data extraction using a standardized form, and the collected data were organized in a Microsoft Office Excel®[4] table. Subsequently, a second author reviewed the extracted data from the studies. The extracted information included the number of participants, registration method, mean errors or precision, and the imaging method utilized.

Critical Evaluation of Studies

Tools were employed to assess the articles based on their study design. For randomized studies, the revised Cochrane risk of bias tool for randomized trials (RoB2)[5] was utilized. Non-randomized clinical studies were evaluated using the Cochrane tool for assessing the risk of bias in non-randomized studies of interventions (ROBINS-I).[6] Cohort and case-control studies were evaluated using the Newcastle-Ottawa tool, while cross-sectional studies were assessed using the Joanna Briggs[7] tool. Diagnostic accuracy studies were evaluated using the revised tool for quality assessment in diagnostic accuracy studies (QUADAS-2).[8] One author critically evaluated all the studies using the appropriate tool for each study design, and discussions were held with a second author.

Statistical Analysis

To perform the meta-analysis means and standard deviations were extracted as effect measures. For studies that presented measures other than averages, such as medians with minimum and maximum intervals or quartile measures, the tool proposed by the Cochrane Manual (The Cochrane Collaboration)[2] was employed, as described and made available by Wang et al. In cases where necessary data were missing, attempts were made to contact the corresponding authors via email. If no response was received, the article was excluded from the synthesis. The measure of central tendency of the target's registration error distribution was considered as accuracy, while the measure of dispersion was considered as precision. The data were synthesized using weighted average grouping. All calculations were performed using R© (version 4.0.3, The R Foundation for Statistical Computing, 2020) and Python (version 3.9.10, NumPy version 1.22.4, Panda's version 1.4.4, and Matplotlib version 3.7.1).

Results

The tables below provide details regarding the analyzed articles, including the authors' descriptions, year of publication, titles, and summaries of each study. The selected articles that best address the research questions are highlighted for easier reference.

Study Selection

A total of 2,581 articles were identified from all databases. After applying the eligibility criteria, 1,942 articles were selected for title and abstract screening. Subsequently, 1,274 articles underwent full-text reading, and among them, 51 articles met the inclusion and exclusion criteria, thus forming the database for this study. Among the selected articles, 12 were included in the meta-analysis.

Quality Evaluation of Studies

The studies were assessed using the tools. The majority (93.2%) of the studies were classified as cross-sectional/accuracy studies and evaluated using the Joanna Briggs (Moola

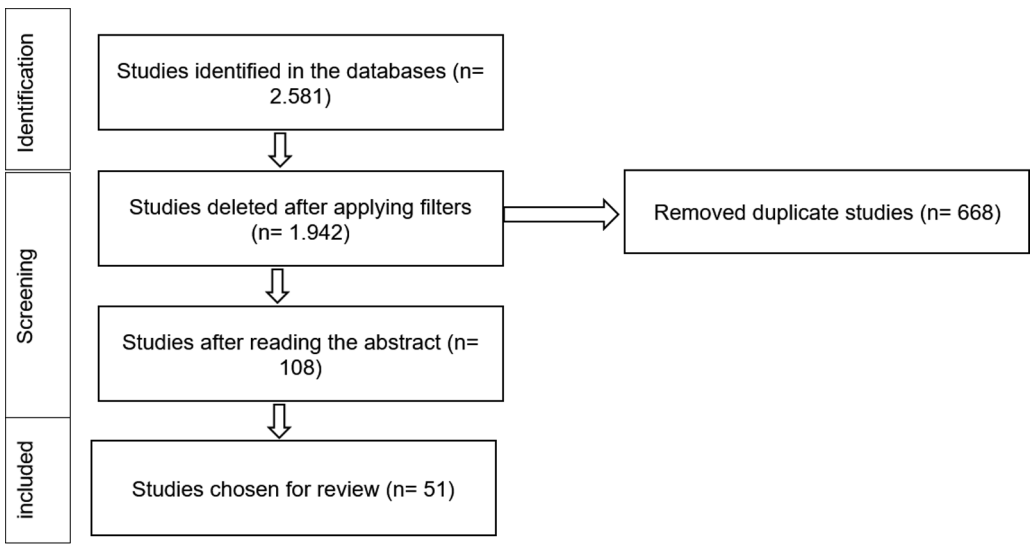

Fig. 1 Flowchart of the process performed to select articles.

et al., 2020) and QUADAS-2 tools. Both tools indicated a low risk of bias for the included studies. Randomized clinical trials, evaluated using the RoB2 tool, represented 5.8% of the included studies. The figure below illustrates the risk of bias for each study (►**Figure 2**):

Characteristics of the Studies

The total sample size included in this review comprised 5,316 procedures. In terms of location, many procedures (80%, $n = 4{,}250$) were performed on the cranium, while 20% ($n = 1{,}066$) were conducted on the spinal column. Among spinal procedures, the thoracolumbar region was the most frequently targeted, accounting for 36.9% ($n = 393$) of the total, followed by the lumbar spine with 34.7% ($n = 370$).

Out of the total procedures, 5,210 had their method of neuronavigation reported. Among these, the optical system (OP) was the most prevalent, comprising 2,673 cases (51.3%), followed by augmented reality (AR) with 1,835 cases (35.2%), and electromagnetic (EM) with 702 cases (13.5%). The method used for registration was mentioned in 40 studies (78.4%), with the fiducial method being the most employed, reported in 22 studies, followed by the anatomical marker method mentioned in 15 articles. It is noteworthy that the studies covered both cranial and spinal procedures (see ►**Chart 1**).

Different studies approached the application error results in various ways. Three studies reported the mean recording error, except for Van Doormaal et al.,[55] who obtained values of 7.20 ± 1.80 mm and 4.40 ± 2.50 mm. The remaining studies reported results ranging from 0.08 to 1.80 mm. Serej et al.[50] evaluated the fiducial registration error (FRE) using different methods. The anatomical landmark method yielded an FRE of 1.20 ± 0.40 mm, the surface method resulted in 1.00 ± 0.30 mm, and the projected method had the lowest value of 0.60 ± 0.10 mm (►**Chart 1**).

The target registration error (TRE) varied between 0.54 and 5.90 mm, with only 5 studies falling outside the commercially expected values. Salma et al.[48] assessed the TRE for different methods used and found that the scalping method had the highest average TRE of 3.24 mm, followed by the registration mask with 3.19 mm, while the bone fiducial method had a TRE within the target range of 1.95 mm. Other methods employed to assess the application error included general and average precision, location, and displacement precision, as well as average deviation (►**Chart 1**).

In ►**Chart 1**, it is evident that most spinal procedures utilized the augmented reality method, with only one study employing the optical method. It is worth noting that the studies with the largest sample size for spinal procedures in this review were Fan et al.,[23] who achieved a location accuracy of 97.8% in a sample of 370, and Elmi et al.,[20] who reported an overall accuracy of 94.1% for procedures performed on 253 spinal columns.

Considering the variation in application error across studies, a meta-analysis was conducted specifically for articles that utilized the fiducial registration error (FRE) as an evaluation method. Six articles assessing the optical system were included in the analysis, with a total sample size of 297 tests, resulting in an average FRE of 2.34 mm and a standard deviation of 1.86 mm.

►**Fig. 3** illustrates that Shamir et al.[51] and Reinges et al.[46] reported the highest values for target registration error (TRE) compared with the overall results, with values of 5.90 ± 4.30 mm and 6.10 ± 3.40 mm, respectively. Conversely, McLaughlin et al.[36] achieved the lowest error with a TRE of 0.90 ± 0.70 mm. Notably, Castilla et al.[15] had an estimated registration error closest to that obtained in the meta-analysis. It is important to highlight that the study conducted by Mert et al.[37] contributed the largest sample size, thus having the highest number of cases among all included studies.

Additionally, six articles utilizing the augmented reality system were evaluated, comprising a total sample size of 195 cases. The average estimated registration error (ERT) for these studies was 2.09 mm, with a standard deviation of 1.42 mm. Consequently, ►**Fig. 4** demonstrates that Maruyama et al.[35] achieved the highest value within the meta-analysis, reporting a skull-based TRE of 3.10 ± 1.90 mm. In Carl et al.'s[12] study, the TRE for the skull was close to the overall value at 2.33 ± 1.30 mm. When comparing it to the spinal column TRE, which was 0.72 ± 0.24 mm, the skull TRE

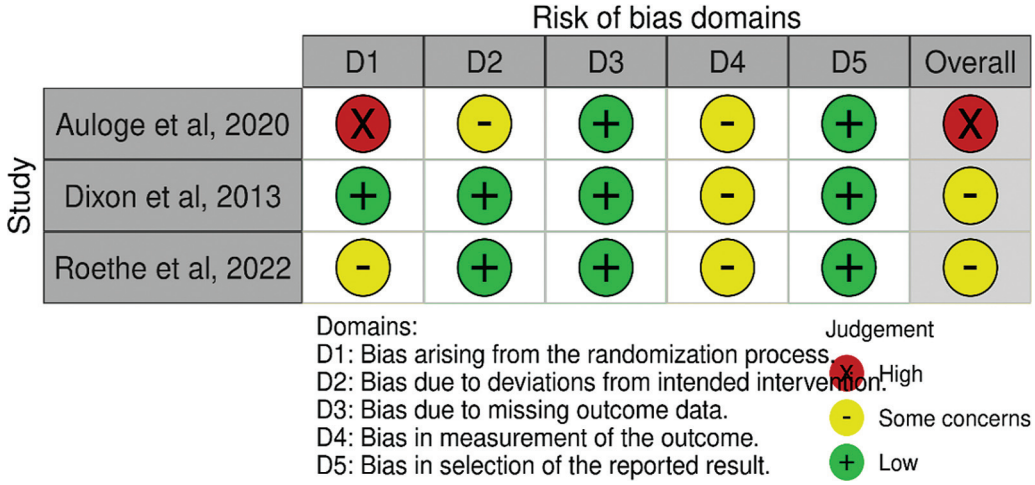

Fig. 2 RoB2 tool signal graph.

Chart 1 Characteristics of the selected studies

Author, year	Kind of study	Country	Study number (Place)	ST	Method	Result
Asano et al, 2017[9]	Accuracy/Transversal	Japão	184 (cranial)	OP	AL	Overall accuracy (average) 72.1%
Auloge et al, 2020[10]	Ensaio randomizado	França	10 (cranial)	AR	Fiducial	Mean precision of the sagittal entry point 1.65 ± 0.23 mm and coronal 1.88 ± 0.28 mm
Bilhar et al, 2018[11]	Accuracy/Transversal	Brasil	40 (thoracic)	AR	___	Failure 2.5% (pedicle violation)
Carl et al, 2019[12]	Accuracy/Transversal	Alemanha	47 (cranial) e 10 (cervical/thoracic)	AR	Fiducial	TRE skull 2.33 ± 1.30 mm PL 0.83 ± 0.44 mm TRE spine 0.72 ± 0.24 mm
Caversaccio et al, 2007[13]	Accuracy/Transversal	Rússia	406 (cranial)	AR	___	Precision range 1.00 - 1.80 mm ($N = 5$)
Carvi et al, 2007[14]	Accuracy/Transversal	Alemanha	36 (cranial)	OP	AL	Technical precision 0.50 mm Clinical Precision 1.20 mm
Castilla et al, 2003[15]	Accuracy/Transversal	Espanha	69 (64 cranial and 5 spinal)	OP	___	TRE 1.60 mm (0.50 - 3.80 mm)
Condino et al, 2021[16]	Accuracy/Transversal	Italia	60 (cranial)	AR	Fiducial	Accuracy level 97% at 1.50mm and 92% at 1.00mm
Deng et al, 2014[17]	Accuracy/Transversal	China	3 (cranial)	AR	AL	Alignment error 1.60 mm - 2.10 mm
Dixon et al, 2013[18]	Ensaio randomizado	Canadá	15 (cranial)	AR	Fiducial	Median distance from target point 2.10 mm, 1.29–2.37 mm
Eboli et al, 2011[19]	Accuracy/Transversal	EUA	208 (cranial)	EM	Fiducial	PL 1.00 - 2.00 mm
Elmi et al, 2018[20]	Accuracy/Transversal		253 (thoracic/lumbar)	AR	___	Overall accuracy 94.1%
Elmi et al, 2019[21]	Accuracy/Transversal	EUA	84 (thoracic/lumbar)	AR	Optical marker on the skin	Accuracy 2.20 ± 1.30 mm (89%)
Enchev et al, 2011[22]	Accuracy/Transversal	Bulgaria	7 (cranial)	OP	Laser	Precision range 1.00–1.70 mm Average 1.30 mm
Fan et al, 2020[23]	Accuracy/Transversal	China	370 (lumbar)	AR	___	PL 97.80%
Finger et al, 2017[24]	Accuracy/Transversal	Alemanha	43 (cranial)	AR	AL	Deviation from the midpoint of the target 1.20 ± 0.40 mm
Grayeli et al, 2009[25]	Accuracy/Transversal	França	1 → $n = 8$ 2 → $n = 25$ (cranial)	EM	AL[1] Invasive[2]	Position accuracy 4.90 ± 0.64 mm[1] 0.00 - 2.30 mm[2]
Gerard et al, 2018[26]	Accuracy/Transversal	Itália	8 (cranial)	AR	___	TRE 0.54–6.36 mm
Guedes et al, 2015[27]	Accuracy/Transversal	Brasil	40 (thoracic/lumbar)	AR	___	PP 77.50%
Hejazi et al, 2005[28]	Accuracy/Transversal	Austria	11 (cranial)	OP	Fiducial	

(*Continued*)

Chart 1 (*Continued*)

Author, year	Kind of study	Country	Study number (Place)	ST	Method	Result
						PL 1.80 - 2.20 mm Average 1.90 mm
Hermann et al, 2015[29]	Accuracy/Transversal	Alemanha	284 (cranial)	EM	Fiducial	Deviation from the surface of the target lesion 2.50 - 5.80 mm (mean 3.90 ± 1.10 mm)
Hermann et al, 2015[30]	Accuracy/Transversal	Alemanha	17 (cranial)	EM	AL	PL 2.00 e 9.00 mm
Inoue et al, 2013[31]	Accuracy/Transversal	Japão	3 (cranial)	AR	Fiducial	FRE 1.79, 1.67 e 1.65 mm
Jung et al, 2006[32]	Accuracy/Transversal	Coreia	420 (cranial)	OP	Fiducial	PL 1.15 mm
Mascitelli et al, 2018[33]	Accuracy/Transversal	EUA	84 (cranial)	AR	___	Accuracy excellent 71.4%; good 20.2%; bad 8.30%
Mascott et al, 2006[34]	Accuracy/Transversal	França	30 (cranial)	OP	Fiducial e AL	Accuracy 4.80 ± 2.00 mm
Maruyama et al, 2018[35]	Accuracy/Transversal	Japão	75 (cranial)	AR	Fiducial	TRE 0.20 to 8.10 mm (mean 3.10 ± 1.90 mm, median 2.70 mm)
McLaughlin et al, 2012[36]	Accuracy/Transversal	EUA	12 (cranial)	OP	Registration mask	TRE 0.90 ± 0.70 mm
Mert et al, 2013[37]	Accuracy/Transversal	Canada	136 (cranial)	OP	SF	TRE 0.70 (0.30 - 1.20 mm)
Muacevic et al, 2000[38]	Accuracy/Transversal	Alemanha	40 (cranial)	OP	Sticky markers	VME 1.45 ± 0.99 and 4.05 ± 3.62 mm
Nimsky et al, 2005[39]	Accuracy/Transversal	Alemanha	16 (cranial)	OP	Fiducial	TRE 1.20 ± 0.460 mm
Novák et al, 2021[40]	Accuracy/Transversal	República Checa	6 (cranial)	OP	Automatic registration	TRE 0.00 - 2.65 mm
Paraskevopoulos et al, 2011[41]	Accuracy/Transversal	Alemanha	10 (cranial)	OP	Fiducial[1] SF[2]	DM 1.45 ± 0.63 mm[1] 1.27 ± 0.53 mm[2]
Pinggera et al, 2018[42]	Accuracy/Transversal	Alemanha	1600 (cranial)	OP	Laser	TRE MD 1.97 mm (1.90 - 2.03 mm)
Pojskic et al, 2022[43]	Accuracy/Transversal	Alemanha	39 (cranial)	AR	Fiducial	TRE 0.82 ± 0.37 mm
Pojskic et al, 2021[44]	Accuracy/Transversal	Alemanha	16 (thoracic/lumbar)	AR	Automatic registration	TRE 0.84 ± 0.10 mm
Raabe et al, 2022[45]	Accuracy/Transversal	Alemanha	34 (cranial)	OP	AL	PL 2.40 ± 1.70 mm
Reinges et al, 2004[46]	Accuracy/Transversal	Alemanha	61 (cranial)	OP	Fiducial	TRE 0.80 - 14.30 mm (average 6.10; SD 3.40)
Roethe et al, 2022[47]	Ensaio randomizado	Alemanha	16 (OP) e 39 (AR) (cranial)	OP AR	___	Median accuracy of depth information OP 5.00 mm and RA 3.00 mm
Salma et al, 2012[48]	Accuracy/Transversal	EUA	20 (cranial)	OP	Bone fiducials,[1] scalp[2] and registration mask[3]	TRE 1.95 mm,[1] 3.24 mm[2]; 3.19 mm[3]

Chart 1 (*Continued*)

Author, year	Kind of study	Country	Study number (Place)	ST	Method	Result
Scheufler et al, 2011[49]	Accuracy/Transversal	Austria	248 (cervical/thoracic)	AR	___	71.4% of cases with excellent/good results
Serej et al, 2015[50]	Accuracy/Transversal	Irã	10 (cranial)	OP	Anatomical landmarks,[1] SF[2] e projected[3]	FRE 1.22 ± 0.43 mm,[1] 0.99 ± 0.31 mm[2], 043 ± 08 mm[3]
Shamir et al, 2011[51]	Accuracy/Transversal	Israel	15 (cranial)	OP	Fiducial AL	TRE 5.90 ± 4.30 mm Navigation record error 1.40 ± 0.40 mm
Suess et al, 2001[52]	Accuracy/Transversal	Alemanha	24 (cranial)	EM	Fiducial	In register 1.30 - 1.50 mm and EM target 3.20 mm
Suess et al, 2007[53]	Accuracy/Transversal	Alemanha	13 (cranial)	OP EM	Fiducial	Precision range 0.83 - 1.85 mm FRE 1.53 ± 0.51 mm
Tabrizi et al, 2015[54]	Accuracy/Transversal	Alemanha	15 (cranial)	AR	Fiducial	Em of projection 0.80 ± 0.25 mm, 1.20 ± 0.54 mm
Van Doormaal et al, 2019[55]	Accuracy/Transversal	Holanda	13 (cranial)	AR	Fiducial	FRE 7.20 ± 1.80 mm FRE 4.40 ± 2.50 mm
Yavas et al, 2021[56]	Accuracy/Transversal	Turquia	8 (cranial)	AR	3D marker	Directing error 0.50 - 3.50 mm; In1.56 mm (SD 0.79 mm and median of 1.56 mm)
Yoshino et al, 2015[57]	Accuracy/Transversal	Japão	9 (cranial)	OP	___	TRE 2.90 ± 1.90 mm
Zhao et al, 2006[58]	Accuracy/Transversal	China	63 (cranial)	OP	MA	Accuracy 2.30 ± 1.10 mm
Zhuang et al, 2011[59]	Accuracy/Transversal	China	11 (cranial)	OP	Fiducial	Prediction error 1.29 - 1.91 mm (1.62 ± 0.22 mm)

Abbreviations: AL, Anatomical Landmarks; AR, Augmented Reality; EM, Electromagnetic; FRE, Mean record error; In, Average Error; MD, Mean Deviation; OP, Optical; PL, Location accuracy; PP, Positioning Accuracy; SD, Standard Deviation; SF, Surface Fusion; ST, System; TRE, Destination accuracy error; VME, mean error value.

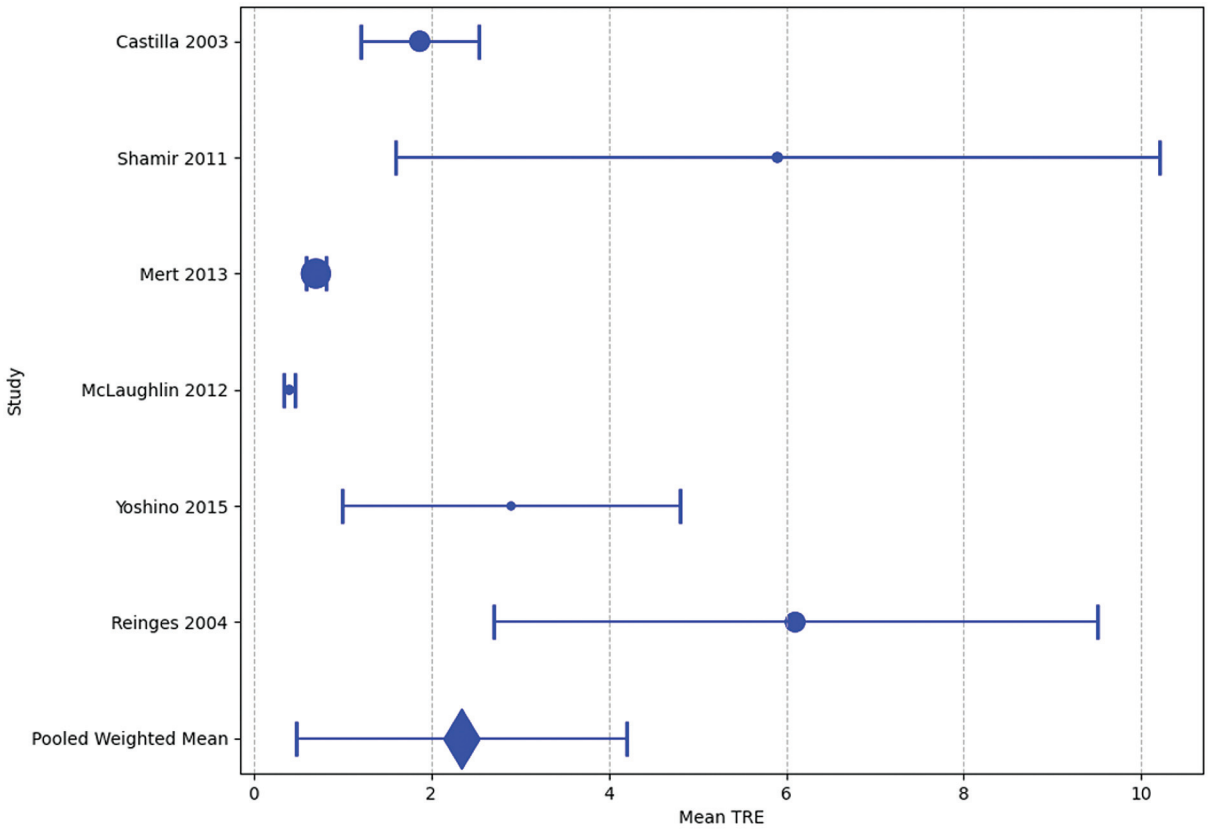

Fig. 3 ERT assessment in studies that used an optical system after the sensitivity of the heterogeneity index.

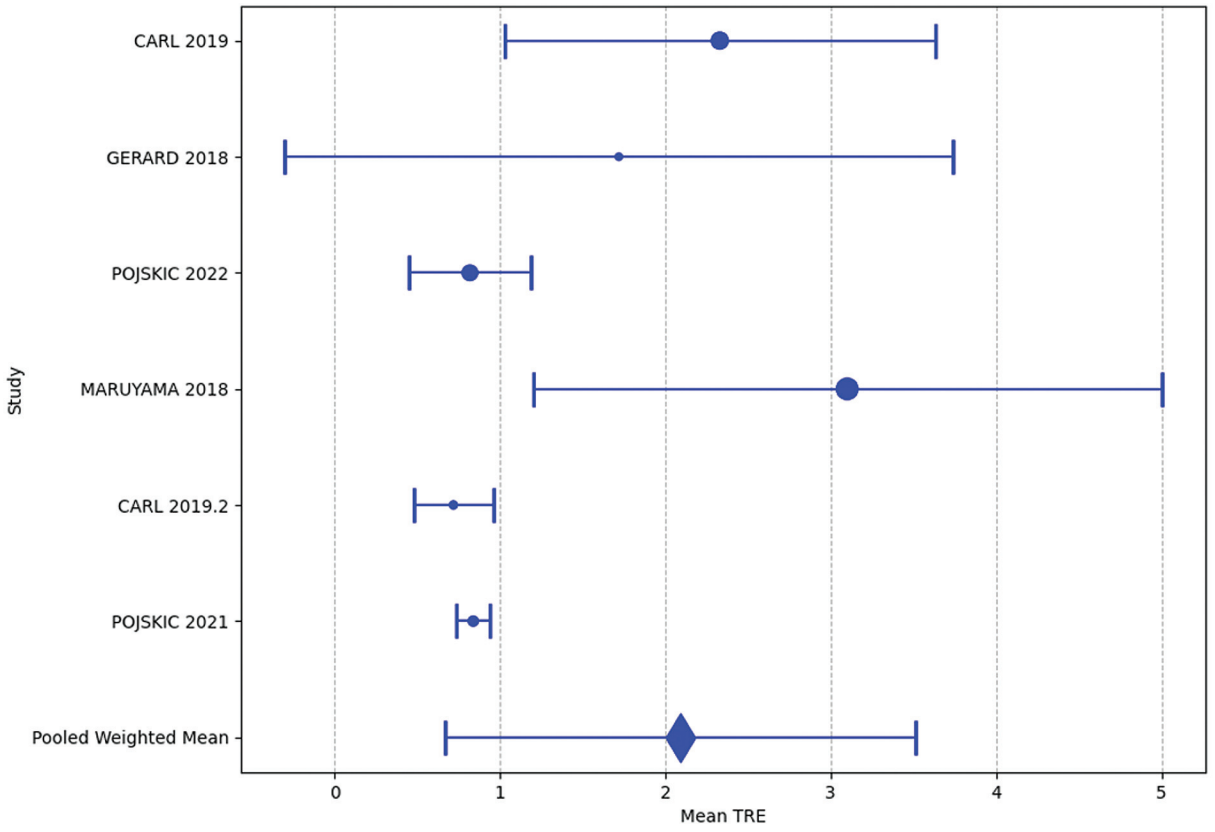

Fig. 4 ERT assessment in studies that used the augmented reality system after the sensitivity of the heterogeneity index.

exhibited higher values, indicating a smaller error than the studies included in the meta-analysis.

Discussion

Neuronavigation is utilized in various cranial and spinal procedures to provide enhanced visualization of spatial relationships between different structures. This is achieved by superimposing data from diverse preoperative imaging methods, allowing for intraoperative correction of displacement known as "Brain-Shift." The acquired information is processed by a computer system that guides the surgeon throughout the procedure.

The application of neuronavigation involves four steps. First, volumetric images are obtained in a modality determined by the surgeon. These images are then imported into the system, initiating the surgical planning. The third step involves patient registration, typically performed on the face using two methods: point cloud or point-to-point mapping with a probe and a fixed reference on the patient's head. The precise acquisition of these registration points and their correlation with pre-defined points in the system enables intraoperative navigation.[60]

Application Errors (AE) arise from failures at any stage of the neuronavigation process and directly impact the accuracy and final clinical outcome. The accuracy of these systems depends on variables inherent to their types, including application and mechanical execution errors during surgery. These errors can be categorized into two subgroups: those related to anatomical differences between the obtained image and the patient, and those associated with failure to transfer the point of interest between the image and the patient. Examples include mean registration error (FRE), target registration error (TRE), and surface registration error (SRE).[60,61]

Errors in the registration phase, which involves transforming the patient's space into image space using fiducials (paired points, skin or bone markers, or surface), are crucial predictors of overall accuracy. Recording errors, combined with errors during mechanical execution in surgery, significantly affect accuracy. Subsequently, errors occurring after the registration phase, such as the root mean squared error of registration (RMSE) and TRE, serve as primary predictors of neuronavigation accuracy.[62] RMSE measures the distance between a fiducial point obtained with the tracker in real space and its corresponding point in the image, while TRE measures the distance between a point in real space and its corresponding point in the image space, representing the clinically more relevant error. The estimated vector of the TRE allows surgeons to correct the path based on visualization.

Accuracy depends on variables specific to the system types, comprising a combination of application errors (AE) and mechanical execution during surgery. Previous studies have defined an upper limit error value of 3.00 to 4.00 mm.[63] However, in the clinical setting, navigation systems typically operate within an accuracy range of 0.50 to 2.70 mm, aiming for a TRE value of 1.00 to 2.00 mm to ensure greater safety.[64]

Multiple factors influence the accuracy of the procedure, including the specific procedure itself, the utilized system, and the mechanical execution. Analysis of the studies revealed that the various techniques for patient registration did not significantly impact accuracy and yielded similar distances when correlated with the surgical point of interest.

Registration based on anatomical landmarks offers advantages such as low cost and improved efficiency in terms of performance time.[65] However, fiducial registration is considered the preferred method among non-invasive approaches, as it demonstrates greater accuracy compared with the combination of anatomical points and surface registration.[41]

Among the different methods, anatomical landmarks exhibit the most discrepant results, whereas the others show comparable levels of precision, leading to satisfactory clinical outcomes. In a comparative study ($N = 30$), a substantial difference in accuracy was observed, with fiducials achieving a precision of 1.70 ± 0.70 mm, while anatomical landmarks yielded 4.80 ± 1.90 mm, placing them outside the security range.[34]

For skull base procedures, the automatic registration mask provided by the system demonstrated favorable results with a target registration error (TRE) of 0.90 ± 0.70 mm. This method proves to be a practical, reliable, and non-invasive alternative for this specific type of surgery.[36]

The use of fiducials was observed in 22 out of 51 evaluated studies, across various procedure types and in conjunction with the three types of systems examined in the research. Although a few results fell outside the acceptable range, most exhibited safe values, justifying the position of fiducial registration as the gold standard among non-invasive methods. Furthermore, the accuracy of fiducial application remains unaffected even when adjusting the patient's head position as necessary.

Regarding the accuracy of different system types, the meta-analysis included 6 values for each system, optical ($N = 297$) and augmented reality (AR) ($N = 195$), resulting in target registration errors (TRE) of 2.34 mm and 2.09 mm, respectively. Both systems exhibit close values and fall within the safety range expected for commercial systems. As for the electromagnetic system, due to a lack of studies establishing the TRE value, an average value could not be determined.

Studies comparing precision values between optical and augmented reality systems did not reveal significant differences in accuracy. However, in a clinical study directly comparing these systems, the augmented reality system demonstrated greater application security by exhibiting better depth accuracy with a median of 3.00 mm, compared with 5.00 mm in the conventional system.[47]

Moreover, the visual coordination between the surgical field and the monitor can be distracting for the surgeon when using the conventional system.[66,67] Therefore, viable and advantageous augmented reality neuronavigation (ARN) techniques have gained traction, as they provide fewer distractions compared with conventional image navigation (CIN) and do not restrict surgical positions.[66] This makes it

possible to use ARN in patients who cannot be stabilized with a head clamp, such as pediatric patients and those with bone fractures.[56]

Regarding the optical and electromagnetic systems, although few clinical studies evaluating the accuracy of the latter were found, studies indicate that although the electromagnetic system enables continuous navigation through tracked instruments and better integration during the intraoperative period, the TRE values were similar to those obtained with the optical system.[37]

While these systems are more commonly used in cranial surgeries, they also offer good accuracy for spinal procedures. In most studies, the augmented reality (ARN) system was employed and consistently demonstrated accurate positioning in pedicle screw insertion, ranging from 77.5% to 97.8%.

However, like conventional methods, current systems are still unable to precisely detect anatomical changes during the surgical period.[56] Despite achieving good clinical results in most analyzed procedures, there is still room for improvement to further minimize application errors within an even narrower safety range, as proposed in more recent studies.

In this context, methods such as intraoperative ultrasonography and augmented reality techniques emerge as valuable tools, allowing for the updating of images during surgery and aiming to further reduce application errors. Influence of different imaging methods.

Various imaging methods serve as additional techniques for different systems. For preoperative image acquisition, computed tomography (CT) and magnetic resonance imaging (MRI) are commonly used and exhibit comparable accuracy and reliability of information.

A more recent method that has gained popularity is the O-Arm Cone Beam Tomography, particularly when combined with the optical system, demonstrating improved accuracy with an average error of 0 mm in two clinical studies.[40] One of the main advantages of this method is the ability to acquire intraoperative images without the need to correlate them with the patient's anatomy. Furthermore, it offers the flexibility to acquire new images if necessary, such as when the patient moves.[40]

Hence, in addition to selecting the optimal system, surgeons need to have access to other techniques that contribute to precision by compensating for brain shifts. Therefore, it is crucial to have imaging tools available that allow the system to be recalibrated using post-craniectomy images, including auxiliary techniques for three-dimensional reconstruction.[68,69]

Neuronavigation is employed in neurosurgery with well-defined objectives, aiming to make procedures less invasive, increase mechanical precision in target localization, and reduce surgical time. The technique provides enhanced safety for both surgeons and patients, making its indications nearly limitless. It proves particularly useful in approaching small, deep brain lesions and operating in eloquent areas, earning its place in brain tumor resection surgeries.[68]

Apart from tumor surgeries, two other well-established indications for neuronavigation are epilepsy and spine surgery. In epilepsy surgery, the technique assists in precisely locating epileptogenic zones for subsequent ablation. While its application in vascular surgery is somewhat limited due to insufficient studies and increased intraoperative time, the few available reviews acknowledge positive aspects of neuronavigation, such as improved anatomical orientation for arteriovenous malformations (AVM) and aneurysms through three-dimensional reconstruction, reducing the risk of damage to adjacent structures.[67]

In the realm of spine surgeries, the use of neuronavigation has been extensively studied for the insertion of pedicle screws in recent years, especially in comparison to the widely used fluoroscopy guidance. In a study conducted on fresh cadavers to evaluate the accuracy of both methods, similar precision was observed, yet neuronavigation provided greater safety for the surgical team by eliminating radiation exposure.[11] Additionally, a retrospective study with the same objective revealed not only superior precision with neuronavigation but also improved clinical outcomes and fewer subsequent surgical interventions.[27]

Conclusion

Augmented reality systems combined with a target registration error of 2.09 mm within the safety range provide the best accurate results. Optical systems also exhibit similar accuracy with a target registration error of 2.34 mm. Various factors influence system accuracy throughout the surgical procedure, and strategies are employed to minimize errors. However, there is a need for standardized predictors to assess accuracy consistently across studies.

Funding

There is no funding source for this article.

Conflict of Interest

All authors declare no conflict of interest.

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Therapy Options in the Management of Brain Abscess. Literature Review

Opções de terapia no tratamento de abscesso cerebral. Revisão da literatura

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Arq Bras Neurocir 2024;43(4):e337–e342.

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Abstract

Introduction Despite the advancements in modern neurosurgical techniques, new antibiotics, neuroimaging technologies, anesthesia practices, and microbial isolation methods, cerebral abscess remains a potentially fatal infection of the central nervous system. Its treatment remains controversial to this day. The combination of clinical and surgical interventions has been widely accepted, yielding satisfactory outcomes.

Methods The literature review process primarily relied on data obtained from the Pubmed database, Bireme (Lilacs, Medline, Scielo, Medicaribe, Cochrane). Key search terms included: central nervous system infection, cerebral abscess, and treatment. After a thorough selection analysis, 103 articles covering the period from 1980 to 2023 were included in this work.

Results The ideal treatment is surgical; however, clinical treatment has been employed in selected cases. Simple aspiration, stereotactic-guided aspiration, and endoscopy have been performed with efficient results. The outcomes of clinical or surgical treatment depend on factors such as the patient's age, neurological status, microbial isolation, primary cause of the abscess, number of infectious foci, location, and stage of abscess development. Corticosteroids have been recommended for cases of vasogenic cerebral edema, while anticonvulsants are indicated for supratentorial abscesses.

Conclusion The combination of aspiration or excision, tailored to the specific cause, number, location, and developmental stage, and intravenous antibiotics has consistently yielded satisfactory results.

Keywords
- brain abscess
- treatment
- outcome

Resumo

Introdução Apesar do advento de modernas técnicas neurocirúrgicas, novos antibióticos, das tecnologias em neuroimagens, avanços no campo da anestesia, novas técnicas de isolamento de microorganismos, o abscesso cerebral permanece como uma infecção potencialmente fatal do sistema nervoso central. Seu tratamento é ainda

received
December 13, 2023
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1795134.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

hoje controverso. A combinação do tratamento clínico e cirúrgico tem sido largamente aceita e com resultados satisfatórios.

Métodos O processo de revisão da literatura baseou-se principalmente em dados obtidos da Pubmed database, Bireme (Lilacs, Medline, Scielo, Medicaribe, Cochrane). Para as buscas foram usadas as palavras-chave: infecção do sistema nervoso central, abscesso cerebral, tratamento. Ao final da análise de seleção, obtiveram-se um total de 103 artigos que compuseram essa obra, com um recorte temporal de 1980 a 2023.

Resultados O tratamento ideal é cirúrgico, porém, o tratamento clínico é realizado em casos selecionados. A aspiração simples, aspiração guiada por estereotaxia e endoscopia são realizadas com resultados eficientes. Os resultados do tratamento clínico ou cirúrgico, vão depender da idade, estado neurológico do paciente, isolamento do microorganismo, causa primária do abscesso, número de focos infecciosos, localização e fase de evolução do abscesso. Corticosteróides é indicado em casos de edema cerebral vasogênico. Anticonvulsivante nos casos de abscesso supratentorial.

Conclusão A combinação de aspiração ou excisão conforme sua causa, número, localização e fase de evolução, associado com antibióticos por via venosa tem apresentado resultados satisfatórios.

Palavras-chave
- abscesso cerebral
- tratamento
- prognóstico

Introduction

A cerebral abscess (CA) is a collection of pus located within its respective site.[1–5] CA typically presents with focal neurological deficit, seizures, or symptoms of increased intracranial pressure, and less commonly as a focal or systemic infection.[6,7] The main causes and risk factors for the development of CA include meningitis, sinusitis, otitis, dental infection, open cranioencephalic trauma, cyanotic congenital heart disease, and previous craniotomy.[8,9]

Neuroimaging studies are employed to determine the location, extent, characteristics of lesions, and course of action.[10,11] Depending on the radiological pattern and stage of lesion development, a differential diagnosis should be considered, ranging from infection to tumor.[12] The combination of clinical treatment (oral, intravenous, intrathecal) and surgical intervention (drainage, aspiration, excision, stereotactic aspiration) is the standard for the curative resolution of CA.[2,13–24] Clinical treatment has been used in cases of cerebritis-phase CA, multiple abscesses, or those located in eloquent areas.[8,9,25] Various surgical procedures have been employed, such as simple aspiration, stereotactic aspiration, ultrasound-guided aspiration, neuronavigation-guided aspiration, or neuroendoscopy,[12,26,27] and primary excision.[22,26,28–33]

Despite advances in medicine through neuroimaging, microbial isolation, antibiotic therapy, and modern neurosurgical techniques (stereotaxy, neuronavigation), the morbidity and mortality rates remain high, particularly in developing countries.[34]

The authors provide a review of CA treatment options and discuss their advantages and disadvantages.

Methods

This is a literature review conducted through searches on the following databases: Pubmed database, Bireme (Lilacs, Medline, Scielo, Medicaribe, Cochrane). The descriptors used were: Central Nervous System Infection, Cerebral Abscess, and Treatment. Articles were selected with a time frame from 1980 to 2023, resulting in a total of 103 articles that met the inclusion criteria based on their citations, respective impacts, and content relevant to the theme.

Pharmacological Treatment

Heineman et al.[35] reported the first successful case of clinical treatment for CA. Pharmacological treatment of CA has been indicated in cases of a single abscess < 1.5 cm, cerebritis phase, multiple abscesses measuring < 1.5 cm in diameter, located in eloquent areas, presence of concomitant infection (meningitis, ependymitis), and patients in the terminal phase.[8,9,14,19,24,25,36–46]

Literature reports the effectiveness of clinical treatment in cases where the causative agent is known through blood culture, cerebrospinal fluid, or drainage from otitis or sinusitis.[10,19,47] According to Armornpojnimman et al.,[38] the success rate for pharmacological treatment is high when initiated during the early cerebritis phase, with lesions measuring <1.5 cm in diameter, in patients with an evolution time of < 2 weeks. Lu et al[10] recommend clinical treatment when the diagnosis is uncertain or unconfirmed. According to Xiao et al,[8] clinical treatment is not effective in patients with risk factors, poor level of consciousness, or immunodeficiency.

It is recommended to initiate empirical antibiotic therapy while samples are being analyzed for microbiological study.[19,21,36,37,48,49] Broad-spectrum empirical antibiotic therapy should be maintained for 6 to 8 weeks, and modified according to the microbiological test results for possible effective therapy. Treatment duration of less than 6–8 weeks is associated with an increased risk of recurrence.[50] When the microorganism is unknown, the empirical antimicrobial therapy used is third-generation cephalosporin (cefotaxime,

ceftriaxone) and metronidazole in the treatment of AC originating from otitis, mastoiditis, or sinusitis, showing good results.[14,20,51] In cases secondary to open cranial trauma or post-craniotomy, a combination of third-generation cephalosporin with vancomycin or oxacillin is recommended. There is no consensus on the duration of antimicrobial therapy, with most authors recommending intravenous therapy for 6 to 8 weeks.[10,44,52–56] Patients undergoing clinical treatment should be monitored clinically, laboratorially, and radiologically[55]; if there is no clinical and/or radiological improvement, immediate surgical treatment should be instituted.[8]

The effectiveness of pharmacological treatment can be observed through clinical improvement[3,36] and laboratory tests such as PCR; when elevated, it indicates that pharmacological treatment is ineffective.[19,57,58]

The use of corticosteroids in CA is controversial.[19,20,59] It has been indicated in cases of CA with local vasogenic edema, causing increased intracranial pressure and significantly increasing morbidity and mortality.[8,24,44] It has been recommended in the perioperative period to reduce intracranial pressure and prevent internal brain herniation.[10,20,21,40,47,59,60] Prolonged use of corticosteroids can decrease antibiotic penetration into the abscess and reduce abscess capsule formation, especially in the cerebritis phase.[8,24,44,61–63]

Seizure is one of the main complications of CA, occurring at the onset of the disease or even after its treatment.[64] Anticonvulsant prophylaxis has been recommended.[10,20,44] The most commonly used anticonvulsant is phenytoin, and for an extended period.

Surgical Treatment

The nature of CA, anatomical location, number of abscesses, size, stage of the lesion, age, and neurological status of the patient all influence the strategy for its treatment.[10] In the historical evolution of CA treatment, in 1924, King[65] introduced the marsupialization technique. Dandy[66] introduced aspiration in 1926. Sargent[67] considered the excision of an encapsulated CA in 1928, but it was Vincent[68] who popularized complete excision and demonstrated its therapeutic value in 1936. The decision on the surgical technique should be made on an individual basis in each case, considering the size, location, overall condition of the patient, and the neurosurgeon's experience.[5,58,69]

Simple Aspiration

There is a consensus that surgical treatment through puncture and aspiration is indicated for abscesses > 2 cm, located in non-eloquent areas, and with a significant mass effect, yielding excellent results.[10,14,20,21,24,42,44,55,70–73] Large abscesses can be aspirated through a trephine hole, leading to an immediate reduction in mass effect and intracranial pressure, facilitating the collection of material for culture and antibiotic sensitivity testing.[10] Simple aspiration has limitations in cases of multiloculated and recurrent abscesses.[63] A disadvantage of this procedure is the need to repeat it in 70% of cases and the risk of abscess rupture into the ventricular cavity or subarachnoid space, which can lead to complications such as meningitis and ventriculitis.[13] Contraindications include the presence of coagulopathies.[20]

Stereotactic-Guided Aspiration

Stereotactic-guided CT or MRI-guided aspiration and puncture in the treatment of CA have been considered the gold standard due to being a minimally invasive procedure and having a low rate of complications compared with excision.[22,26,30,71,74,75] Advantages of this approach over other procedures include its use in cases of deeply located abscesses, eloquent areas, the brainstem, multiple abscesses, and when excision is deemed inappropriate.[20,22,24,25,42,54,57,74,76–86] In stereotactic-guided aspiration, a biopsy of the abscess capsule can be performed.[54] According to Kondziola et al,[77] this technique is optimal for abscesses larger than 3 cm. Stapleton et al[87] suggest it as the method of choice for cases of superficial and large abscesses. Stereotactic surgery with neuronavigation allows for aspiration to be indicated without considering the phases of the abscess and enables the collection of material for laboratory study.[10,18,36,88]

Endoscopic Aspiration

The treatment of CA through endoscopy has been infrequently performed.[27,89] In comparison with stereotactic-guided aspiration, neuroendoscopy offers some advantages such as direct visual control, the possibility of treating cases with multiseptated CA, addressing intraventricular purulent collections, cases of associated subdural empyema, and control of intraoperative bleeding.[6,12,27,31,32,53] Endoscopic instruments can be flexible or rigid.[6,12,27] Longatti et al[6] used a flexible endoscope as it proved more effective in certain treatment scenarios, such as aspiration and inspection of the abscess in all spaces and directions. In cases where the capsule membrane is firm or elastic, its perforation may sometimes require the use of scissors or other instruments to facilitate the procedure.[12,31]

Surgical Excision

Excision is generally recommended in cases of cerebellar abscess.[19,20,44,54,90–93] Primary excision of the abscess and its capsule has also been performed in cases of multiloculated abscesses, cases due to more resistant pathogens that do not respond to multiple aspirations.[20,39,54,62,63,94] Abscesses containing gas are resistant to antibiotics and are best treated through excision.[95] Post-traumatic abscesses containing foreign bodies or contaminated bone fragments are indicated for excision to prevent recurrence.[19,44,71,91,96,97] Abscesses resulting from communicating fistulas, such as in cases of trauma or congenital dermal sinuses, require excision of the infected granulation tissue and closure of the fistula.[10] Abscesses located in a lobe and contiguous to the primary source of infection show better results when subjected to excision along with the primary focus. Other authors indicate excision during the late stage of capsule formation or after unsuccessful aspiration.[22,23] Primary excision is contraindicated in cases of cerebritis, deep abscesses, those located in eloquent areas, multiple abscesses, and patients at high surgical risk.[10,13,98]

Complete excision of the CA is indicated in the following cases: 1. superficially located abscess in a non-eloquent area; 2. abscess suspected of fungal, Mycobacterium tuberculosis, Actinomyces spp, or Nocardia spp infection; 3. abscess resulting from congenital diseases or acquired fistula; 4. multiloculated abscesses; 5. abscess caused by a parameningeal septic focus; and 6. failure of previous treatment.[10,58]

Intraventricular Abscesses

Cerebral abscesses located deep, multiloculated, and close to the ventricular wall increase the chances of intraventricular rupture in 10% of cases.[99] There is no efficient treatment of choice, and it presents a high mortality rate.[100–102] Yang and Zhao[103] propose urgent craniotomy with abscess drainage. Other authors 39,101 suggest craniotomy followed by drainage of the abscess cavity, washing of the ventricular system, along intravenous and intrathecal antibiotic therapy for six weeks.

Conclusion

The synergistic approach of aspiration or excision, tailored to the specific cause, number, location, and developmental stage of cerebral abscess, coupled with intravenous antibiotic therapy, has demonstrated consistently satisfactory outcomes. Furthermore, the effective management of cerebral abscesses necessitates a comprehensive, multidisciplinary team, comprising neuroradiologists, neurologists, pediatric neurologists, infectious disease specialists, and neurosurgeons.

Conflicts of Interest
The authors report no conflicts of interest.

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Partial Sacrectomy in the Management of Sacral Chordoma: Case Report and Literature Review

Sacrectomia parcial no manejo do Cordoma Sacral: Relato de caso e revisão da literatura

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Arq Bras Neurocir 2024;43(4):e343–e346.

Abstract

Chordomas are rare neoplasms of low to intermediate grades, which arise from ectopic remnants of notochordal tissue, presenting a slow growth pattern and locally aggressive behavior. Due to their insidious course, the diagnosis is late, requiring immediate therapeutic intervention. The main prognostic factor is total surgical resection with wide margins. This therapeutic objective is only achieved in 40% to 55.6% of the cases, since chordoma tends to present an aggressive behavior, invading adjacent tissues and neurovascular structures. Currently, the main challenge of sacrectomy is to balance a wide resection with the preservation of the neurological function of the patient. Despite cases of successful gross total resection, local recurrence is an inevitable reality, and the overall survival is relatively low. The indication of adjuvant therapies is not well stablished in the literature, since the response to radiotherapy is not satisfactory for these tumors. The aim of the present study is to present a report the case of a patient with sacral chordoma (SC) who underwent partial sacrectomy and to carry out a brief review of the literature on sacrococcygeal chordomas.

Keywords
- sacrectomy
- Sacral Chordomas
- partial sacrectomy

Resumo

Cordomas são neoplasias raras de graus baixo a intermediário, que surgem de remanescentes ectópicos de tecido notocordal, e apresentam padrão de crescimento lento e comportamento localmente agressivo. Devido ao seu curso insidioso, o diagnóstico é tardio, e necessita de intervenção terapêutica imediata. O principal fator prognóstico é a ressecção cirúrgica total com margens amplas. Esse objetivo terapêutico somente é atingido em 40% a 55,6% dos casos, pois o cordoma tende a apresentar um comportamento agressivo, pois invade tecidos adjacentes e estruturas neurovasculares. Atualmente, um dos principais desafios da sacrectomia é equilibrar uma ampla ressecção com a preservação da função neurológica do paciente. Apesar

received
April 29, 2023
accepted
January 26, 2024

DOI https://doi.org/10.1055/s-0044-1785523.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Palavras-chave
- sacrectomia
- Cordomas Sacrais
- sacrectomia parcial

dos casos de ressecção total bem-sucedida, a recorrência local é uma realidade inevitável, e a sobrevida global é relativamente baixa. A indicação de terapias adjuvantes não está bem estabelecida na literatura, uma vez que a resposta à radioterapia não é satisfatória para esses tumores. O objetivo deste trabalho é relatar o caso de um paciente com cordoma sacral (CS) submetido à sacrectomia parcial e fazer uma breve revisão da literatura sobre cordomas sacrococcígeos.

Introduction

Chordomas are rare malignant neoplasms of low to intermediate grades, which arise from ectopic remnants of notochord tissue, presenting a slow growth pattern and locally aggressive behavior.[1] They affect the midline along the neuroaxis, with preferential involvement of the sacrum (50% of the cases), followed by the spheno-occipital region (25% to 30%), the cervical vertebrae (10%), and the thoracolumbar vertebrae (5%).[2–4] Due to its invasive behavior, the lesion may infiltrate adjacent muscles, sacral nerve roots, pelvic viscera, and sacroiliac joints.[5]

They correspond to 1% to 4% of primary bone malignancies, representing the most common primary malignant bone tumor of the spine,[2,5] with male predominance in a ratio of 2:1.[1] The peak incidence is between 50 and 60 years of age,[2,4,5] and children and adolescents are rarely affected ($<$ 5% of the cases).[2] Chordoma has a relatively high mortality rate, with an average life expectancy of 5 to 7 years after the diagnosis, abbreviated to 1 year in individuals not submitted to adequate treatment.[6]

Case Report

We herein report the case of an 80-years-old female patient who, 3 years before, had started to feel severe sacrococcygeal pain (8/10 on the Visual Analog Scale, VAS), without irradiation and refractory to analgesia. The pain worsened progressively, reaching 10/10 on the VAS 3 months prior to hospital admission. Upon admission, the patient presented without neurological deficits, but with mild constipation.

A computed tomography (CT) scan showed an expansive lesion affecting the sacrococcygeal region with cortical rupture, associated with a large soft tissue component with an expansive infiltrative aspect, measuring $6.2 \times 6.6 \times 9.1$ cm (►**Figure 1**), with compression of the upper and middle thirds of the rectum, but without intestinal obstruction. The patient underwent an open biopsy of the sacral lesion, with the diagnosis of chordoma. During hospitalization, the patient evolved with a neurogenic bladder.

A partial sacrectomy (►**Figure 2**) was performed below S3 and the lesion was removed en bloc after retroperitoneal dissection in an area previously approached via the anterior route by general surgery. There was no injury to the sacral nerves. The immediate postoperative period was uneventful. At the last follow-up, two months after surgery, the patient maintained fecal incontinence and a neurogenic bladder, without neurological deficits. Adjuvant therapies were not indicated.

Discussion

Due to slow and indolent growth, sacral chordomas (SCs) generally remain clinically silent for long periods, delaying

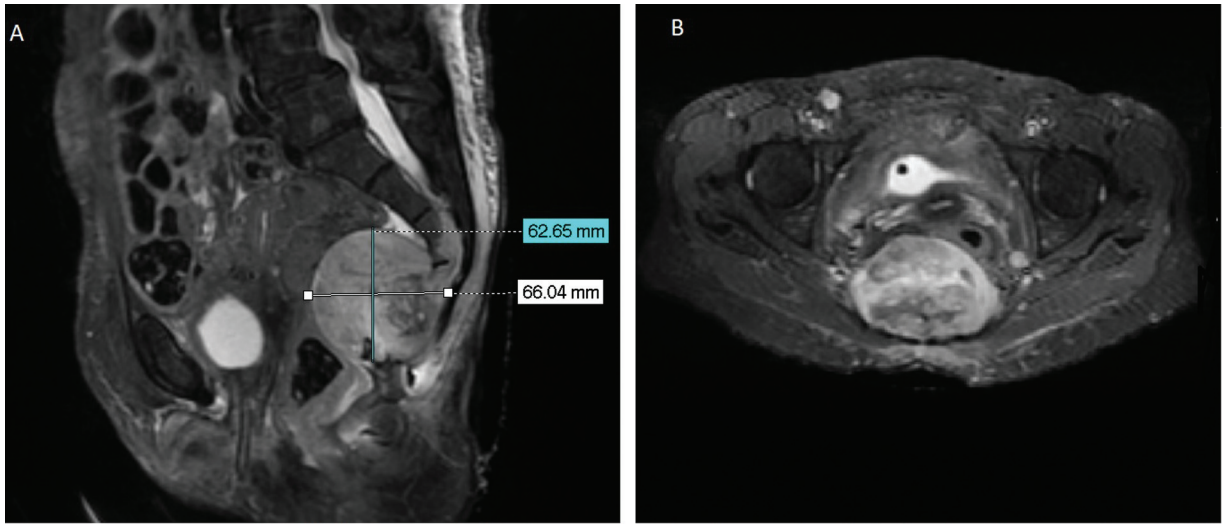

Fig. 1 Magnetic ressonance imaging scan in short tau inversion recovery (STIR) sequence showing a regular hypodense mass ventral to the sacrum (sacral chordoma), in (**A**) sagittal incidence and (**B**) axial incidence.

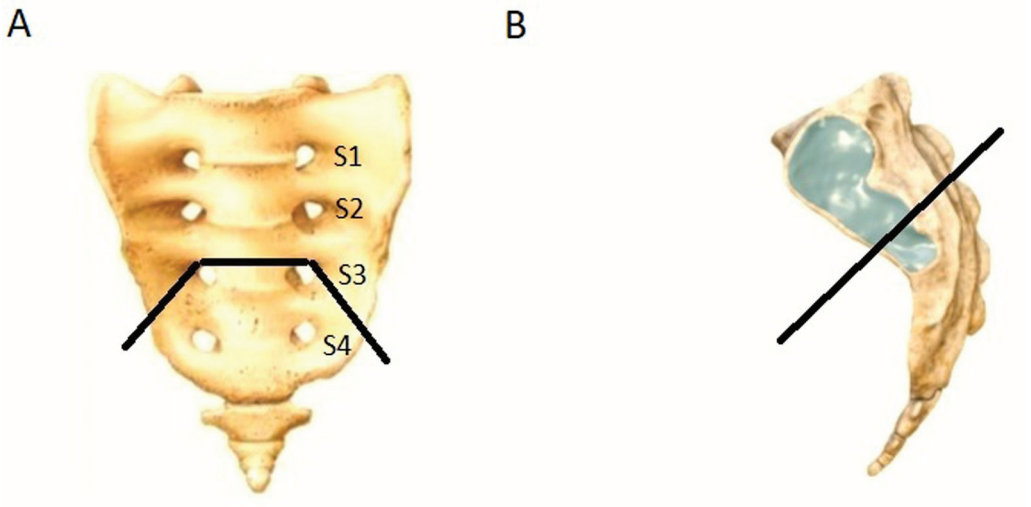

Fig. 2 Schematic representation of a partial sacrectomy in (**A**) coronal and (**B**) sagittal views.

diagnosis until 12 to 14 months from first manifestation.[1] Therefore, these tumors are often diagnosed incidentally or at an advanced stage, with destruction of adjacent structures and soft tissue invasion.[4] The main differential diagnosis is chondrosarcoma, a similar neoplasia both in terms of radiology and histology.

The most frequent clinical manifestation of CS is persistent low back pain. Compression of the sciatic nerve or the iliolumbar trunk causes radicular pain and nerve root involvement, ultimately leading to anorectal and urogenital neurological dysfunctions, with 1/3 of patients developing urinary tract infections and 10% manifesting constipation.[1,4]

In case of suspicion of SC, percutaneous needle biopsy is considered the gold standard.[1] Imaging exams are essential in the preoperative phase, for they enable the assessment of tumor location, staging, extension, and the relationship with adjacent structures. The detailed study of the local anatomy is essential for the success of the procedure and to achieve good functional outcomes.[7]

Enneking's principles define wide resection en bloc as the surgical strategy for SCs.[2,5] However, wide resection is a challenge, considering the aggressive behavior of the tumor and its infiltrative nature and poor marginalization.[8] Good preoperative planning with adequacy of imaging exams and a multidisciplinary approach regarding the surgical specialties (such as general, vascular and neurosurgery) become essential for a better outcome of wide tumor resection with maximum preservation of nearby noble structures[2]

Due to these challenges, a standardized description of the surgical technique has not yet been well established. The amplitude of sacral resection is based on the experience of the surgeon, lesion extension and nervous tissue infiltration.[3] Total sacrectomy is bilateral resection and fixation of the dural sac below S1, with resection extended to L5, L4, and to the iliac region, if necessary.[7] It normally occurs in two stages: an anterior approach and a posterior approach.[2] The anterior approach enables greater visualization and protection of visceral organs; however, in a recent multicenter study, it was a predictor of tumor recurrence. The posterior approach is single-staged, shorter in duration, and enables better handling of adjacent neural elements; however, it presents a greater risk of injury to large vessels and visceral organs.[5] The combined approach, in turn, is related to longer operative and recovery times.[6] Currently, the posterior approach has been more accepted,[4] mainly for disorders caudal to the S2 vertebra (caudal sacroiliac joints).[5] Partial sacrectomy is indicated over total sacrectomy with resection up to S1 when the printed margins below S3 can be reached.[6]

Marginal resection is achieved in only 35% to 81% of SCs, as it often involves nerve roots. Thus, there must be a balance between the chance of recurrence and the maintenance of the neurological function and the integrity of the visceral organs.[2,7]

Low sacral amputations (distal to the level of S3) tend to present a minimal deficit, with preservation of almost 100% of the permanent and intestinal function.[6] High sacral amputations and total sacrectomies cause greater spinosacral and sacropelvic instability and sexual and sphincter dysfunction, when S1 is bilaterally injured.[2] In some patients, embolization may be an alternative to reduce the extension of the tumor, minimizing the loss of additional neural function.[6]

On average, 60% of patients undergoing surgery develop complications associated with sacrectomy. Among the main complications, we can mention surgical site infection (the most common), wound dehiscence, cerebrospinal fluid (CSF) leak, sacral hernia, and failure in the musculocutaneous reconstruction process.[3,5,7] Radiotherapy (RT) may account for complications in the postoperative period.

The indication of pre-, post- or combined pre- and postoperative RT is controversial, with conflicting results in the literature, demonstrating the resistance of chordomas to adjuvant therapy and no clear association with better rates of local recurrence, metastatic disease or disease-specific survival. Radiotherapy remains reserved for unresectable patients and incomplete resection margins, considering

the surgical possibilities, the presence of associated comorbidities, and the patient's functional status.[5,7]

Sacrectomy is a procedure with high morbidity and mortality.[7] The rate of recurrence after surgery is of 40% to 50%,[9] with local recurrence 3 times higher in patients submitted to partial resection when compared to those who underwent total resection.[4] The indicators associated with poor oncological outcome are: inadequate surgical margins, history of recurrence after previous resection, infiltration affecting muscle and/or the sacroiliac joint, lesion larger than 8 cm in diameter, and locations above S3.[2,8] Despite the recurrences, tumor resection is essential for symptomatic relief of the patient and increased survival.

The risk of metastasis is relatively low, of around 5%.[1] The occurrence is mainly associated with local recurrence of the tumor, which tends to occur in later stages of the disease. It can affect adjacent areas, such as pelvic viscera and sacroiliac joints, and more distant sites, such as the lungs, liver and bone.[3,4,8] Despite the low tendency for metastasis to occur, approximately 40% to 60% of the patients develop distant metastases over the course of the disease.[9]

Currently, specific preoperative planning techniques, such as three-dimensional (3D) printed osteotomy, may be used for a better anatomical study of the region, with greater precision of the surgical procedure.[4]

Conclusion

Sacral chordomas are rare malignant neoplasms with an aggressive behavior. Total or partial sacrectomy is the main treatment of choice, being a complex procedure with high morbidity and mortality. The wide resection margin is the main prognostic factor, associated with a lower rate of local recurrence. Tumor recurrence is the most important predictor of metastasis and mortality. Preoperative planning with a multidisciplinary approach is essential to plan an accurate resection with a lower rate of complications. Chordomas are generally resistant to conventional RT treatments, which are indicated just in specific and individualized cases.

Conflict of Interests

The authors have no conflict of interests to declare.

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Intracranial Solitary Fibrous Tumor with Concurrent Meningioma: Case Report and Review of the Literature

Tumor Fibroso Solitário Intracraniano com meningioma concorrente: Relato de caso e revisão da literatura

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Arq Bras Neurocir 2024;43(4):e347–e354.

Abstract

Introduction The present study describes a case of an intracranial solitary fibrous tumor (iSFT) concurrent with meningioma in different anatomical regions.

Case Description A female patient, 64-years-old, presented with an 18-month history of progressive vision impairment in the right eye and no other neurological symptoms. The magnetic resonance imaging (MRI) revealed two solid and expansive lesions: one with right interhemispheric occipital location and dependent on the falx cerebri, and another located in the anterior skull base. We opted for a right frontotemporal craniotomy for the first tumor, and a right occipital craniotomy, 41-days later, for the second one, showing no postoperative complications. Histological and immunohistochemical findings confirmed the diagnosis of a grade-I fibrous meningioma and a grade-III SFT. After 9 months of follow-up, the patient showed vision improvement and no signs of neurological compromise or tumor recurrence in the last MRI.

Conclusions The present study describes the first reported case of a patient with an intracranial SFT associated with a meningioma in different anatomical locations. The involved pathogenesis and evolution of both coexisting tumors are still unknown, which highlights the need for more case reports on them.

Keywords
- intracranial solitary fibrous tumor
- meningioma
- mesenchymal neoplasm
- case report
- surgical treatment

received
February 17, 2024
accepted
May 16, 2024

DOI https://doi.org/10.1055/s-0044-1788604.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Introdução O presente estudo descreve um caso de tumor fibroso solitário intracraniano (TFSi) concomitante a meningioma em diferentes regiões anatômicas.

Descrição do Caso Paciente do sexo feminino, com 64 anos de idade, apresentava história de comprometimento visual progressivo no olho direito há 18 meses e sem outros sintomas neurológicos. A ressonância magnética revelou duas lesões sólidas e expansivas: uma com localização occipital interhemisférica direita e dependente da foice cerebral, e outra localizada na base anterior do crânio. Optamos por craniotomia frontotemporal direita para o primeiro tumor e craniotomia occipital direita 41 dias depois para o segundo, sem complicações pós-operatórias. Os achados histológicos e imunohistoquímicos confirmaram o diagnóstico de meningioma fibroso grau I e TFS III. Após 9 meses de acompanhamento, a paciente apresentou melhora visual e não apresentou sinais de comprometimento neurológico nem de recidiva na última ressonância magnética.

Conclusões O presente estudo descreve o primeiro caso relatado de um paciente com TFS intracraniano associado a um meningioma em diferentes localizações anatômicas. A patogênese e a evolução envolvidas nos dois tumores coexistentes permanecem obscuras, o que destaca a necessidade de mais relatos de casos sobre eles.

Palavras-chave

- tumor fibroso solitário intracraniano
- meningioma
- neoplasia mesenquimal
- relato de caso
- tratamento cirúrgico

Introduction

Solitary fibrous tumors (SFTs) are fibroblastic neoplasms with a genomic inversion at the 12q13 locus, leading to the fusion of the genes NGFI-A-binding protein 2 (NAB2) and signal transducer and activator of transcription 6 (STAT6), as well as STAT6-gene nuclear expression.[1]

These tumors are commonly found in the mediastinum and visceral pleura, and in extra-pleural locations, such as the head and neck, pericardium, peritoneum, thyroid, liver, sinuses, and orbits, in a smaller proportion.[1] In the central nervous system (CNS), SFTs are located intracranially, while a smaller proportion are intraspinal.[2–4] The cerebellopontine angle, spinal dura, parasagittal area, meninges, and intraventricular region are common sites for this condition.[5] Meningeal SFT is a rare form with greater aggressiveness and recurrence, being derived from smooth muscle pericytes surrounding the intraparenchymal microvasculature, also known as Zimmerman pericytes.[6,7]

Intracranial SFTs (iSFT) account for around 2.5% of all meningeal-based tumors and less than 1% of all intracranial ones, whereas meningiomas represent approximately 20% of primary intracranial tumors.[8,9] Furthermore, SFTs are mostly diagnosed at around 50 to 60 years old, with equal gender prevalence.[10–12]

A recent cohort study of 31 patients diagnosed with iSFT, who underwent surgery from 2008 to 2021, exhibited a 1-year recurrence rate of 6.5% and a 5-year recurrence rate of 22.6%.[13] Liu et al. reported that 38 iSFT patients, who underwent surgery from 2008 to 2020, exhibited a 3-, 5-, and 10-year progression-free survival of 82.2, 62.8, and 21.4%, respectively; and a 3-, 5-, and 10-year overall survival of 97.1, 86.9, and 64.2%, respectively.[14]

In 2016, the world health organization (WHO) granted the combination of both SFT and hemangiopericytoma (HPC) entities into SFT/HPC since these tumors, despite differing in terms of recurrence and aggressiveness, share the same genetic abnormality, a chromosomal inversion in the 12q13 locus, allowing a fusion of the NAB2 and STAT6 genes and, thus, the formation of the fusion gene NAB2-STAT6.[15–18]. Nonetheless, in the most recent classification published by the WHO in 2021, CNS5, the term SFT/HPC was discarded and SFT was established as the only terminology.[19] Currently, the WHO classifies these tumors into three categories: benign, not otherwise specified (NOS) rarely metastasizing, and malignant.[20]

Meningiomas are the most common benign primary CNS tumor, whereas malignant meningiomas are an uncommon type of primary brain tumor.[21] The WHO grading system classifies benign meningiomas with indolent behavior as grade I, whereas those with atypical-to-malignant histology are assigned grades II and III.[21] Furthermore, a high K_i-67 proliferation index is associated with an increase in recurrence rate and a decrease in overall survival (OS), regardless of the tumor's grade.[22] The 10-year overall survival of grades I, II, and III are 83.7, 53, and 0%, respectively.[17]

The present study describes the first reported case of a patient with iSFT associated with a meningioma in different anatomical locations. We show histopathological findings that display the coexistence of a meningioma and a solitary fibrous tumor in different intracranial sites.

Case Report

A 64-year-old, Hispanic woman presented to the clinic with an 18-month history of progressive vision loss in the right eye and, in recent months, a decrease in the temporal field of the right eye. She had medical history of arterial hypertension. The neurological examination revealed a great compromise of visual acuity in the right eye, 0.3 on the Snellen test,

and right temporal hemianopsia. The left eye was normal. The rest of the neurological examination was normal.

A cerebral magnetic resonance imaging (MRI) revealed two expansive lesions: the first was a right interhemispheric occipital solid lesion, dependent on the falx cerebri, with well-defined lobulated borders with intermediate signal on T1 and T2 (►**Fig. 1A** and **B**), and intralesional serpiginous voids. The lesion demonstrated intense and heterogeneous enhancement following the intravenous administration of gadolinium (►**Fig. 1C, D**, and **E**), measuring 34 × 38 × 38 mm in the transverse, anteroposterior, and craniocaudal direction, suggestive of meningioma of the falx cerebri, causing compression of the cortical sulci of the right occipital lobe.

The second was a solid lesion with smooth, well-defined margins, and homogeneous enhancement following the administration of gadolinium, dependent on the dura mater and anterior floor of the skull base (►**Fig. 1C, D**, and **E**), measuring 28 × 34 × 20 mm, occupying the suprasellar cistern, compressing the infundibular stalk and prechiasmatic optic nerves and chiasm, suggestive of meningioma.

Surgical Management

The patient underwent a right frontotemporal craniotomy, and complete excision of the sellar tubercular meningioma was achieved.

The postoperative brain computed tomography (CT) scan showed signs of right frontal craniotomy and complete resection of anterior skull base lesion. There were also signs of intraparenchymal hemorrhage in the right parieto-occipital lobe, causing a mass effect on the midline and lateral ventricle (►**Fig. 2**).

No complications appeared following surgery. The patient was discharged 3 days later.

Pathological Examination

The pathologic examination of the first tumor showed a fibrous mass with tendency toward lobularity, compounded by fascicular cells with oval nuclei, with some vacuolated inclusions and occasional psammoma bodies. The mitoses are hard to find, and the immunostainings showed positivity to epithelial membrane antigen (EMA) antibodies and progesterone receptors, with a proliferative index evaluated with a K_i 67 of 2%. The glial fibrillary acid protein (GFAP) immunostaining was negative when looking for brain parenchyma trapped, which confirmed the benign characteristics of the tumor, grade I on the WHO classification (►**Fig. 3**).

The pathologic examination of the second tumor showed a cellular mesenchymal solid tumor with a ramified hemangiopericytoma vascular pattern, compounded by cells with round and ovalated nuclei, with up to seven mitoses per mm^2, and a fibrous background. The immunostains are

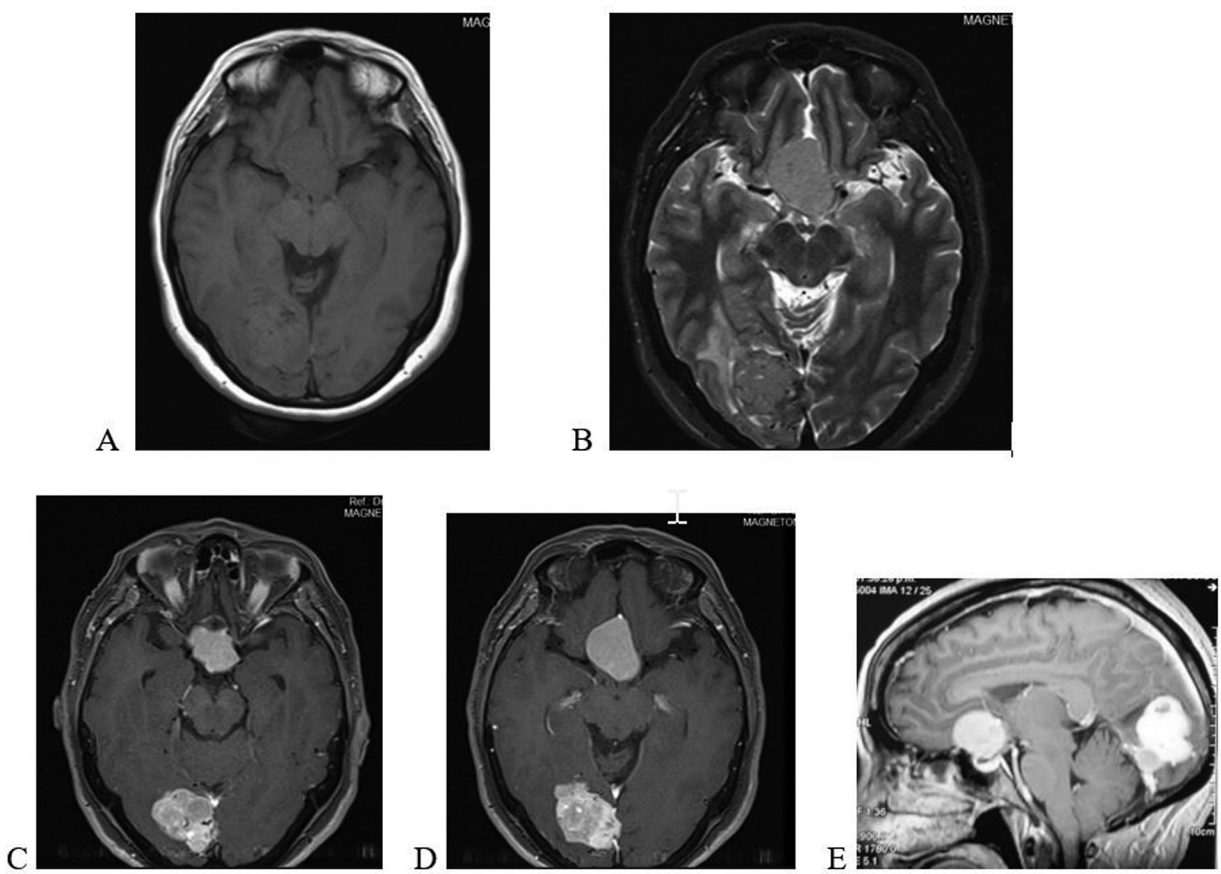

Fig. 1 The magnetic resonance imaging (MRI) of both brain tumors are isointense on T1 (**A**) and T2 (**B**) sequences; T1-weighted MRI exhibiting strong enhancement of the two brain tumors following gadolinium administration (**C**, **D**, and **E**).

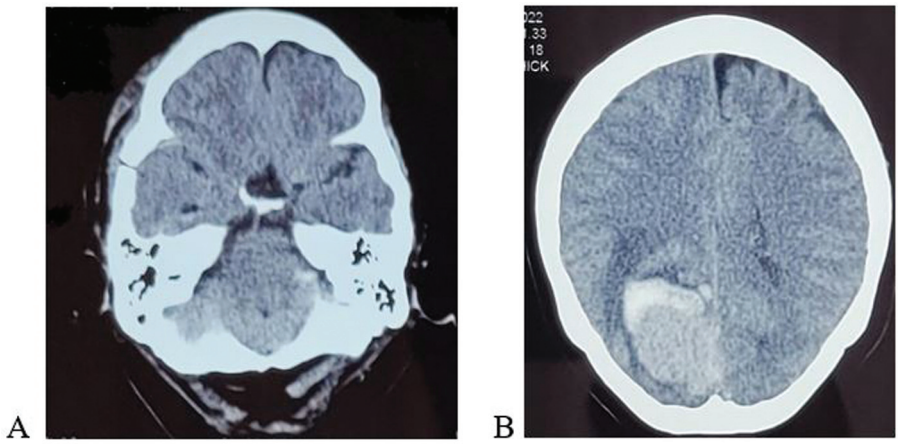

Fig. 2 Postoperative brain computed tomography. Shows total resection of anterior skull base lesion (**A**) and spontaneous bleeding from right occipital lesion (**B**).

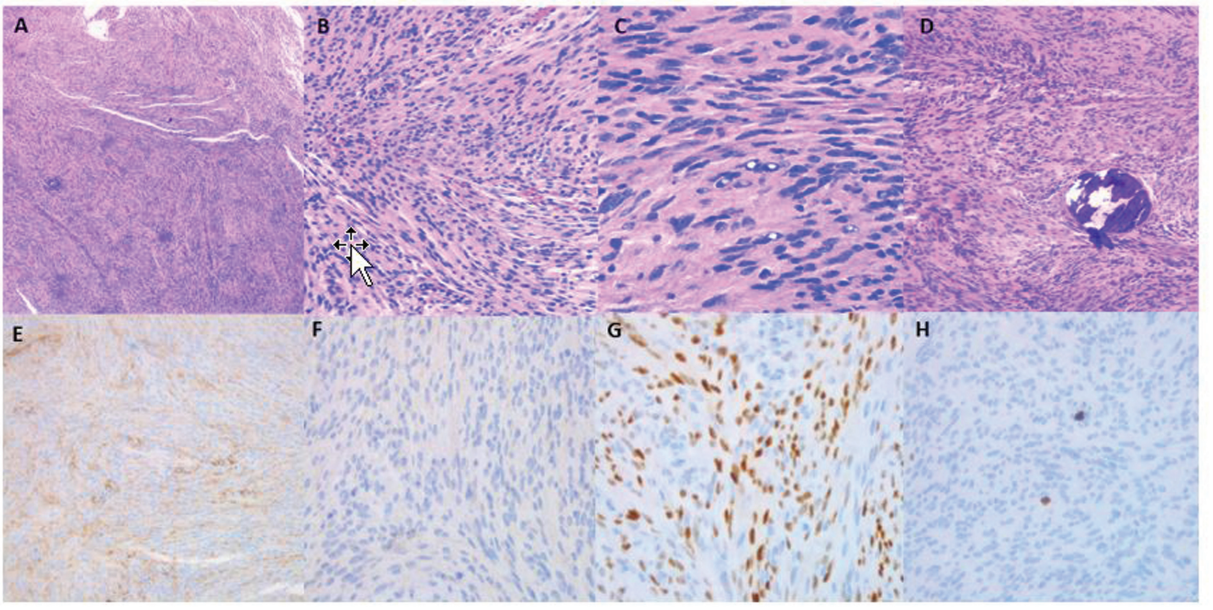

Fig. 3 Histopathological findings and immunohistochemistry: meningioma grade 1 of the World Health Organization (WHO) classification. (**A**) The slide observed under the 5x objective (50 microscope magnification) of the hematoxylin and eosin (H&E) stain revealed a fusocellular proliferation of cells with elongated and oval nuclei and fibrous morphology. (**B**) It is the objective of 10x (100 magnification) H&E staining to enhance the fibrous tissue bands interlacing in a fascicular pattern in the fibrous tissue. (**C**) In the 40x objective (400 magnification), the H&E staining revealed an enhanced lobular pattern in certain areas, as well as intranuclear inclusions, which are evident in the meningioma. (**D**) Based on the 10x objective in H&E stain, the interlacing fibrous bands of tissue contain calcification of the psammoma type. (**E**) EMA-immunohistochemistry stain in 20x objective (200 magnification), that is a positive faint stain in cytoplasmic pattern. (**F**) STAT6-negative immunostain in 40x objective (400 magnification). (**G**) Progesterone-receptor positive immunostain in nuclear pattern, 40x objective (400 magnification). (**H**) Ki67-immunohistochemistry stain in 20x objective (200 magnification), to evaluate the proliferative rate that showed minimal nuclear stain of less than 1%.

positive for CD34 and STAT6 in cytoplasmic and nuclear patterns, respectively. A subpopulation of tumoral cells was positive for CD99, and the proliferative index evaluated with Ki67 was around 10%. Furthermore, the EMA, progesterone receptor, and glial fibrillary acidic protein (GFAP) immunostains were negative. This finding is consistent with the diagnosis of SFT WHO classification grade II (►**Fig. 4**). The second brain tumor was operated on 41 days after the first surgery. The lesion was approached through a right occipital craniotomy, and complete excision of the tumor was obtained. The postoperative course was uneventful, and the patient was discharged after a few days.

Follow-up

After a 9-month follow-up, the patient showed improvement in both visual acuity (Snellen test: 0.7 improvement) and visual fields on the right eye (full recovery) and did not develop any neurological deficits or impairments in life functioning. Additionally, the last brain MRI (►**Fig. 5**)

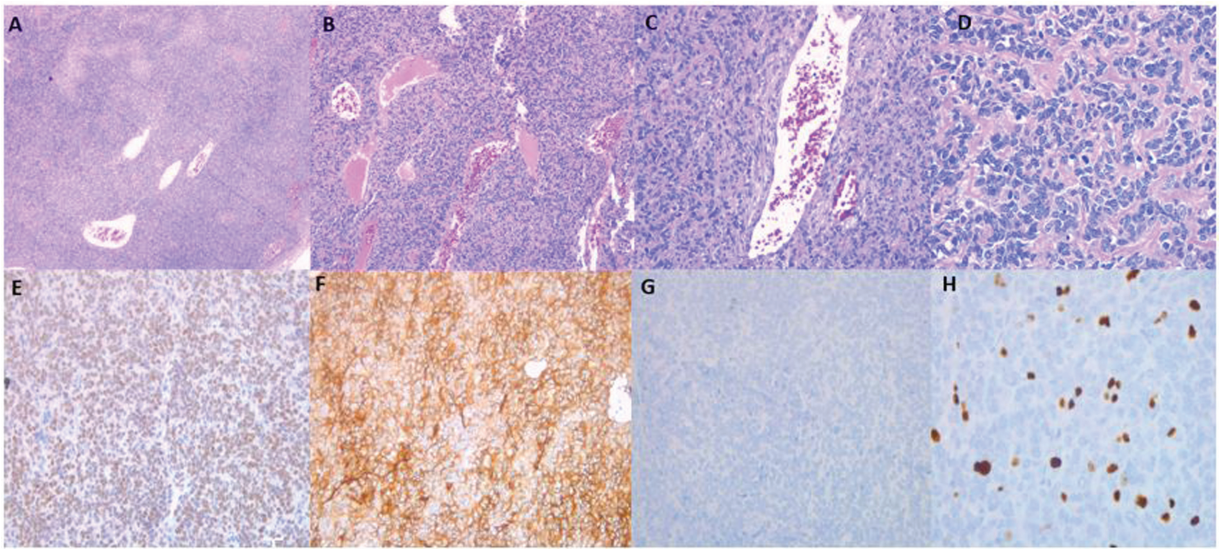

Fig. 4 Histopathological findings and immunohistochemistry: Solitary fibrous tumor WHO grade II. (**A**) The slide observed under the 5x objective (50 microscope magnification) of the H&E stain revealed a cellular tumoral proliferation of basophilic cells with oval nuclei and some dilated vessels. (**B**) In the 10x objective (100 magnification), the H&E staining revealed a hemangiopericytoid pattern characterized by a staghorn vascular pattern and dense collagenous stroma. (**C**) At 200x magnification using the 20x objective, the H&E staining revealed a close-up of the staghorn vascular pattern. (**D**) In the 40x objective (400 magnification), the H&E staining revealed the pink collagenous stroma in the background of a cellular tumor composed of cells with oval nuclei with scant cytoplasm and fibrous bands. (**E**) STAT6-positive nuclear immunostain in 20x objective (200 magnification), characteristic of solitary fibrous tumor. (**F**) CD34 cytoplasmic-positive immunostain, 20x objective (200 magnification). (**G**) Negative EMA-immunohistochemistry stain in 20x objective (200 magnification). (**H**) Ki67-immunohistochemistry stain in 20x objective (200 magnification), to evaluate proliferative activity showed in the nuclear stain of 10%.

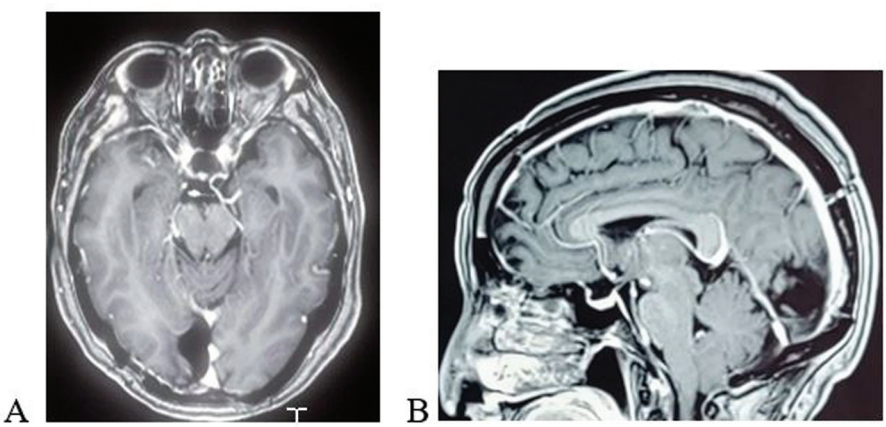

Fig. 5 Brain magnetic resonance imaging (MRI). (**A** and **B**) T-weighted MRI, showing non-enhancement of both surgical sites after gadolinium administration, suggestive of absence of residual tumor.

showed postsurgical changes in the right frontal lobe and occipital lobe with residual collection, compatible with sequelae encephalomalacia and thin capsule. The fluid attenuated inversion recovery (FLAIR) and T2 showed no signs of recurrence, no restriction in the diffusion sequence, and no signs of peripheral gliosis in both operated areas. The MRI scan results showed no contrast enhancement (►**Fig. 5-A, B**).

Discussion

The concurrence of tumors could be considered purely coincidental. Besides our study, there are three other case reports of intracranial collision tumors of SFT and meningioma.[23–25] Collision tumor is a lesion in which two histologically different neoplasms coexist in the same location.

Wang et al.[4] report a meningioma component (WHO grade was not mentioned) and a WHO grade I SFT. The case report by Ashisawa et al.[23] describes a WHO grade-I meningioma and a grade III SFT. Furthermore, Binello et al.[24] reports a case with a WHO grade-I meningioma and a grade-II SFT.

Some hypotheses have been proposed to explain the association between different coexisting brain tumors in the same patient. Local tissue irritation from perilesional edema caused by the first tumor has been considered a factor

that induces astrocyte or arachnoid cell transformation, causing future neoplastic proliferation.[26,27] However, this hypothesis does not explain the presence of different tumors in distant places. Most reported cases have presented with common intracranial tumors that were not in juxtaposition.[28] Other hypotheses have been proposed as a common genetic pathway, such as disruption of p53 and receptor tyrosine kinase signaling, molecules that have platelet-derived expression growth factor receptors (PDGFRs).[29]

Other theories have been proposed, stating that there may be unidentified carcinogens serving as stimuli that result in the development of tumors in different tissues, or that residual embryonic structures may instead form the basis of multiple lesions.[30,31]

The clinical manifestations of iSFTs are highly unspecific and associated with tumor location, with the most common being headaches, epilepsy, weakness of the extremities, paresthesia, visual impairment, anosmia, memory loss, dysphasia, hyponatremia, amenorrhea, and hypoglycemia.[32] Location and histological subtype may influence the evolution and prognosis of patients presenting similar cases. Due to the meningioma's location, size, and anatomical relationship with the surrounding structures, achieving a gross total resection (GTR) can be challenging. This is particularly true for skull-base meningiomas, in which a radical excision may represent a challenge and sometimes even be detrimental, especially when cranial nerve and vascular structures are involved.[33]

For an accurate iSFT diagnosis, the WHO has established as indispensable the confirmation of the NAB2/STAT6 fusion gene or the immunochemical confirmation of STAT6 protein.[34] The STAT6 protein's detection is regarded as a sufficient marker for routine diagnosis, since it is considered an effective diagnostic tool with a sensitivity of 98% and specificity greater than 85%.[35–39] Furthermore, CD34 positivity and EMA negativity in SFT are useful in the differential diagnosis with meningioma, which is CD34 negative and EMA positive.[40] However, 5 to 10% of SFTs were negative for CD34.[12,41]

Progesterone-receptor staining is more common in meningiomas but may be present in iSFT. Likewise, the K_i-67/MIB-1 index exhibits utility as both a risk of recurrence and a tumor grade marker when determining prognosis in CNS SFTs.[40] Further, several studies have identified an association between preoperation elevation of fibrinogen and TP53 gene and/or TERT gene mutations with the presence of malignant SFT.[25]

Histologically, SFTs are comprised of atypical spindle cells with an unpatterned architecture, surrounded by dense stromal collagen with collagen bands and, often, a staghorn vascular pattern.[25,42] However, although histological characteristics may be suggestive of SFT, they are not exclusive to it, since they can also be observed in other mesenchymal tumors.[17,43] Meningiomas and schwannomas can also mimic the histological and radiological forms of SFTs, so it is important to consider differential diagnoses, as these similarities can make it difficult to identify these pathologies.[40]

The radiological differences between SFTs and meningiomas must be considered. The first generally present lobulated margins and frequent flow-related serpiginous voids, whereas meningiomas feature smooth margins and abundant calcification.[44,45] In MRI imaging, iSFT's unique features include a narrow base of attachment, irregular cross-leaf growth, intratumoral calcification absence, related osseous hyperostosis, bone erosion, and heterogeneous gadolinium contrast enhancement.[46,47]

Surgery is the gold standard for intracranial SFT treatment, combined with stereotactic and beam radiation therapy for tumor remnants or unresectable recurrences.[3] Likewise, recent studies show that surgical treatment alone could have a 1-year recurrence rate of 88 to 100%, whereas its combination with postoperation radiotherapy could reduce this rate from 88 to 12.5%.[48] Nonetheless, these results vary across studies, so its indication remains uncertain.[49]

Treatment for meningiomas can vary depending on clinical manifestations and tumor size, resulting in two main groups: asymptomatic tumors managed with routine surveillance imaging, and symptomatic or growing tumors managed with surgical resection.[50] The goal for surgery in patients with grade-I meningiomas is GTR with routine follow-ups, or subtotal resection (STR) followed by rounds of stereotactic radiotherapy (SRT) or stereotactic radiosurgery (SRS). For grade-II meningiomas, the treatment is GTR with close follow-ups or STR with either SRT or SRS. In contrast, grade-III meningiomas require adjuvant radiotherapy following surgery, regardless of the resection degree.[51]

Conclusion

The SFT is an ultrarare mesenchymal ubiquitous tumor, with an incidence rate < 1 case/million people/year. The diagnosis of iSFTs relies on a comprehensive assessment encompassing clinical manifestations, imaging findings, pathological examination, immunohistochemical analysis, and molecular characteristics.

The present article illustrates a rare case of two different and simultaneous coexisting brain tumors: meningioma and SFT, emphasizing the rarity of primary iSFTs. This is the fourth reported case of meningioma and SFT coexisting as primary intracranial tumors. Nonetheless, this case differs from the previously mentioned articles both in the meningioma's histology subtype and tumor location. The current research exhibits a grade-I fibrous meningioma located at the base of the anterior skull, and a grade-II SFT with a right interhemispheric occipital location and dependent on the falx cerebri. The pathogenesis and evolution involved in the two coexisting tumors remain unclear, which highlights the necessity of more case reports about them.

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Spinal Dural Arteriovenous Fistula, a Rare and Frequently Misdiagnosed Cause of Mielopathy – Case Report and Review of the Literature*

Fístula arteriovenosa dural espinhal, uma causa de mielopatia rara e frequentemente não diagnosticada – Relato de caso e revisão da literatura

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Arq Bras Neurocir 2024;43(4):e355–e359.

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Abstract

Spinal dural arteriovenous fistulas (SDAVFs) are rare vascular malformations with unspecific clinical manifestations, which often lead to misdiagnosis and delay in the establishment of effective therapies. Since the neurological prognosis depends on symptom duration and pretreatment neurological status, rapid identification and obliteration of the fistula are key to provide patients with a better quality of life. We herein describe an illustrative case of an elderly patient presenting with progressive myelopathy, with a definitive diagnosis of SDAVF after 18 months of the initial symptoms. We also review the core concepts regarding this condition and discuss strategies to prevent misdiagnosis and worsening of the neurological outcome.

Keywords
- arteriovenous fistulas
- dural
- myelopathy
- spinal cord disease

Resumo

Fístulas arteriovenosas durais espinhais (FADEs) são malformações vasculares raras e com manifestações clínicas pouco específicas, o que frequentemente leva a erros diagnósticos e ao atraso no estabelecimento de terapias efetivas. Considerando que o prognóstico neurológico depende da duração dos sintomas e do *status* neurológico prévio, a agilidade na identificação e obliteração da fístula são essenciais para prover melhor qualidade de vida aos pacientes. Neste estudo, descrevemos um caso ilustrativo de um paciente idoso com quadro de mielopatia progressiva, com diagnóstico definitivo de FADE após 18 meses do início dos sintomas. Realizamos ainda uma revisão sobre os conceitos principais da doença e discutimos estratégias para prevenir atrasos diagnósticos e piora neurológica.

Palavras-chave
- fístulas arteriovenosas
- dural
- mielopatia
- doença da medula espinal

* *Study conducted at the Teaching Hospital of Universidade Estadual de Campinas, Campinas, SP, Brazil.*

received
August 1, 2023
accepted
May 16, 2024

DOI https://doi.org/10.1055/s-0044-1788603.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Introduction

Spinal dural arteriovenous fistulas (SDAVFs) are acquired vascular malformations characterized by anomalous connection of a radicular artery and a medullary vein, with no capillaries between them.[1–3] The higher pressure from the shunt elevates intradural venous pressure, causing venous congestion, which leads to medullary edema and ischemia.[1,2] Chronic hypoxia results in progressive myelopathy.[1,2]

The manifestations of SDAVF myelopathy are unspecific and follow a variable course, potentially delaying diagnosis and proper management.[2] In fact, one study[4] has found that more than 81% of the affected patients were initially misdiagnosed, and 62% were submitted to incorrect treatments. Although the treatment is effective in obliterating the fistula, the prognosis depends on symptom duration and pretreatment neurological status,[1,2] highlighting the importance of an accurate and rapid diagnosis.

We herein describe a well-documented case of SDAVF with an important diagnostic delay, exemplifying the impact of misdiagnosis; we also discuss strategies to prevent misdiagnosis and worsening of the neurological outcome.

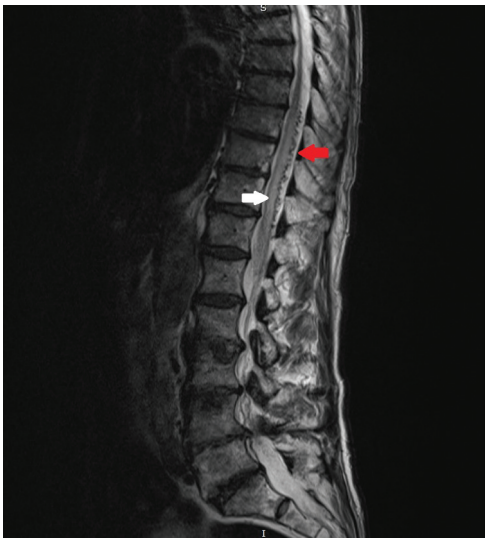

Fig. 1 Typical characteristics of a spinal dural arteriovenous fistula (SDAVF) on magnetic resonance imaging (MRI), as represented by the case herein reported. Images of the T2-weighted sequence: centromedullary edema represented by spinal cord hyperintensity (**white arrow**) and dilated posterior veins shown as serpiginous flow voids (**red arrow**). In the case herein described, alterations were observed from T7 to the conus medullaris.

Case Report

An 80-year-old man presented to our hospital's emergency room complaining of difficulty in walking that had worsened in the past year, with progressive shortening of walkable distance. Since the previous month, he had been unable to ambulate without assistance. Lower mechanical back pain and burning sensation in the lower limbs were associated; the symptoms were more prominent on the left side and were not responsive to a previous therapeutic test with gabapentin. The upper limbs were asymptomatic. Furthermore, he complained of urinary and fecal incontinence that had initiated one year and a half and four months before arriving at our service, respectively. He had a medical history of arterial hypertension, benign prostate hyperplasia, and had had previous diagnoses of syphilis and tuberculosis (both allegedly fully treated). He was also a former smoker and alcoholic. Before reaching our institution, he was first referred to an orthopedic surgeon, who diagnosed degenerative spinal disease, and to a neurologist, who established the syndromic diagnosis of spastic paraparesis and also prescribed baclofen.

After the initial assessment, he was referred to the Neurology Department for further investigation. A neurological examination showed impairment in strength in the lower limbs, almost symmetrical (discreetly worse on the right side). There was also tactile hypoesthesia in the right leg and hypopallesthesia in both lower limbs. The tone was normal.

The main primary hypotheses were neurosyphilis, subacute combined degeneration of the spinal cord, polyneuropathy, and compressive myelopathy. A cerebrospinal fluid examination did not detect any significant pathological change, and the serum levels of B12 were within the normal range. Magnetic resonance imaging (MRI) was performed to evaluate cord compression, and indirect signs of SDAVF were observed: spinal cord edema in the thoracic level as well as flow voids suggestive of a vascular lesion (►**Fig. 1**). Because of the MRI findings, a digital subtraction angiography (DSA) was performed and confirmed a dural fistula from the intercostal arteries entering just below the right pedicle of the T9 level and the radicular vein (►**Fig. 2**).

After discussion with the Neuroradiology Division, we decided to refer the patient to surgical occlusion of the dural fistula. A T9 laminoplasty was performed, with dural opening. The right T9 nerve root was found, and the main artery entering the neural foramen was coagulated—after a brief period of transient clipping. The medullary veins just after artery ligation decreased their flow. The dura mater was

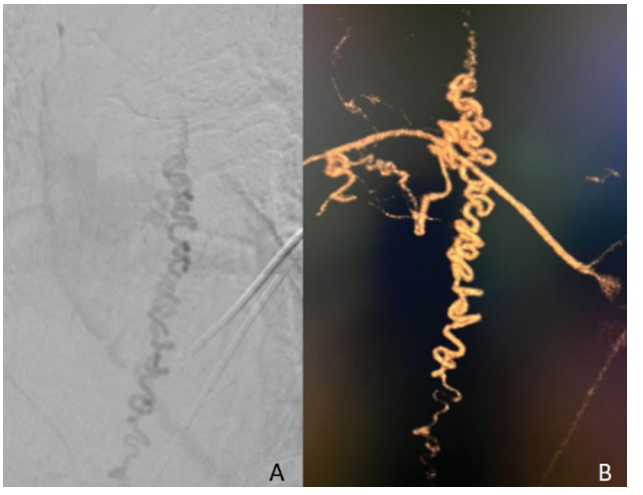

Fig. 2 Digital subtraction angiography (DSA) findings (**A**) and three-dimensional (3D) reconstruction (**B**): SDAVF at the level of T9, draining to a dilated and tortuous posterior medullary vein, with both ascending and descending flow; signals suggestive of venous congestion.

tightly closed, and the T9 lamina was fixed with miniplates. The surgical technique used in the procedure is shown and described in ►**Fig. 3**.

Standard postoperative care was offered, and the patient was in discharge conditions 48 hours after surgery, reporting an immediate improvement in lower-limb strength (from grade 2 proximally just before surgery to grade 3). A postoperative MRI scan showed resolution of the posterior flow void and decrease in the centromedullary hypersignal intensity on the T2-weighted imaging (►**Fig. 4**).

Discussion

Spinal vascular malformations are mainly classified based on anatomic or angioarchitecture features. The first descriptions were made by Di Chiro[7] according to angiographic characteristics, and he divided this group of pathologies into three categories: type I – single-coiled vessel; type II – glomus; and type III – juvenile.[8] With posterior actualizations including a fourth type, intradural perimedullary arteriovenous fistula,[5,6] this classification remains one of the most widely accepted (►**Table 1**).[7,8] More recently, extensive surgical experience gave rise to an anatomical categorization by Spetzler et al.[9] based on the location of the disease and its relation to the spinal cord and the spinal dura mater (►**Table 2**). An endovascular classification by Rodesch et al.[10] is also frequently used when considering endovascular treatment, and it divides these entities into arteriovenous malformations and fistulas, subdividing fistulas into macro and micro types, and adding a genetic classification as hereditary, non-hereditary or single lesions.

Among spinal vascular malformations, SDAVFs are the most common comprehending 60 to 80% of all cases.[2,11] They correspond to Di Chiro's type I or Spetzler et al.'s dorsal

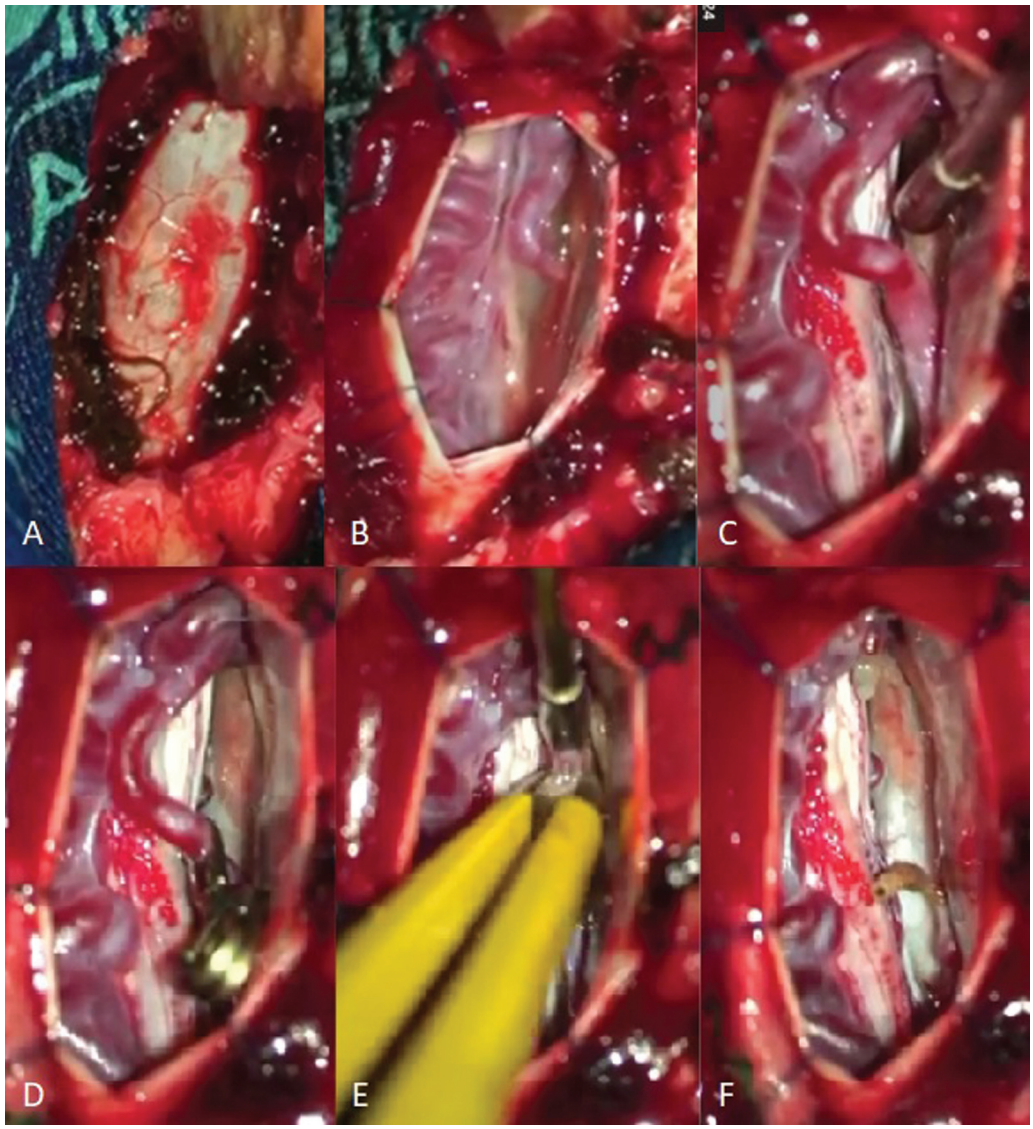

Fig. 3 Surgical approach to SDAVF. (**A**) Standard T9 laminoplasty was performed, and the dura mater was exposed. (**B**) After dural opening, visualization of tortuous, congested posterior venous system. (**C**) After finding the right T9 nerve route, the location of the arterialized draining vein was confirmed, and the vessel, dissected. (**D**) Clipping of the draining vein to prevent bleeding during coagulation. (**E**) Coagulation of the draining vessel with bipolar cautery. (**F**) Final aspect of the procedure. The dura mater was closed watertight, and the T9 vertebra was fixed with miniplates.

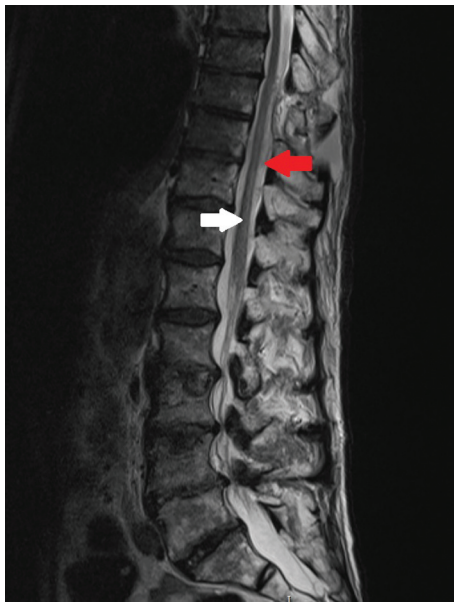

Fig. 4 Postoperative MRI scan acquired on the fourth postoperative day, showing decrease in the centromeddulary hypersignal (**white arrow**) on T2-weighted imaging, indicating improvement in cord edema, and disappearance of posterior flow voids (**red arrow**).

intradural arteriovenous fistulas, which can be further subdivided into subtype A or B, single or multiple arterial feeders respectively.[2,11] The SDAVFs are composed of a radicular artery shunting into a medullary vein through a complex network of arteriovenous microfistulas within the dural nerve root sleeve, with no capillary system interposed.[3,11] This connection raises venous blood pressure, generating venous congestion and cord edema, ultimately leading to myelopathic symptoms.[2] Their etiology is not yet clear.[2,12] Epidemiologically, they more commonly affect men aged approximately 55 to 60 years, with a male:female ratio of up to 6:1.[2,11]

The symptoms manifest as those of progressive myelopathy. A large retrospective study[4] including 326 affected patients reported that the most common findings at the initial presentation were lower-limb motor deficits and sensorial alterations (pain, dysesthesia, paresthesia, and/or hypoesthesia), present in 71.8% and 70.2% of the patients, respectively. With disease progression, weakness and sensory disturbance not only worsened, but were more frequently accompanied by sphincter abnormalities (especially urinary incontinence), shown by 52.5% of patients by the time of diagnosis.[4] Other less prevalent symptoms included headache and vomit—associated with subarachnoid hemorrhage

Table 1 Di Chiro's[7] classification of spinal vascular malformations (modified by Rosenblum et al.[8])

Type	Description/name
I	Dural arteriovenous fistula
II	Intramedullary glomus arteriovenous fistula
III	Intramedullary juvenile arteriovenous fistula
IV	Intradural direct arteriovenous fistula

Table 2 Spetzler et al.'s[9] SDAVF classification

Type	Description/name
AVF	Extradural arteriovenous fistula
	Intradural ventral arteriovenous fistula
	Intradural dorsal arteriovenous fistula
AVM	Extradural-intradural arteriovenous malformation
	Intradural compact arteriovenous malformation
	Intradural diffuse arteriovenous malformation
	Intradural conus arteriovenous malformation

Abbreviations: AVF, arteriovenous fistula; AVM, arteriovenous malformation; SDAVF, spinal dural arteriovenous fistula.

—dizziness, upper-limb weakness, and thoracic pain.[4] Similarly, other studies[12–14] have reported gait disturbances, lower-extremity motor impairment, sensory alterations, sphincter dysfunctions, and pain as the most common initial symptoms. In accordance with the literature, the patient herein described was affected by lower-limb weakness, urinary and fecal incontinence, and pain.

The unspecific nature of the clinical presentation makes SDAVFs a diagnostic challenge, which may lead to diagnostic delay and/or misdiagnosis, favoring unnecessary interventions.[4,13,15–17] Donghai et al.[4] found that most affected patients (81.3%) had at least 1 previous misdiagnosis before reaching the reference center—with the most common ones being degenerative disc disease, myelitis, prostatic hyperplasia, and intramedullary tumors. A substantial amount (19%) remained with a mistaken diagnosis even after evaluation at the reference hospitals—69.3% of whom were submitted to surgical treatment for alternative etiologies.[4] The prognosis worsened after unnecessary medical therapies or procedures.[4] Other studies[13,16,17] have confirmed this tendency towards misdiagnosis and unnecessary invasive treatments. The average diagnostic delay ranges from 12 to 24.6 months,[4,12,14,17–19] but it can reach more than 20 years[4,14] and may be associated with misdiagnosis and worsened prognosis.[13,15,18] Though presenting classical signs of the disease, the patient herein described remained undiagnosed for one and a half years since the first symptom (urinary incontinence). Moreover, the initial diagnostic hypotheses ranged from degenerative diseases to infectious and metabolic disturbances, but SDAVF was not suspected until neuroimaging scans were acquired. The clinical picture was worsening, but, fortunately, no major procedure was performed prior to proper elucidation. Syphilis and vitamin deficiency still have high prevalence rates, especially in low- and middle-income countries,[20,21] and may present as differential diagnoses of myelopathy, both also considered hypotheses for our patient. Providers should have SDAVF in mind as a differential for these diagnoses and rule it out when appropriate.

After the initial suspicion raised on clinical grounds, MRI is usually the first imaging modality performed to guide the diagnosis.[22] The classic signs according to Fox et al.[18] are depicted in ►**Fig. 1**. The definitive diagnosis is ideally based

on DSA, but even this gold standard is not 100% sensitive, and repeating the exam may be necessary if clinical suspicion is high.[4] The DSA is also useful for planning fistula occlusion, especially in terms of precisely locating the fistula level.[2] Noninvasive imaging techniques (such as MRI or computed tomography angiography) may be useful to narrow down the vertebral segments requiring DSA.[4] Segments T6 to L2 are the most affected, being responsible for around 80% of SDAVFs,[2,11,23] as represented by the T9 fistula in the case herein reported.

The treatment is curative, and to date surgery is still considered the gold-standard therapy. Details on the technique used on the patient herein described are available in ►**Fig. 3**. The surgical procedure is relatively simple and safe,[24] and, despite the advances in endovascular embolization, it results in higher occlusion and lower recurrence rates, with better neurological outcomes without adding significant complications or morbidity.[15,24–26] The main pitfall in the surgical treatment is the adequate location of the level of the draining vein,[24] highlighting the importance of careful evaluation of preoperative DSA. After successful obliteration, strength and gait tend to improve at higher rates than urinary function.[13,15,26] Shorter times between onset and adequate treatment are associated with better prognosis[13,15]

In sum, we have described a patient with a typical presentation of an SDAVF, illustrating misdiagnosis, diagnostic delay, worsening of symptoms, and the final resolution with surgical obliteration of the fistula. We hope that, by sharing this case, we will assist in reducing the time until the correct diagnosis and institution of treatment, contributing to minimize the neurological impairments caused by the disease.

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Brachial Plexus Schwannoma: Case Report and Literature Review

Schwannoma do Plexo Braquial: Relato de Caso e revisão da literatura

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Arq Bras Neurocir 2024;43(4):e360–e364.

Abstract

Schwannomas are mostly benign and solitary tumors that originate from Schwann cells. Macroscopically, they appear as rounded masses with a smooth surface. Schwannomas rarely affect the brachial plexus, accounting for approximately 5% of all cases of schwannomas, presenting a challenge for surgeons. The objective of this article is to describe a case report of a brachial plexus schwannoma in a hospital located in the Northeast of Brazil. A 49-year-old male patient presented pain resulting from the appearance of a left anterior cervical bulging with progressive growth. On physical examination, he had a Medical Research Council (MRC) score of 3 in left arm abduction and paresthesia in the left lateral forearm and arm. On magnetic resonance imaging (MRI), the lesion arises from the C4-C5 junction, measuring 5.9 × 5.4 × 5.5 cm, and the electroneuromyography showed chronic pre-ganglionic involvement of C5 to C7 bilaterally. A left cervicotomy was performed with a horizontal incision at the level of the laryngeal eminence. Brachial plexus lesions with progressive growth tend to be managed surgically. This diagnosis hypothesis should be considered in patients

Keywords
- Brachial Plexus
- Neural Sheath Tumors
- Schwannoma

received
June 1, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1796657.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

presenting progressive neck bulging in inspection during physical examination. This is an easy and cheap method of suspicion that can be used by health professionals.

Resumo

Os schwanomas são, em sua maioria, tumores benignos e solitários originados das células de Schwann. Macroscopicamente, aparecem como massas arredondadas com superfície lisa. Os schwannomas raramente afetam o plexo braquial, sendo responsáveis por aproximadamente 5% de todos os casos de schwanomas, representando um desafio para os cirurgiões. O objetivo deste artigo é descrever um relato de caso de schwanoma do plexo braquial em um hospital localizado no Nordeste do Brasil. Paciente do sexo masculino, 49 anos, apresentava dor decorrente do aparecimento de abaulamento cervical anterior esquerdo com crescimento progressivo. Ao exame físico, apresentava pontuação 3 do Medical Research Council (MRC) na abdução do braço esquerdo e parestesia na lateral do antebraço e braço esquerdo. Na ressonância magnética (RM), a lesão surge da junção C4-C5, medindo $5{,}9 \times 5{,}4 \times 5{,}5$ cm e a eletroneuromiografia mostrou envolvimento pré-ganglionar crônico de C5 a C7 bilateralmente. Foi realizada cervicotomia esquerda com incisão horizontal ao nível da eminência laríngea. Lesões do plexo braquial com crescimento progressivo tendem a ser tratadas cirurgicamente. Essa hipótese diagnóstica deve ser considerada em pacientes que apresentam abaulamento progressivo do pescoço na inspeção durante o exame físico. Este é um método de suspeita fácil e barato que pode ser utilizado por profissionais de saúde.

Palavras-chave
- Plexo Braquial
- Tumores de Bainha Neural
- Schwanoma

Introduction

Schwannomas are mostly benign and solitary tumors that originate from Schwann cells.[1] They are more frequent in adults over 40 and more frequent in females.[2,3] They are usually found on the peripheral nerves of the upper limbs and neck. They can also reach the spinal nerve roots, being extra axial and extradural masses that grow through the intervertebral foramen, compressing the nerves.[4] Macroscopically, they appear as rounded masses with a smooth surface.[5]

Schwannomas rarely affect the brachial plexus, accounting for approximately 5% of all cases of schwannomas.[6,7] Since brachial plexus schwannomas are a rare entity and, due to the brachial plexus anatomic complexity, schwannomas in this region present a challenge for surgeons. The objective of this article is to describe a case report of a brachial plexus schwannoma in a hospital located in the Northeast of Brazil.

Case Report

We present the case of a 49-year-old male patient who complained of pain resulting from the appearance of a left anterior cervical bulging one and a half years ago, with progressive growth (►**Fig. 1**). On physical examination, he had a Medical Research Council (MRC) score of 3 in left arm abduction and paresthesia in the left lateral forearm and arm. He denied other motor or sensory alterations. On ultrasonography (US), there were no changes in vessel caliber. On magnetic resonance imaging (MRI), the lesion arises from the C4-C5 junction, measuring $5.9 \times 5.4 \times 5.5$ cm (►**Fig. 2**). Electroneuromyography showed chronic pre-ganglionic involvement of C5 to C7 bilaterally. Fine-needle aspiration biopsy (FNAB) revealed the proliferation of spindle cells without atypia, suggestive of a benign mesenchymal neoplasm, schwannoma (neurilemoma).

With the patient in dorsal decubitus, a left cervicotomy was performed with a horizontal incision at the level of the laryngeal eminence. The platysma muscle was incised, and the carotid sheath was exposed. The carotid sheath was then bluntly dissected to isolate the vascular complex with the vagus nerve. The phrenic nerve from the lesion on the left was identified and isolated using neurostimulation. Brachial plexus microsurgery was performed with neurolysis exploration and interfascicular grafts. Tumor lesions were debulked for sitereduction, peripheral nerve tumors were excised, and the surgical site was closed by planes with reinsertion of the sternocleidomastoid muscle (►**Figs. 3** and **4**).

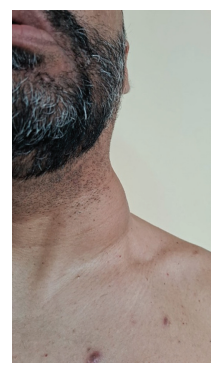

Fig. 1 Left anterior cervical bulging with progressive growth.

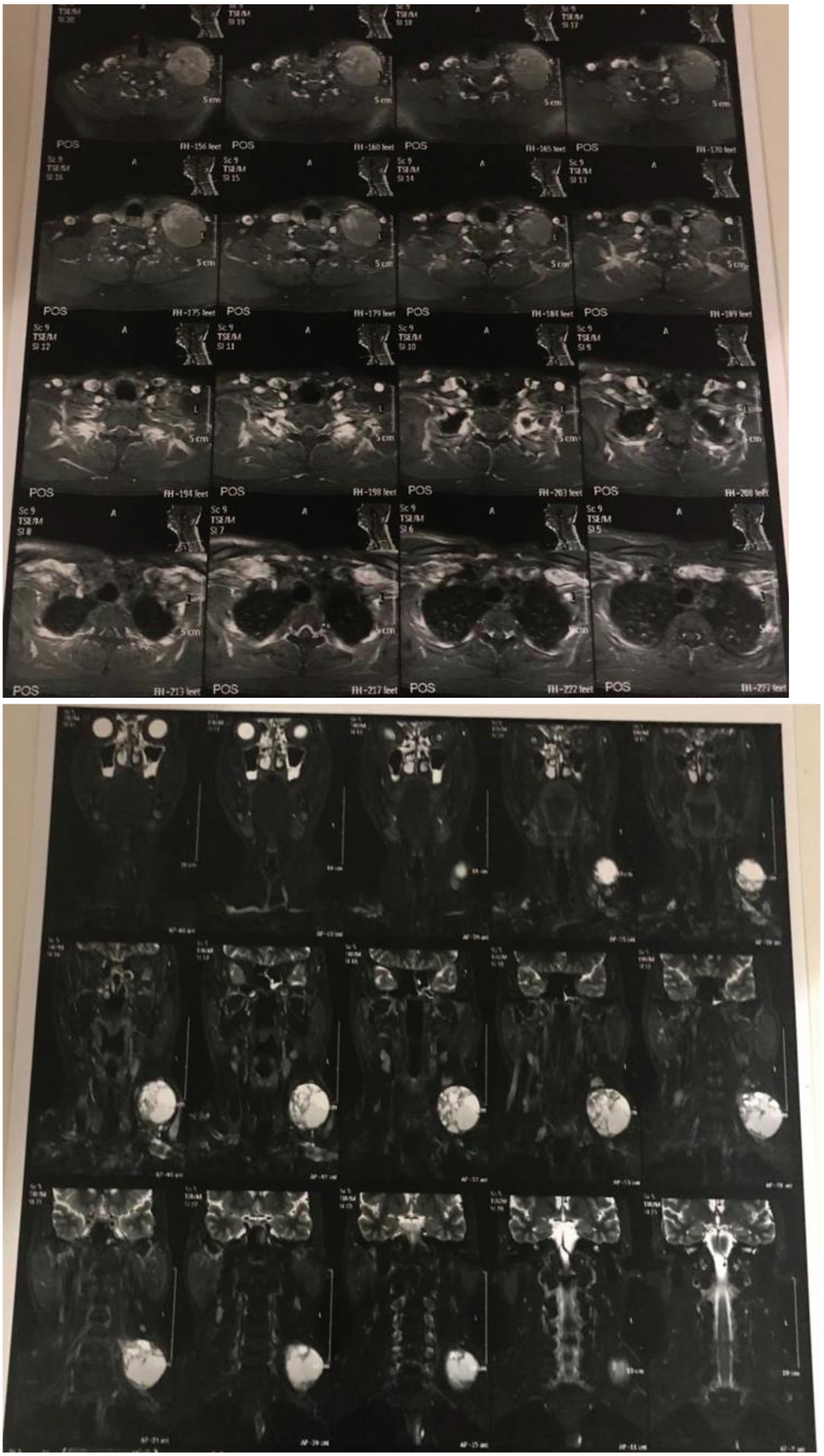

Fig. 2 Magnetic Resonance Imaging showing left brachial plexus schwannoma in axial view (a) and coronal view (b).

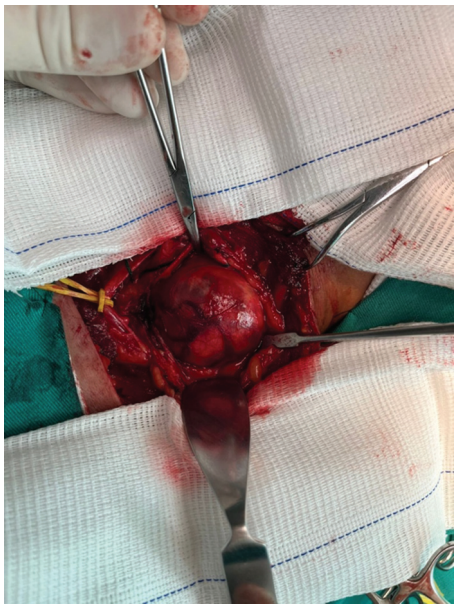

Fig. 3 Intraoperative view of left brachial plexus schwannoma.

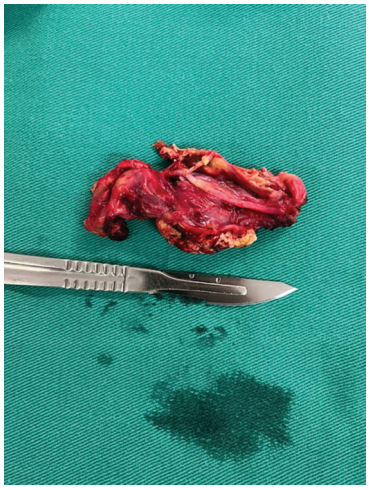

Fig. 4 Brachial plexus schwannoma after complete resection.

In macroscopy, the material exhibited irregular tissue formation, with a brownish to tan color, and elastic consistency, measuring $3.8 \times 3.2 \times 2.0$ cm and weighing 67g. Other irregular tissue fragments were also removed, measuring $2.2 \times 1.5 \times 0.8$ cm, and the aggregate measured 5.0×4.5 cm. Microscopically, compatibility with Grade 1 WHO Schwannoma was observed, with signs of hemorrhage at various stages of resolution.

In the postoperative period, the patient-maintained muscle weakness, particularly in arm abduction, scoring 3 on the MRC scale. Six months after surgery, the patient reported persistent intermittent pain, described as squeezing and burning with paresthesia, radiating to the arm. He reported peaks of intensity and variations in thermal sensation in the left arm and forearm. He denied limitation of movement. He was taking 75mg of pregabalin and 3mg of eszopiclone and was referred to improvement of these sensory alterations.

Discussion

Tumors of the brachial plexus are very rare. Schwannoma is one of the types of brachial plexus tumor characterized as a benign primary neoplasm. Considering it is a subtype of brachial plexus tumor, it is an even rarer lesion in this topography.[6,8,9] The clinical presentation of brachial plexus tumors may vary according to their location, extension, neural elements involved, and pathology.[2]

Symptoms can be caused by direct nerve invasion, infiltration of surrounding tissues, or local mass effect.[2] Schwannomas in this region usually present as a local slow-growing mass but in some cases present with symptoms of nerve compression.[10] According to Go *et al.* the most common presenting symptom was growing mass (95.4%), sensory deficit (54.5%), motor deficit (40.9%), direct tenderness and pain (27.2%), followed by included radiating pain (22.7%).[2]

The surgical approach for treatment depends on where the tumor is located. Brachial plexus lesions with progressive growth tend to be managed surgically. Lesions involving roots and trunks are commonly treated with an anterior supraclavicular approach as observed in the present case. The lower tumors involving cords and terminal nerves require an anterior infraclavicular approach, with or without a section of the clavicle.[2]

Conclusion

Brachial plexus schwannoma is a rare benign tumor. This diagnosis hypothesis should be considered in patients presenting progressive neck bulging in inspection during physical examination. This is an easy and cheap method of suspicion that can be used by health professionals. MRI is one of the most common supplementary radiological exams used to diagnose brachial plexus tumors. Patients with progressive neck lesions and cervical root involvements tend to be managed surgically with a supraclavicular approach, as shown in this case.

Conflict of Interest

None.

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Vertebral Artery Stenosis Caused by Cervical Osteophyte: A Rare and Reversible Cause of Vertebrobasilar Insufficiency. Case Report

Estenose da artéria vertebral causada por Osteófito Cervical: Uma causa rara e reversível de insuficiência vertebrobasilar. Relato de caso

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Arq Bras Neurocir 2024;43(4):e365–e368.

Abstract

Bow Hunter syndrome manifests when the vertebral artery is compressed following head rotation. Symptomatic compression with vertebral artery stenosis due to cervical osteophytes is a rare cause and occurs due to a progressive degenerative process. In most cases, compression originates anteromedially from the uncinate process and is asymptomatic due to the competence of the contralateral vertebral artery. In the described patient, compression presented superomedially due to osteophytes in the superior articular facet of the C5 vertebra, and the contralateral vertebral artery was obstructed. Careful evaluation with imaging, mainly preoperative 3D angiotomography, is necessary to determine the most beneficial approach for decompression. The treatment of choice for symptomatic compression induced by cervical spondylosis is decompression surgery.

Keywords
- vertebral artery
- vertebrobasilar insufficiency
- osteophyte
- Bow Hunter's Syndrome

Resumo

A síndrome de Bow Hunter se manifesta quando a artéria vertebral é comprimida após a rotação da cabeça. A compressão sintomática com estenose da artéria vertebral devido a osteófitos cervicais é uma causa rara e ocorre devido a um processo degenerativo progressivo. Geralmente, a compressão se origina anteromedialmente do processo uncinado e é assintomática devido à competência da artéria vertebral

received
April 7, 2024
accepted
October 18, 2024

DOI https://doi.org/10.1055/s-0044-1795135.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Palavras-chave
- artéria vertebral
- insuficiência vertebrobasilar
- osteófito
- Síndrome de Bow Hunter

contralateral. No paciente descrito, a compressão se apresentou superomedialmente devido a osteófitos na faceta articular superior da vértebra C5, e a artéria vertebral contralateral estava obstruída. Uma avaliação cuidadosa com imagens, principalmente angiotomografia 3D pré-operatória, é necessária para determinar a abordagem mais benéfica para a descompressão. O tratamento de escolha para compressão sintomática induzida por espondilose cervical é a cirurgia de descompressão.

Introduction

Vertebral artery stenosis (VAS) can be caused by intrinsic lesions (such as atherosclerosis, vascular dissection, and vasculitis) and extrinsic lesions (including neoplasia, infections, fractures, fibrosis, and osteophytosis).[1,2] Approximately a quarter of ischemic strokes occur in the territory of the posterior cerebral circulation, and 20-25% of these are caused by VAS.[1,3]

Symptomatic compression with stenosis of this vertebral artery due to cervical osteophytes is a rare cause and occurs due to a progressive degenerative process affecting cervical vertebral bodies and intervertebral discs. This condition can lead the patient to present with ischemic strokes and/or Transient Ischemic Attacks (TIAs), also described as Vertebrobasilar Insufficiency (VBI).[4–7]

In most cases, compression originates anteromedially from the uncinate process and is asymptomatic due to the contralateral vertebral artery's competence.[7,8] In the described patient, compression presented superomedially due to osteophytes from the superior articular facet of the C5 vertebra, and the contralateral vertebral artery was obstructed.

Case Report

A 76-year-old male patient, hypertensive, diabetic, and with chronic atrial fibrillation, sought medical attention due to multiple falls associated with vertigo for 2 months, worsening with rotation and extension of the head. Cardiovascular etiologies were ruled out, and he underwent cranial and cervical vessel angiotomography (ATC), showing complete occlusion of the right VA and stenosis of the left VA at the level of C4-C5 due to an osteophyte originating from the superior facet of the C5 vertebra with a superolateral direction, invading the vertebral foramen, with 80% occlusion (►**Fig. 1**).

Surgical treatment was proposed for AV decompression with posterior cervical arthrodesis using lateral mass screws at the level of C3-C4, C4-C5, and C5-C6, sparing the fourth and fifth left cervical vertebrae. Decompression of the left vertebral foramen at the level of C4-C5 was performed, with confirmation of arterial patency with intraoperative ultrasound.

The patient was discharged on the second postoperative day, with complete improvement of vertigo and falls. Follow-up angiotomography showed complete decompression of the vertebral foramen and removal of the osteophyte, with patent VA (►**Fig. 2**).

Discussion

VA compression due to cervical spondylosis is an uncommon cause of VBI. When the symptomatology is generated by specific head movements, it is called Bow Hunter syndrome, described by Sorensen in 1978.[8–12]

Arterial blood flow can be impaired by intrinsic lesions (60%), with atherosclerosis being the most common cause, and extrinsic lesions (40%). Extrinsic compression due to osteophytes originating from the superior facet joint is rare and accounts for 6% of cases. The primary level of cervical involvement is C5-C6, with only 18% of cases at the C4-C5 level. More than 60% of patients with VBI experience at least

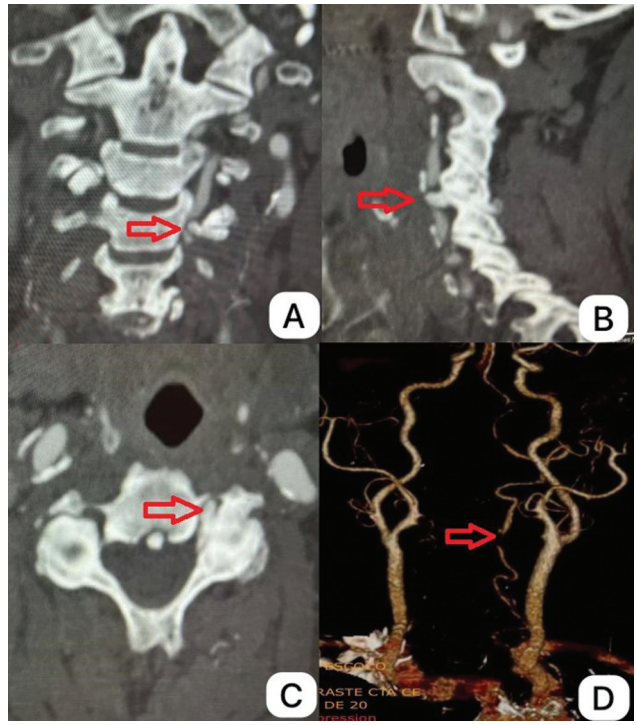

Fig. 1 CT of cervical vessels - coronal (**A**), sagittal (**B**), and axial (**C**) views showing osteophyte invading the vertebral foramen, with 80% occlusion of its diameter and compression of the left vertebral artery. Originating from the superior articular facet of the fifth cervical vertebra. Image D, 3D reconstruction showing interruption of flow through the left vertebral artery (red arrow).

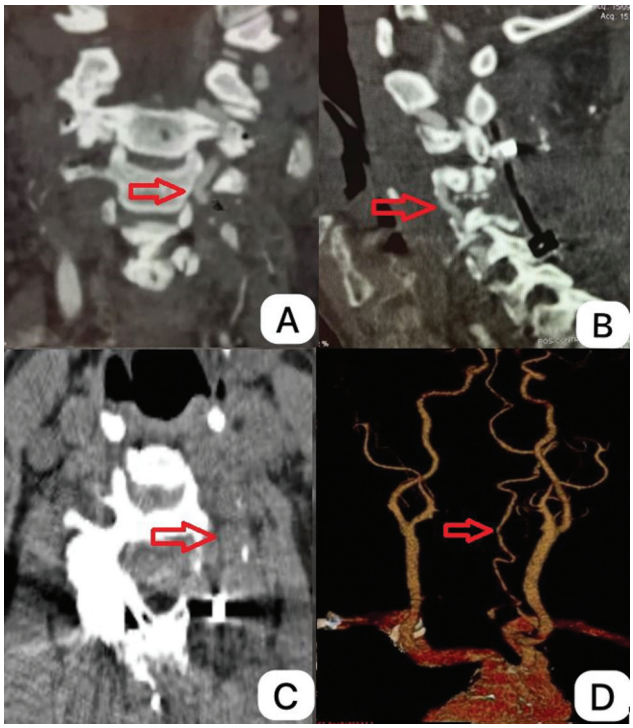

Fig. 2 Postoperative CT - coronal (**A**), sagittal (**B**), and axial (**C**) views showing decompressed left VA with preserved diameter. Image D, 3D reconstruction showing resumption of flow through the left vertebral artery with preservation of its diameter (red arrow).

one episode of vertigo during the disease. The most frequent symptoms are visual disturbances (diplopia, visual hallucinations, and blindness); sudden falls secondary to loss of tone in the lower limbs, without loss of consciousness, incoordination, and muscle weakness.[13–19]

Symptomatology is evident when the contralateral VA is congenitally atretic or hypoplastic, terminates as the posterior inferior cerebellar artery, or is occluded or stenosed by acquired processes. Neck movement to the ipsilateral side of the compression and neck extension typically intensify symptoms. ATC is widely used due to its availability and speed in obtaining a diagnosis, and when performed with 3D reconstruction, it can clearly show the extent of osteophyte formation and its relationship with the VA, facilitating appropriate surgical planning.[15,20,21]

The treatment of choice for symptomatic compression induced by cervical spondylosis is decompression surgery. There are reports of antiplatelet therapy and other conservative therapies, but they are less effective. Regarding surgical strategies, some authors advocate the resection of non-bony tissues, such as muscle tendon, bone membrane, and other perivascular fibrous bands, in addition to osteophyte removal, to allow the VA to regain its initial caliber.[21–24]

In a recent systematic review of VAS caused by osteophytosis, which evaluated 214 articles on the subject, surgical management with osteophyte resection was achieved in 45% of cases through anterior discectomy with fusion, followed by anterior decompression without fusion (28%), posterior decompression without fusion (21%), and only 3% with posterior decompression with fusion as described in our case.[25]

The posterior surgical approach is indicated for the resection of osteophytes originating from the superior articular facet due to direct visualization of compression and complete resection thereof. We chose to perform arthrodesis of the affected levels in our patient due to the aggressiveness of the decompression and excision of the inferior articular facet of C4 and superior articular facet of C5 to access the vertebral artery located anterior to the nerve root.[17,26,27]

During surgery, we utilized pre- and post-decompression osteophyte ultrasound to assess vascular patency, which proved to be an easy, instantaneous, effective, reliable, and cost-effective procedure, particularly considering the high cost of neuroimaging exams. Additionally, we avoided using electrical bipolar during vertebral artery and venous plexus manipulation to preserve vascularization.[28]

Other surgical approaches may be used depending on osteophyte origin for better visualization and decompression. The anterior approach is suitable for marginal osteophyte resection, typically compressing the VA medially, while the anterolateral approach provides a better operative field for safely removing both superior articular and anterior transverse process osteophytes.[17,26,27]

Solo decompressive surgery preserves the cervical range of motion, which is an important factor in the patient's functional ability to return to daily activities and quality of life. However, some authors report that isolated decompression carries a higher risk of postoperative recompression, leading authors to conclude that fusion is the safer option for patients.[21,29,30]

Conclusion

Compression and insufficiency of the vertebral artery (VA) resulting from cervical spondylosis are relatively uncommon occurrences. Typically, they remain asymptomatic owing to the compensatory function of the contralateral VA. Therefore, patients experiencing persistent vertigo and sudden drop attacks despite normal cardiological evaluations should undergo a thorough examination to investigate the possibility of vertebral artery occlusion and vertebral basilar insufficiency. Precise preoperative evaluation, notably with the aid of 3D angiotomography, becomes imperative to ascertain the optimal approach for decompression.

Conflict of Interests

The authors have no conflict of interest to declare.

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A Rare Case of Drop Metastasis along Lumbar Column of Glioblastoma Multiforme

Um caso raro de metástase em gota ao longo da coluna lombar de glioblastoma multiforme

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Arq Bras Neurocir 2024;43(4):e369–e371.

Abstract

Glioblastoma Multiforme (GBM) is a malignant primary brain tumor. Drop metastasis is an intradural extramedullary spinal lesion that originates from an intracranial site. It is rare to have the incidence of drop metastases in a patient diagnosed with Glioblastoma Multiforme. We present and discuss a case report on a 35-year-old patient treated for GBM who presented drop metastases after the surgical procedure.

Keywords
- Glioblastoma Multiforme
- drop metastasis
- neuroimaging

Resumo

Glioblastoma Multiforme (GBM) é um tumor cerebral primário maligno. Metástase em gota é uma lesão espinhal extramedular intradural que se origina de um sítio intracraniano. É raro ter a incidência de metástases em gota em um paciente diagnosticado com Glioblastoma Multiforme. Apresentamos e discutimos um relato de caso sobre um paciente de 35 anos tratado para GBM que apresentou metástases em gota após o procedimento cirúrgico.

Palavras-chave
- Glioblastoma Multiforme
- metástase em gota
- neuroimagem

Introduction

Glioblastoma Multiforme (GBM) is a malignant primary brain tumor and reaches from 12% to 15% of the intracranial neoplasms.[1] It usually occurs in older patients and has a median survival of 15 months.[2,3] Drop metastasis is an intradural extramedullary spinal lesion that originates from a superior site inside the central nervous system. This is a rare incident and appears in only 1-2% of patients with GBM.[1] The mechanism proposed is tumor extravasation via cerebrospinal fluid, and the likelihood increases with surgical manipulation. Herein, we present a case report on a 35-year-old patient treated for GBM who presented drop metastases along the spinal cord after a surgical procedure.

received
November 3, 2023
accepted
October 21, 2024

DOI https://doi.org/10.1055/s-0044-1795136.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Case Report

A 35-years-old man presented to our neurosurgical department presenting a 1-month behavior changes, memory impairment and heavy bilateral headache. At this moment, the patient was also experiencing nausea, vomiting, phono and photophobia. The physical examination showed presence of palmomental reflex asymmetric at the right while the stimulus was in the left hand; Hoffman's sign and grasp reflex were also present only in the left hand. There was not any other strength, sensibility or reflex alteration and Mini Mental State Examination presented 32 points with deficiency to remember the three words The patient was submitted to magnetic resonance imaging (MRI) that demonstrated a right frontal expansive cystic lesion, which measuring 7.4 cm causing mass effect. The diagnostic suspicion at the time neuroimaging was released was Glioblastoma Multiforme considering the accelerated evolution and the absence of any other malign lesion. As the patient was young, had only 1 lesion and was presenting symptoms of intracranial hypertension, we judged to precede the neurosurgical intervention. Neurosurgical treatment was realized, and the pathological exam diagnosed Glioblastoma Multiforme WHO grade IV. After the surgery, the patient presented strength alteration in the left arm, 4/5, that improved completely after 5 days of recovery; he was referred and initiated radiotherapy with Temodal.

Six months after the first medical appointment, the patient was referred to neurosurgery after falling from their own height, nausea, vomiting, confusion and headache. The physical examination had no alteration. MRI and lumbar puncture were obtained, and infectious hypothesis was excluded. Symptoms were discussed as possible radiotherapy side effects. Approximately 20 days after this episode, the patient evolved with important neck and legs pain, difficulties walking, mental confusion, disorientation, vomiting, and headache. Physical examination findings were ataxic walk, dysmetria and dysdiadochokinesia; inferior members' strength impairment 3/5 and hyperactive tendon reflexes. Further neuroimaging was required, and brain and spine MRI were performed (►**Figs. 1**–**3**). The patient continued to lower the level of consciousness. Neuroimaging identified the possibility of base disease's liquoric dissemination to cerebellar vermis, 9-11th cranial nerves bilaterally and to cervical, thoracic and lumbar spine (drop metastases).

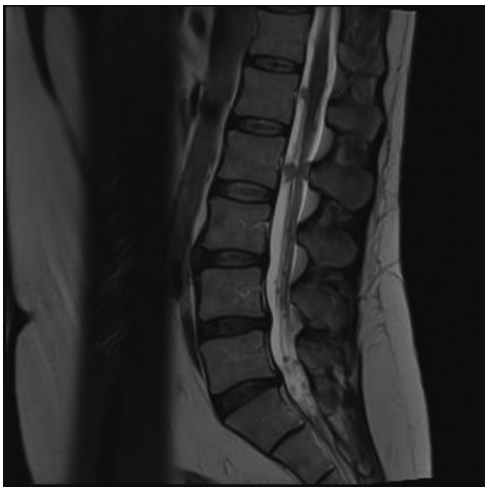

Fig. 1 Sagittal post contrast MRI T1 of the lumbar and lumbosacral spine showing dural lesion at the level of L1 until conus medullaris.

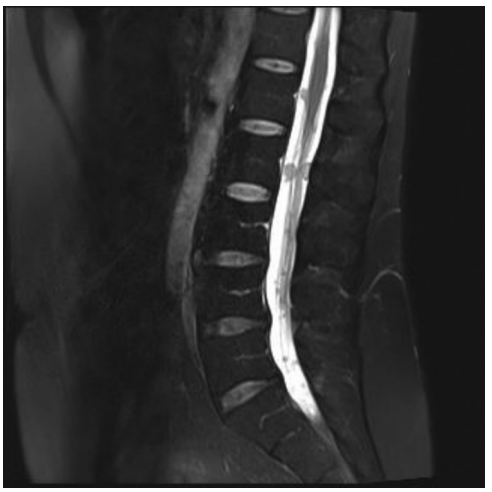

Fig. 2 Sagittal post contrast MRI T2 of the lumbar and lumbosacral spine showing dural lesion at the level of L1 until conus medullaris.

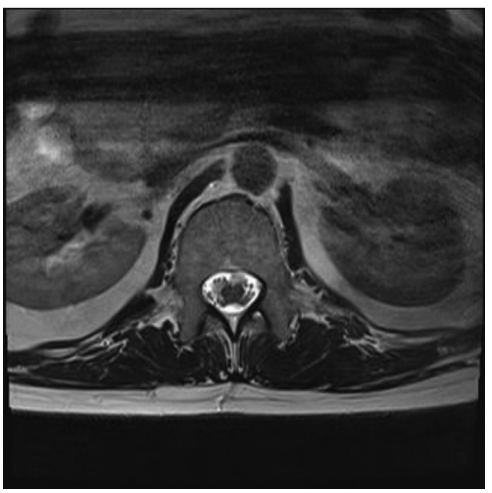

Fig. 3 Axial post contrast MRI T2 of lumbar spine showing dural lesion at level of L1.

Discussion

Glioblastoma Multiforme is the most aggressive diffuse glioma of astrocytic lineage and is classified based on World Health Organization (WHO) as grade 4. GBM is the most common brain and central nervous system (CNS) malignancy, computing 45.2% of malignant primary brain and CNS tumors. The incidence rate reaches 3.19/100,000 patients per year, the median age of diagnosis is 64 years and the survival average is 15 months.[2] Despite treatments, only 5% survive during 5 years after diagnosis.[4] Our patient was 35-years-old, the incidence of GBM in patients with 35-39 years old is

<2%[2] and despite our effort and treatment survived 7 months after the diagnosis, lower than the average. Likewise, we present a rare case for its clinical findings.

It is recognized that approximately 2% of patients who undergo surgical resection of GBM later present spinal drop metastasis.[1] The mechanism proposed is the mechanical rupture of the blood-brain barrier. This affection is considered rare. Our patient was affected by Glioblastoma located in right frontal lobe, but after presented metastases in brain steam, cerebellum and cervical, thoracic and lumbar spine. The most common locations for metastases are lumbar and lumbosacral regions, even if it is rare.[4] In many cases, patients with spinal drop metastasis remain asymptomatic, with pain presented only 25% to 33% of the cases.[1] This is an example of the value of MRI when this type of complaint is seen, as our case reported.

The spinal dissemination of GBM is related with promptly deterioration and the management is primarily palliative.[1] Treatment for metastasis of cerebral GBM is not consensus, the undefined margins turn challenging the surgical resection of intramedullary GBM. Radiotherapy is the most frequently proposed treatment modality, and this treatment is only palliative for a temporary pain decreased but no neurological improvement.[4] After the diagnosis of intramedullary metastases, the survival time diminishes to 3-4 months.

In our case report, we were faced with a patient with a few important symptoms. Our decision to treat right the time when the first MRI was obtained should have increased the survival time and further quality of life for 4 months. However, advancements in detection and therapeutic approaches have resulted in increased survival time and therefore increased detection of extracranial metastases of GBM.[1] At newer manifestations, the patient was undergoing radiotherapy, and the evidence were according to possible side effects. The patient presented affected imaging together with the clinical worsening and with poor physical findings.

Conclusion

Our case reports rare aspects of a patient affected by Glioblastoma Multiforme. This case highlighted the importance of adequate conduct in front of patients who undergo malignant lesions and have minor physical findings. Even with the efforts, GBM continues to be a challenge to neurosurgeons, radiologists, and oncologists.

Conflict of Interest

The authors declare that there is no conflict of interest.

Acknowledgments

The authors received no financial support for the research, authorship and/or publication of this article.

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Thoracolumbar Fractures Due to Speed-humps: A Case Series of Spine Fractures from an Atypical Cause of Injury

Fraturas toracolombares por lombadas: Uma série de casos de fraturas da coluna vertebral por uma causa atípica de trauma

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Arq Bras Neurocir 2024;43(4):e372–e377.

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Abstract

This retrospective case series investigates thoracolumbar fractures resulting from speed humps during bus travel in Rio de Janeiro. The study encompasses 19 patients who experienced such fractures between 2013 and 2021 without collision events. Factors examined included demographics, injury specifics, management strategies, and outcomes. The study aims to elucidate the prevalence, characteristics, and treatment of these injuries. Analyses were conducted using clinical evaluations, AOSpine classification, Visual Analog Scale (VAS) for pain, and TL AOSpine Injury Score (TL AOSIS). Surgical and non-surgical interventions were compared, highlighting the need for strict traffic regulations and preventive measures to mitigate such accidents. Results reveal a predominance of fractures in women, with a mean age of 61.26 years, and an emphasis on L1 vertebra involvement. Surgical intervention was required in over 50% of cases, demonstrating favorable outcomes. However, limitations due to the study's retrospective nature and the tertiary care setting were acknowledged. The study concludes by emphasizing the importance of preventive measures, such as stricter traffic regulations, mandatory seatbelt use in public transportation, and enhanced speed-hump safety measures to curtail these accidents and subsequent injuries.

Keywords

- thoracolumbar fractures
- spinal cord injuries
- speed-hump
- low back pain

Resumo

Esta série de casos retrospectiva investiga fraturas toracolombares resultantes de lombadas durante viagens de ônibus no Rio de Janeiro. O estudo abrange 19 pacientes que sofreram tais fraturas entre 2013 e 2021 sem eventos de colisão. Os fatores

received
October 28, 2023
accepted
October 21, 2024

DOI https://doi.org/10.1055/s-0044-1796659.
ISSN 0103-5355.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

examinados incluíram dados demográficos especificidades da lesão estratégias de tratamento e resultados. O estudo visa elucidar a prevalência características e tratamento dessas lesões. As análises foram conduzidas usando avaliações clínicas classificação AOSpine Escala Visual Analógica (VAS) para dor e TL AOSpine Injury Score (TL AOSIS). Intervenções cirúrgicas e não cirúrgicas foram comparadas destacando a necessidade de regulamentações de trânsito rigorosas e medidas preventivas para mitigar tais acidentes. Os resultados revelam uma predominância de fraturas em mulheres com idade média de 61 26 anos e ênfase no envolvimento da vértebra L1. A intervenção cirúrgica foi necessária em mais de 50% dos casos demonstrando resultados favoráveis. No entanto limitações devido à natureza retrospectiva do estudo e ao cenário de cuidados terciários foram reconhecidas. O estudo conclui enfatizando a importância de medidas preventivas como regulamentações de trânsito mais rigorosas uso obrigatório de cinto de segurança no transporte público e medidas de segurança aprimoradas em lombadas para reduzir esses acidentes e ferimentos subsequentes.

Palavras-chave
- fraturas toracolombares
- lesões da medula espinhal
- lombada
- dor lombar

Introduction

Speed humps are devices placed in the path of traveling vehicles intended to cut down the relatively high rate of in-city motor vehicle accidents. Their main benefit lies in reducing vehicle speed, and thus improving traffic safety for residents and pedestrians in the neighboring area. They are placed predominantly on minor roads, which are both crowded by pedestrians and where vehicles are likely fast cruising. Unfortunately, speed humps are not always built according to regulations and vary from the original designs and can unintentionally cause spinal column injuries.[1–3]

Thoracolumbar traumatic injury ranges from 12 to 50 million patients annually in the United States and fractures in this area account for approximately three-quarters of all spinal fractures.[4,5] The T10-L2 junction is a biomechanical area of susceptibility to fractures due to the transition between the relatively stiff thoracic spine and the flexible lumbar spine. This area corresponds to 50–60% of the thoracolumbar spine injuries.[5,6]

The most common type of fracture that needs surgical intervention is the burst fracture, which is also the most severe of the compression fractures, as it can cause retropulsion of endplate fragments into the spinal canal leading to neurological deficit.[4,5,7] Mechanisms of injury include high-velocity pattern of axial compression as the most common, such as falls from height, motor vehicle crashes, pilot ejection, parachute jumping, vertical acceleration and sports impacts.[4,5,8]

The most common population of general thoracolumbar fractures is young adults and adolescents between 15–29 years.[5] Younger patients are more likely to have a high-energy spinal cord injury associated with other organ lesions, and elderly individuals are more susceptible to low-energy mechanisms such as low fall. However, both groups have their morbidity to be a burden to the society.[6]

The mechanism of these fractures was well described by Munjin et al.[3] A torque is generated when the vehicle rises while passing over the speed hump, and the magnitude of this force is determined by the speed at which the vehicle impacts the device and the distance between its application point and the axis of the wheel that remains in contact with the road. The torque then generates a catapult effect on the vehicle's suspension system and, as a result, the passenger elevates suddenly from his seat, falling back abruptly and hitting the seat shortly because of gravity, generating an axial force that is then absorbed by the spine, explaining the fact that all of the patients in this series presented compression fractures.

The lap-shoulder belt in association with airbags reduced the incidence rate of these injuries,[6] however the extent of these protection gadgets does not go further as they are not well established for public transportation.[3]

There are only three studies that report a case series of this type of injury,[1–3] since it's a recognized cause of spine fracture and chronic low back pain. We now present a series of cases of thoracolumbar fractures caused by vertical dislocation in patients on bus seats in the city of Rio de Janeiro.

Methods

This study is a single-center, retrospective, consecutive case series review performed at the Division of Neurosurgery of Gaffrée and Guinle University Hospital (HUGG), Federal University of the State of Rio de Janeiro. HUGG's Research Ethics Committee approved the study and dismissed the application of the Free and Informed Consent Term, as the study consists of a retrospective review of data collected from previously operated patients' charts. Preferred Reporting of Case Series in Surgery (PROCESS) guidelines were followed.[9]

Our sample is composed of 19 patients who suffered thoracolumbar fractures during bus travels in the period between 2013 and 2021, without any collision event. We registered age, sex, comorbidities, date of injury, type of treatment, presence of radicular pain, ASIA score before and after treatment,[10] AOSpine thoracolumbar spine injury classification,[11] levels of injury, Thoracolumbar AOSpine Injury Score (TL AOSIS)[12] and Visual Analog Scale (VAS) score[13] of all the patients and evaluated them 2 weeks, 3 months,

6 months, 12 months, and 24 months after the surgery or the first use of the Putti vest. Each patient management was based on the findings of each case: stable fractures were treated with analgesics, orthoses (Putti vest), and mild rest for 3 months; unstable fractures (AO spine fracture types A3 and A4) received surgical intervention with spinal decompression and arthrodesis; and patients with important refractory pain after 3 months of conservative treatment received kyphoplasty.

Statistical analyses were performed using the Python programming language (Python Software Foundation, Delaware, USA). Outcome variables were assessed before and after the intervention, using the Wilcoxon test or paired *t*-test as appropriate. The rank biserial correlation (RBC) was calculated for each relationship, with values from 0.2 to 0.5 considered a mild association, 0.5 to 0.8 a moderate association, and above 0.8 a strong association. A p-value < 0.05 was used as statistically significant and a 95% confidence interval and standard deviation were calculated when appropriate.

Results

The results obtained are summarized in ►**Table 1**. All our patients were evaluated using clinical and imaging exams, in which none presented any kind of myelopathy, any motor deficit, M1 modifier on the AOSpine classification, or a TL AOSIS greater than 5. None of the patients were bus drivers and all of them were sitting on the bus bench during the accident, without the use of seat belts. All patients reported that their lumbar pain began after the bus drove by a speedbump at high speed.

Among the sample, 17 (89.47%) patients were women, and the ages ranged from 33 to 82 years (mean age of 61.26 years $\pm$ 11.2). Of all the patients, only two (10.52%) had a second thoracolumbar fracture on another date by the same cause, and of those one (5.26%) had conservative management on the first trauma and surgical management on the second, and the other needed surgery on both events. Concerning the management choice, ten (52.63%) individuals

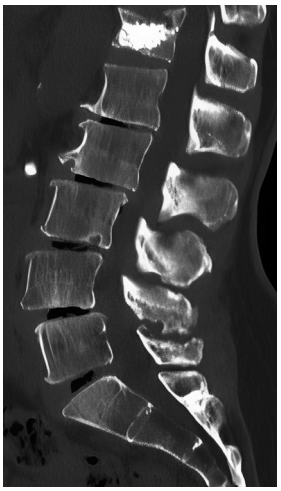

Fig. 2 Patient 19: CT scan showing the intravertebral cement in the T12 vertebra.

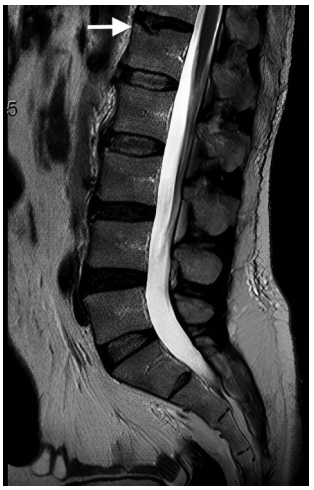

Fig. 3 Patient 13: T2-weighted MRI showing an A1 fracture of the L1 vertebra (white arrow).

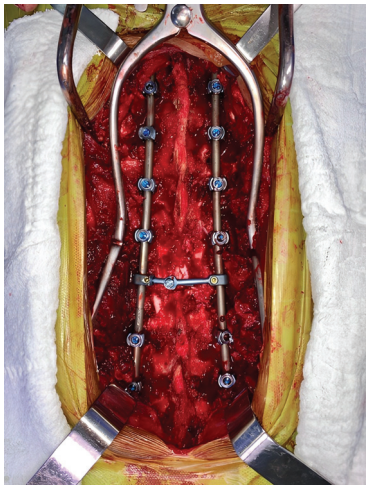

Fig. 1 Patient 2: intraoperative picture of T10-L3 transpedicular arthrodesis.

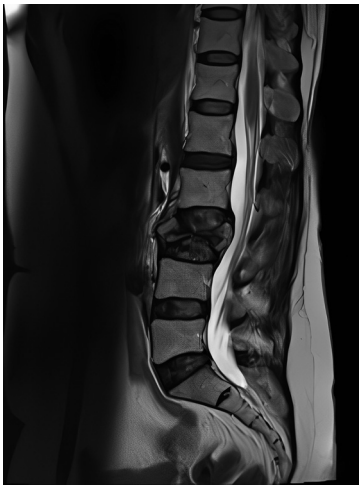

Fig. 4 Patient 14: T2-weighted MRI showing an A4 fracture of the L3 vertebra.

Table 1 Patient Demographics and Trauma Characteristics

Name	Age	Sex	Date of Trauma	Comor-bidities	Type of Treatment	Type of Surgery	AOSpine thoracolumbar spine injury classification	TL AOSIS	Fracture Level	Radiculo-pathy	AVS before treatment	AVS after 2 weeks of surgery	AVS after 3 months of intervention	AVS after 6 months of intervention	AVS after 12 months of intervention	AVS after 24 months of intervention
Patient 1	67	F	2017	HBP and Osteopenia	Surgical	Kyphoplasty	A2N0M2	2	T11	No	10	1	3	3	3	1
Patient 1	67	F	2019	HBP and Osteopenia	Conservative	–	A1N0M2	1	T12	No	8	–	5	2	2	1
Patient 2	58	F	2018	–	Surgical	T10-L3 Arthrodesis	A3N0	3	L1	No	10	2	2	3	3	3
Patient 3	66	F	2013	HBP	Surgical	Kyphoplasty	A1N0M2	1	T11	No	10	3	1	1	1	1
Patient 3	66	F	2016	HBP	Surgical	T10-L2 Arthrodesis	A4N0M2	5	L1	No	10	3	1	1	1	1
Patient 4	82	F	2017	Osteopenia	Conservative	–	A2N0M2	2	L2	No	9	–	5	2	0	0
Patient 5	64	M	2017	–	Surgical	Kyphoplasty	A1N0	1	L2	No	10	4	3	2	2	1
Patient 6	62	F	2017	–	Surgical	L3-L5 Arthrodesis	A1N2	3	L4	Left (L4)	8	4	3	4	4	3
Patient 7	69	F	2015	HBP	Conservative	–	A2N0M2	2	L3	No	9	–	4	4	4	2
Patient 8	71	F	2013	DM	Surgical	Kyphoplasty	A1N0M2	1	L2	No	8	3	2	2	2	1
Patient 9	57	F	2018	–	Conservative	–	A2N0	2	T11	No	10	–	5	1	1	1
Patient 10	56	F	2019	–	Conservative	–	A2N0	2	T12	No	10	–	6	2	2	1
Patient 11	64	F	2020	–	Conservative	–	A1N0	1	L2	No	7	–	3	0	0	0
Patient 12	68	F	2019	–	Conservative	–	A2N0	2	L1	No	8	–	4	1	1	0
Patient 13	60	F	2020	–	Conservative	–	A1N0	1	L1	No	5	–	3	3	3	2
Patient 14	33	F	2014	–	Surgical	L2-L4 Arthrodesis	A4N2	5	L3	Right (L3)	9	3	1	1	1	1
Patient 15	36	F	2016	–	Conservative	–	A2N0	2	T11	No	8	–	4	0	0	0
Patient 16	74	M	2018	HBP	Surgical	T11-L3 Arthrodesis	A3N0	3	L1	No	9	4	4	2	2	2
Patient 17	59	F	2020	DM	Conservative	–	A2N0M2	4	T10	No	8	–	4	1	0	0
Patient 18	57	F	2020	HBP	Surgical	T11-L3 Arthrodesis	A1N0M2	1	L1	No	10	2	1	0	0	0
Patient 19	61	F	2021	–	Surgical	Kyphoplasty	A2N0	2	T12	No	7	3	2	1	1	1

needed surgical treatment which varied between arthrodesis ($n = 6$, 31.58% - ►**Figure 1**) and kyphoplasty ($n = 5$, 29.41% - ►**Figure 2**).

The 2 most frequent AOSpine thoracolumbar spine injuries of all the 21 fractures evaluated were the split/AO type A2 ($n = 9$, 42.86%) and wedge compression/AO type A1 ($n = 8$, 38.1%) fractures (►**Figure 3**), followed by incomplete burst/AO type A3 ($n = 3$, 14.29%) and burst/AO type A4 ($n = 1$, 4.76% - ►**Figure 4**), and concerning the level of the fractures we found that the most injured vertebra was the L1 ($n = 6$, 28.57%), followed by T11 ($n = 4$, 19.05%), L2 ($n = 4$, 19.05%), T12 ($n = 2$, 9.52%) and L3 ($n = 2$, 9.52%), T10 ($n = 2$, 9.52%) and finally L4 ($n = 1$, 5.26%). Of the two (10.53%) patients that had two subsequent fractures, one had formerly an A2 and later A1 fractures of the T11 and T12 vertebrae, respectively, and the other one had an A1 fracture at first and an A4 injury on the second event of the vertebrae T11 and L1, also respectively.

To better understand the pain manifestations of each patient, we evaluated the presence of radiculopathy and the affected root and used VAS to measure pain. Only 2 (10.53%) patients had radiculopathy after the trauma (AOSpine N2), which improved right after the surgical procedure. Since two of our patients had two fractures on different occasions, we evaluated twice their VAS, so considering 21 VAS evaluations, we had a mean score of 8.71 ± 1.31 before intervention, 2.91 ± 0.9 after 2 weeks of surgical procedure (in those operated - $n = 11$), 3.14 ± 1.46 after 3 months of intervention, 1.71 ± 1.16 after 6 months of intervention, 1.57 ± 1.26 after 12 months of intervention and 1.05 ± 0.89 after 24 months of intervention.

None of the patients had an additional injury to the tension band (modifier M1) and eight patients (42.11%) had an M2 modifier (presence of co-morbid condition). Using the TL AOSIS, we found that considering 21 fractures, we had a mean score of 46 ± 1.22, in which 3 patients (14.29%) had a score between 4 and 5, and 85.71% had a score lower than 4 points.

Discussion

In Brazil, all speed bump implementation needs to be approved by the National Transit Council (Conselho Nacional de Trânsito - CONTRAN). Since 1998 all speed bumps have been forbidden by law and built only in specific situations and with the authorization of CONTRAN following a list of specifications so that the device can be safely used in traffic.[13] Unfortunately, they are not always built according to regulations, and vary from the original designs, and can unintentionally cause accidents, including spine injuries. Another problem that Brazilian traffic faces is that the installation of seat belts is not obligatory in vehicles that allow passengers to ride standing, like most of the public buses in Brazil.[14]

The most common population of general thoracolumbar fractures is young adults and adolescents between 15–29 years.[5] However, when we look at the other studies regarding specifically speed bump fractures,[1–3] Mujin et al.[3] found a mean age of 48.5 years and in our series, we observed that our mean age was 61.26 and the youngest patient was 33 years. The literature usually finds a slightly greater incidence in men,[5,6,16] although when speed humps injuries are investigated, Munjin et al.[3] and our study found a greater incidence in women, 80.4% and 88.2% respectively. We believe that this divergence from the general causes is due to the risk factors involved, that increase the incidence of fractures in this setting since most of the patients are postmenopausal women, a group that has a greater predisposition to fractures from low energy traumas.[17]

It is important to note that none of our patients was the bus driver and that all of them were sitting on a bus. Workers who stay too long seated and are subjected to vibrations from a vehicle ride have an increased risk factor for cervical and lumbar pain and spine degeneration. It is estimated that 80.5% of bus drivers experience some kind of back or neck pain, without any assistance or type of rehabilitation, unfortunately, there has never been a study to quantify and investigate degenerative spine diseases in this group of patients.[18,19] Following Mujin et al. line of work, we can theorize that bus drivers don't usually have this kind of fractures because they are seated on the place with the least torque inside a bus during the accident.[3]

Regarding the most vulnerable vertebra, L1 is found to be the most fractured in thoracolumbar traumas in both high and low-energy situations. Katsuura et al, Li et al and Munjin et al found, respectively, 34.4%, 35.6%, and 44.2% cases of L1 fracture in their studies, being the most common site of fracture.[3,6,7] This was also the most common fracture in our series, representing 28.57% of our cases. Regarding the type of AOSpine fracture, our study observed that a split/AO type A2 fracture was the most common (42.86%) but not significantly different from the wedge compression/ AO spine type A1 fractures (38.1%), Munjin et al found that the A1 fracture was the most common in their study, with an incidence of 57.7%.[3] Comparatively, Katsuura et al found that the incomplete burst/AO type A3 fractures were the most common morphology 39.50%.[7] We believe that since our work and the one from Munjin et al study low-energy fractures, we would find injuries that needed more conservative management, and since Katsuura et al evaluate other types of injuries, they would find more severe fractures that needed surgical treatment.[3,7] It is also worth pointing out that despite 4 of our patients having more than 50% of their vertebral body collapsed, only two patients had sensitive manifestations, represented as radiculopathy.

The management of thoracolumbar injury is controversial but some cases require surgical approaches, which happened in 52.63% of our sample.[3,5,16,20] We treated them following some criteria: A3 or A4 fractures were submitted to spinal decompression and transpedicular arthrodesis (4 levels in 3 patients and 2 levels in the rest), accordingly to each patient and fracture level, and following the load-sharing classification[21,22]; and patients with A1 or A2 fractures with important refractory pain after 6 months of conservative treatment received kyphoplasty. Only one patient treated surgically needed a new approach, she received a kyphoplasty initially, and after 3 years she had a new fracture and was submitted to posterior arthrodesis. Munjin et al. study observed that 21.7%

of their patients were submitted to surgery, including patients with A2 fractures who were surgically treated to avoid the risk of pseudoarthrosis, as a result of disc herniation into the vertebral body, unfortunately, it is not known if any patient treated initially conservatively needed surgery in the follow-up.[3] We compared our patients' management with the proposed by the TL AOSIS and observed that our study agreed with the suggestions based on the patient's score.

At the first evaluation, we had a mean score of 8.71 regarding all patients, and after 3 months we found a score of 2.91 in the group submitted to surgery ($n = 11$) and 4.3 in the conservative group ($n = 10$). After 12 months, we observed a mean VAS score of 1.82 in the surgical group ($n = 11$) and 1.3 in the conservative one ($n = 10$). When compared, the intervention group had a faster and greater recovery compared with the conservative group, demonstrated by the effect size of 0.56 (moderate association) when comparing these data, which may cause the early return to work and impact better recoveries with increased life quality.[3] As far as we know, this is the first study that quantifies pain and uses the AVS to evaluate it.

Our study is not free of limitations, since our study is inherently limited by its small sample and its retrospective nature, burdening the formulation of hypotheses and associations between variables. Another problem we faced is that our hospital is a tertiary care facility without an emergency room, and all patients are referred from other specialties or hospitals, a fact that can explain the number of patients we treated with this condition since we believe there are even more individuals with thoracolumbar fractures in Rio during public transport.

Conclusion

Regarding the pain, the results in surgical and non-surgical cases were satisfying. We could also better understand an important cause of thoracolumbar fractures in which ~50% of patients will need neurosurgery. However, the most important "treatment" is the prevention of these accidents with quality work of the government with safer and stricter traffic rules, including the obligation of seatbelt use in public transportation, better signaling for the decrease of speed limit violations, and the inspection of speed-humps.

Conflict of Interest

None.

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Information Note regarding: Correspondence to "Intracranial Pressure Monitoring and Unfavorable Outcomes" Arq Bras Neurocir 2023; 42(3): e266–e268

Nota informativa referente: Correspondência para "Monitorização da Pressão Intracraniana e Desfechos Desfavoráveis" Arq Bras Neurocir 2023; 42(3): e266–e268

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Arq Bras Neurocir 2024;43(4):e378–e380.

Below is a clarification note regarding the recently published letter in Lancet Neurology titled "Thank you very much, SYNAPSE-ICU." We have received criticism for our letter and want to address any misunderstandings it may have caused.

We want to clarify that we are the main advocates of intracranial monitoring, and any suggestion to the contrary is false. At no point in our letter did we state that the AMIB or any other society class representative did not recommend ICP monitoring. The editorial board of Lancet Neurology had to remove some excerpts from our letter due to word count constraints, but this does not change our message.

As Rojas et al. state, Brazil is a big country with almost European dimensions, and medical conduct has several differences. We believe such differences cannot exist, especially concerning ICP monitoring. Such a privilege should not be for a few services but for the entire population.

We aim to draw health managers' attention to the importance of using intracranial monitoring catheters, especially in the public health network. We believe every patient has the right to ICP monitoring, and we will not rest until this becomes a reality. Furthermore, we hope this clarification note will set the record straight and show our commitment to advocating for better healthcare. Below is the transcript originally sent to Lancet Neurology to clarify any disagreements.

Thank you very much, SYNAPSE – ICU

In underdeveloped countries, intracranial pressure monitoring may be considered a luxury item. Unfortunately, in the public health network, which covers a large portion of the population, the management of intracranial hypertension in acute neurological situations is practically based on radiological findings.[1] However, these findings do not present a direct correlation with the occurrence of intracranial hypertension. This fact has been known since the 1980s. Even more serious is knowing that it has been well established, for more than 60 years, that there is a direct relationship between intracranial hypertension and death. Nevertheless, studying the waveform's compliance is essential to predicting earlier brain changes.[1,2]

Many public and private health authorities have recently used The BEST Trip Trial as a theoretical and dogmatic basis for not including intracranial pressure monitoring technology in managing neurocritical patients in our country3. Despite being published in a high-impact journal, The Best Trip Trial study has significant limitations. This work was the object of various criticisms and raised controversies of all

DOI https://doi.org/10.1055/s-0044-1795137.
ISSN 0103-5355.

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kinds.[4] The study was not designed to assess intracranial pressure monitoring; its objective was to analyze two approaches to the same problem: intracranial hypertension. Despite being a beautiful job, there were interpretation distortions by local managers, and it does not make sense that all non-invasive and invasive technology available nowadays is unused. Multimodal monitoring is recommended in critical care patients.[1,2] The recent publication of SYNAPSE-ICU opens our horizons for local managers to include this technology as the minimum necessary for the care of the neurocritical patient. More important than diagnosing intracranial hypertension, knowing what to do with this parameter is what changes outcomes.[4,5]

We believe the monitoring register would be of value to neurocritical patients in several circumstances. Its advantages are affordability, efficiency, and simple and practical handling and it is used to better understand the natural history of the patient's disease. Many thanks to Lancet Neurology and the team involved in this work.

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ISSN 0103-5355

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