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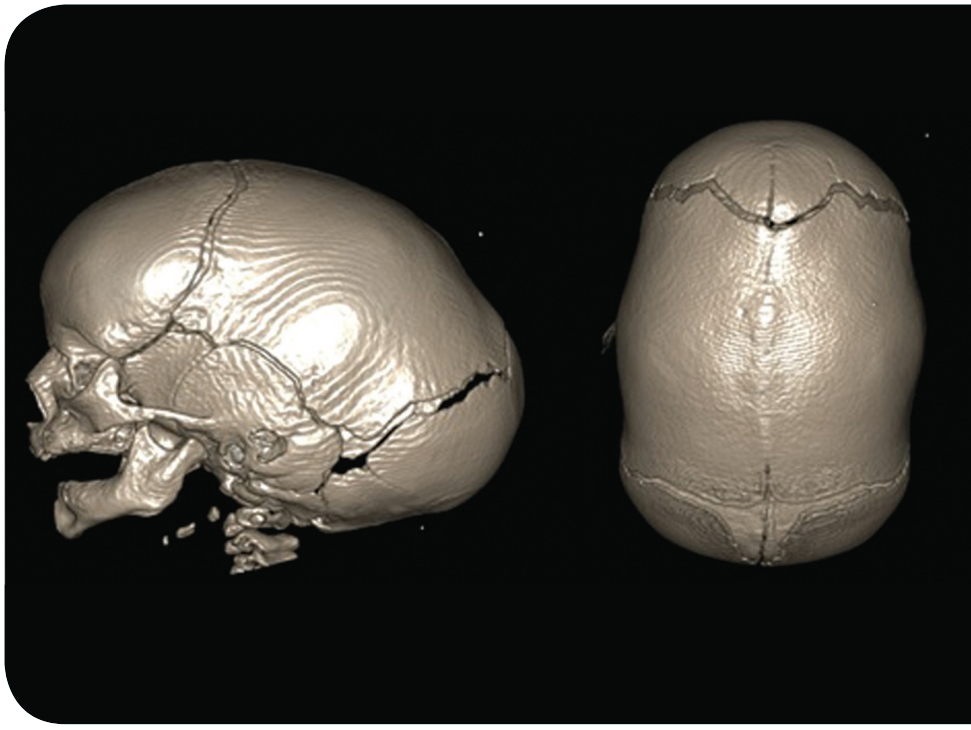

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Translation and Cross-Cultural Adaptation of the Florida Surgical Questionnaire for Parkinson Disease (FLASQ-PD)

Tradução e adaptação transcultural do questionário Florida Surgical Questionnaire for Parkinson Disease (FLASQ- PD)

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Abstract

Introduction Parkinson's disease is the most frequent progressive neurodegenerative pathology among movement disorders. To facilitate the diagnosis, referral and subsequent treatment of the patient, the Florida Surgical Questionnaire for Parkinson's disease (FLASQ-PD) was created, which elects parkinsonian patients to undergo surgical treatment.

Objective To perform the translation, cross-cultural adaptation, and content validation of the FLASQ-PD into Portuguese.

Materials and Methods The process of translation and cross-cultural adaptation consisted of the stages of translation, evaluation by an expert committee, pre-tests, content validation, back-translation, and final analysis.

Results Regarding the evaluation of the expert committee, 8 of the 10 suggestions were accepted for modifications that would not alter the original structure of the article. Four questions and two response items were modified in the pretests. All items were valid to measure the domain that was intended in content validation. There were no discrepancies between the original instrument and the back-translated version into

Keywords
- Parkinson disease
- diagnostic techniques
- neurology
- deep brain stimulation
- validation study

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English, and the final analysis showed that the instrument has objectivity, coherence, ease of application, and intercultural similarity when compared with the original.

Resumo

Introdução A doença de Parkinson é a patologia neurodegenerativa progressiva mais frequente entre as desordens do movimento. Com o objetivo de facilitar o diagnóstico, a referência e o posterior tratamento do paciente, foi criado o Florida Surgical Questionnaire for Parkinson Disease (FLASQ-PD), que elege pacientes parkinsonianos para realização de tratamento cirúrgico.

Objetivo Realizar a tradução, adaptação transcultural e validação de conteúdo do FLASQ-PD para a língua portuguesa.

Materiais e Métodos O processo de tradução e adaptação transcultural constou das etapas de tradução, avaliação por comitê de especialistas, pré-testes, validação de conteúdo, retrotradução e análise final.

Resultados Sobre a avaliação do comitê de especialistas, foram aceitas as modificações que não alterariam a estrutura original do artigo, 8 das 10 sugestões. Quatro questões e dois itens de resposta foram modificados nos pré-testes. Todos os itens foram válidos para medir o domínio que se pretendia na validação de conteúdo. Não houve discrepâncias entre o instrumento original e a versão retrotraduzida para o inglês, e a análise final mostrou que o instrumento possui objetividade, coerência, facilidade de aplicação e similaridade intercultural quando comparada com o original.

Palavras-chave

- doença de Parkinson
- técnicas de diagnóstico
- neurologia
- estimulação cerebral profunda
- estudo de validação

Introduction

Parkinson's disease (PD) is a neurodegenerative, progressive, and the most frequent pathology of the movement disorders. Its development occurs in the 55-to-65 years age group, affecting 1 to 2% of the population over 60 years.[1] The prevalence corresponds to ~ 100 to 150 cases per 100 thousand inhabitants, and the incidence is ~100 to 200 new cases per 100 thousand inhabitants.[2] Symptoms such as resting tremor seen in one or both hands, less observed in chin, lips, tongue, and feet, bradykinesia, stiffness, and postural instability are part of the syndromic picture. Parkinson's disease requires an early diagnosis and treatment, because of its degenerative character.[3] Therefore, it is important to note that chronic diseases are best managed by specialists, due to the possible unusual presentations and specific therapy.[4]

There are several drug therapies for PD, with the most frequent and effective choice being levodopa, which is, generally, well tolerated by patients. When the patient develops any medication-related complications or even has a decrease in its effectiveness due to the evolution of the disease, its clinical management can represent a challenge.[5,6] For these cases, the surgical treatment known as deep brain stimulation (DBS) has been increasingly recommended, as it is a safe and effective treatment for some patients with refractory PD[7]. Another type of minimally invasive surgery for these cases is brain radiofrequency ablation, which consists of the precise and localized application of radiation in a targeted area of the brain affected in PD, usually administered in a single dose. This procedure destroys tissue that produces abnormal chemical or electrical impulses that cause tremors and other symptoms of PD.[8,9] A lesion of the globus pallidus, called pallidotomy, is the most common ablative surgery for PD. Deep brain stimulation emerged in a context of greater pathophysiological knowledge and development of stereotaxic methods and electrical neurostimulation. The surgical technique consists of placing one or more electrodes that are connected to an electrical pulse generator device to modulate neural signaling within a specific region. In PD, the target regions are usually the subthalamic nucleus and the globus pallidus internus, areas that are affected in the disease pathophysiology.[7,10–12]

There is no consensus in the literature about the best time to submit the patient to surgical treatment. Deep brain stimulation is the standard of care. This predilection is due to reversibility of the method, as well as the possibility of outpatient adjustment and few side effects; Nonetheless, there are few studies comparing the ablative techniques to this procedure.[11–13] Several forms of evaluation of these patients are being elaborated; however, its use is restricted to specialists, which results in a deficit in primary care for these patients.[4] Moro et al. demonstrate in their study that ~ 63% of patients referred to DBS were not eligible for surgical treatment, highlighting the need to optimize the preselection of candidates for DBS.[14] To make not only the diagnosis more objective, but also the reference and subsequent treatment of patients, the Florida Surgical Questionnaire for Parkinson Disease (FLASQ-PD) was created to elect PD patients for surgical treatment by DBS.[14,15]

The FLASQ-PD is a five-section questionnaire: a) criteria for the diagnosis probable idiopathic PD; b) potential contraindications to DBS; c) general characteristics of the patient; d) Favorable/unfavorable characteristics; and e) subscores on

the use of medications. The score on this scale points out that higher scores would indicate better candidates for DBS therapy. The best score in the FLASQ-PD is 34 with no alarm signals and the worst result is 0 with 8 alarm signals. When present, the alarm signal automatically indicates that the patient in question presents a high risk of surgical complications.[15]

However, the FLASQ-PD was elaborated based on the North American reality, and like other questionnaires, its translation requires cultural adaptation for application in Brazil. The procedures adopted in this process must be careful, since translation and adaptation are so important for the consolidation of a new instrument in other countries.[16] This adaptation can contribute to the realization of cross-cultural studies that can bring greater clarification and understanding about the frames in study and its specificities in different languagesand cultures.[17] Moreover, it can allow the comparison of different populations and the exchange of information without bias cultural and linguistic barriers.[18]

Faced with the need for objective methods to evaluate the indication for surgical treatment of PD, which facilitates not only the referral of patients to surgical therapy but also the comparison of the Brazilian casuistry with the international one, the present work aimed to carry out the translation and cross-cultural adaptation of the FLASQ-PD.

Materials and Methods

Study Design

A qualitative study of translation and adaptation was performed, with subsequent cultural validation for the Portuguese language. The translation process and cross-cultural adaptation followed the model proposed by Guillemin et al. and Borsa et al.[16,19] It consisted of the stages of translation, technical, semantic and conceptual evaluation (committee of experts), evaluation by the target audience (pretests), content validation, back-translation, and final analysis. The study sample was composed of 28 physicians evaluators chosen by convenience, including general practitioners, neurologists, neurosurgeons, and geriatricians. The sample size was calculated according to Guillemin et al..[16]

Translation

In this phase, the purpose was to obtain a version in Portuguese, linguistically correct and equivalent to the original version. Two translators, who are native Portuguese speakers and fluent in English, translated the questionnaire, resulting in two versions in Brazilian Portuguese. Then, reconciliations were made, and the content was analyzed and compressed into the first version in Portuguese with the researchers' participation.

Technical, Semantic, and Conceptual Evaluation (Expert Committee)

The proposed version was subjected to a critical evaluation by a committee of experts, formed by four neurologists/neurosurgeons selected for convenience, who evaluated the items of the instrument in terms of content, technical, linguistic, and semantic aspects of each item, in addition to the adequacy of the instrument. The objective of this phase was to obtain semantic, idiomatic, experiential and conceptual equivalence between the original version and the synthesis of the translations. This assessment was made through individual analysis and, later, collectively through discussions between the members of this experts panel.

Evaluation by the Target Population (pretests)

This stage of the process aimed to verify that the items, instructions, and response scale were understandable to the target audience.[19] Potential users of the questionnaire in question are doctors who deal with PD in their clinical practice, but who are not necessarily subspecialists in movement disorders. The translated and adjusted version by the expert committee was evaluated by geriatricians and/or general neurologists. The analysis was performed through successive pretests in which a dichotomous scale was used, with "C" for understandable items and "NC" for non-understandable items. This process aimed to investigate if the instructions and terms in the items and expressions were, respectively, clear, appropriate, and corresponded to those used in the routine of the clinical practice.[19] The questions with a "non-comprehensible" index higher than 15% were modified, and other pretests were performed until the entire questionnaire reached 100% comprehension.

Content Validation

The evaluation of this phase focused on analyzing the clarity, theoretical relevance and practical relevance of the items and included a new panel of specialists composed of neurosurgeons and neurologists. A 5-point Likert scale was used to judge the criteria by scoring them from 1 to 5, according to which 1 = strongly disagree, 2 = disagree, 3 = neither agree nor disagree, 4 = agree, and 5 = strongly agree; a box of suggestions was also placed for the evaluators if necessary. The items that did not reach 80% agreement between the evaluators (content validation coefficient [CVC] < 0.8) were modified, while the other items were left for the researchers to decide whether to accept the suggestions made.

Back-translation

To identify words that were not clear in Brazilian Portuguese, as well as inconsistencies and conceptual errors, a native English translator performed the back translation. The result was compared with the original questionnaire and the differences found were debated among the researchers to originate the partial Portuguese questionnaire version.

Final Analyses

The instrument was assessed for applicability and understanding, for which the researchers were able to call the committee of experts again and/or request the evaluation of the original author. After discussion, the final version of the adapted translation of the FLASQ-PD into Brazilian Portuguese was obtained.

Results

Participants

Of the 28 participants, among generalists, general neurologists, geriatricians, and neurosurgeons, 6 were eliminated for not responding to the instrument as instructed by the researchers. Thus, 22 physicians made up the final sample (14 professionals participated in the pretest, 4 were part of the expert panel A, and 4 were part of the expert panel B). The average time for reading and evaluating the questionnaire was 30 minutes. Most participants were female (59.09%). The group included professionals from the North, Northeast, and Southeast of Brazil.

Cross-cultural Translation and Adaptation

The two translations performed were synthesized in a single initial version by the researchers. This questionnaire was evaluated by the expert committee regarding technical aspects, content, language, and semantics. The composition of the expert panel A was three neurologists and a neurosurgeon, all subspecialists in movement disorders.

There was disagreement in 10 points of the questionnaire, the suggested changes included approximation of the language to the terms used in Brazilian medical practice, as well as replacement of words translated by others with a meaning equivalent to the original word and the withdrawal of drugs that are not used in Brazil. Nine suggestions given by the evaluators were accepted (►**Table 1**), two modifications could not be made as that would alter the structure of the original questionnaire, which is outside the scope of this work.

Evaluation by the Target Population (pretests)

The first pretest was performed by a group of seven neurologists without subspecialty and geriatricians, numbered from 1 to 7. There were disagreements on nine questions and five answer items. Most of the suggestions concerned the use of clearer synonyms, to make the language more accessible and objective. Four questions and 2 response items were modified, corresponding to the disagreeing items by more than 15% of the group (1.05 of the evaluators). (►**Table 2**)

The second pretest counted with the participation of a new group formed by 7 doctors, all neurologists without subspecialty, numbered from 8 to 14. There was disagreement in 2 questions and 10 answer items for the evaluators. The suggested changes included corrections of concordance, symbols, and exchanges for synonyms. Suggestions of nominal agreement and uniformity in the writing of symbols were accepted by the researchers, but there were no major changes, since none of the items and questions reached 15% of the total number of evaluators. Thus, the pretest step was completed, giving rise to a new version of FLASQ-PD.

Content Validation

This phase was performed by a new panel of specialists (B), formed by three neurosurgeons and a neurologist, who sought to analyze the clarity, theoretical relevance, and practical relevance of the items. All items were relevant to represent the domain they intended to measure, that is, there was an agreement between the evaluators of 80% or more for all items (►**Table 3**). Thus, the researchers chose not to modify the questionnaire after this analysis.

Back translation

The back-translation of the study version of the FLASQ-PD was performed and compared with the original instrument. With the equality of languages, no discrepancies were seen between the modified terms and the equivalence of meaning was maintained in every questionnaire.

Table 1 Results after evaluation by the expert committee

Original version	First translation	Modified version
"excellent response (70–100%) to levodopa"	"resposta excelente (70–100%) à levodopa"	"resposta excelente à levodopa"
"memory difficulties or frontal deficits"	"queixas de memória ou déficits cognitivos frontais"	"queixas de memória ou disfunções frontais"
"severe depression with vegetative symptoms"	"depressão grave com sintomas vegetativos"	"depressão grave com sintomas de somatização"
"trial of Sinemet* (carbidopa/levodopa or Madopar or equivalent)**	"teste terapêutico com Sinemet (carbidopa/levodopa ou levodopa + benserazida ou equivalente)"	"já fez uso de Carbidopa/Levodopa ou levodopa +b enserazida?"
"trial of dopamine agonist"	"teste terapêutico com agonista dopaminérgico"	"já fez uso de agonista dopaminérgico? (exceto os agonistas de liberação prolongada)"
"trial of either tolcapone or entacapone"	"teste com tolcapona ou entacapona"	"já fez uso de entacapona?"
"trial of a combination of Sinemet or equivalent with a dopamine agonist"	"teste terapêutico de combinação de Sinemet ou equivalente com agonista dopaminérgico"	"teste de carbidopa/levodopa ou levodopa + benserazida ou equivalente com agonista dopaminérgico"

Notes: *Sinemet is manufactured by Merck Sharp & Dohme, New York, NY, USA. **Madopar is manufactured by Roche Holding AG, Basel, Switzerland.

Table 2 Results after pre-tests

Original version	Postcommittee version of experts	Modified version
"...meets the UK Brain Bank Criteria"	"...preenche os critérios clínicos da 'UK Brain Bank'"	"...preenche os critérios clínicos do 'UK Brain Bank'"
"Postural instability not caused by primary visual, vestibular, cerebellar, proprioceptive dysfunction"	"Instabilidade postural que não seja justificada por déficit visual, disfunção vestibular, cerebelar ou proprioceptiva"	"Instabilidade postural que não seja justificada por déficit visual, vestibular, cerebelar ou proprioceptivo primário."
"On-off fluctuations (medications wear off, fluctuate with dyskinesia and akinesia)?"	"Flutuações "on-off" (diminuição do efeito das medicações, flutuações com discinesia e acinesia)?"	"Flutuações "on-off" (diminuição do efeito da medicação antes do horário da próxima dose)?"
"Gait freezing"	"'Freezing' da marcha"	"Congelamento da marcha"
"Swallowing function"	"Disfagia"	"Deglutição"
"severe depression with vegetative symptoms"	"depressão grave com sintomas de somatização"	"depressão grave com sintomas somáticos"
"Trial of dopamine agonist"	"já fez uso de agonista dopaminérgico? (exceto os agonistas de liberação prolongada)"	"já fez uso de agonista dopaminérgico? (exceto os agonistas de liberação prolongada). Ex.: pramipexol, ropinirol.
"Trial of a combination of Sinemet or equivalent with a dopamine agonist"	"Já fez uso da combinação de carbidopa/levodopa ou levodopa + benserazida ou equivalente com agonista dopaminérgico?"	"Já fez uso da combinação de carbidopa + levodopa ou levodopa + benserazida ou equivalente com agonista dopaminérgico?"

Final Analysis

Ather evaluation and analysis by the members of the expert committee (panel of experts A) about the terms used, questions applicability, and facility use of the scale, the translated instrument was judged as applicable and coherent, considering that it will be used, mostly, by neurologists and geriatricians.

Discussion

The adaptation of a foreign scale can bring advantages beyond its purpose, such as providing a standard measure for application in different cultural contexts, which makes it possible to compare the same phenomenon in different cultures.[20]

The instruments need to present two requirements: reliability and validity to be able to reproduce true and equivalent results in different realities.[21] Cross-cultural adaptation is the first step in the validation process that guarantees such principles. Borsa et al. and Sardinha et al. report that it is not only about literal translation, but also about a meticulous evaluation, considering the cultural aspects, beliefs, behaviors, and specific contexts.[19,22] Pilz et al. describe the even greater difficulty that Brazil presents in this regard, since it has continental dimensions with different regionalisms.[23] For this reason, the present study counted on a panel of specialists formed by doctors from different regions and Brazilian states, with different and regional clinical practices, for the instrument evaluation and adaptation.

Sardinha et al. highlight the importance of having two people to carry out the translation, so that the two versions could be compared and discussed to elaborate the synthesized version.[22] This was seen in the present study, where the discussion between translators and researchers raised discrepancies that could be corrected. In the same work, the translators were not laymen in the topic addressed. However, this fact did not generate differences in the results at this stage.[22]

The evaluation by the expert committee allowed grammatical and vocabulary disagreements to be corrected, as well as words to be exchanged or inserted according to what is recommended in Brazilian medical practice. The pretests performed by the target population, on the other hand, detected errors and assessed the understanding of the items. Gasparino and Guirardello showed that the changes made at this stage of the process guarantee clarity and understanding for the target audience. In this phase, other grammatical corrections were accepted for a better instrument understanding.[24] The content validation constitutes the third stage of items analysis, and the instrument proved to be relevant to its purpose. All items were considered validated regarding

Table 3 Content validation coefficient

Content validation coefficient	Number of questions		
	Perspicuity	Pertinence	Theoretical relevance
0.91–1.0	22	24	25
0.8–0.9	7	5	4
< 0.8	0	0	0

their content, since they exceeded the standard of at least 80%, according to the methodology. Thus, there were no changes to the questionnaire at this stage due to the high CVC values obtained. Such a fact may be the result of the steps preceding this or the large number of items in the instrument, sufficient to reduce sampling error, however not excessive to the point of causing exhaustion among the evaluators, as was also described by Santos et al.[21]

The translation and cross-cultural adaptation of the FLASQ-PD into Brazilian Portuguese met the requirements of similar previous works, showing acceptability, relevance, and adequacy in all its items.[20,25,26] As for the item's clarity and comprehensibility, this work showed that with a validation process, it is possible to provide an instrument capable of evaluating PD patients, to choose them according to defined criteria for surgical treatment with DBS, and also to predict more accurately which patients will have a better postsurgical prognosis.

Conclusion

The present study created a Brazilian Portuguese version of the FLASQ-PD instrument that has cross-cultural similarity when compared with the original questionnaire in English. This version can be adopted in research works or even included in medical practice, filling the gap in this work field.

Author's contribution

Ethical Aspects

The current study was approved by the Ethics and Research Committee of Uniervsidade Federal de Sergipe under registration code 29326620.8.0000.5546. To perform the instrument's analysis steps, the evaluators signed the informed consent form. Participants were assured of the confidentiality that ensured their privacy and anonymity regarding the data provided during the assessment.

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Conflict of Interests

The authors have no conflict of interests to declare.

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The Impact of Surgery on Butterfly Gliomas – A Real-life Study of Biopsy versus Surgical Resection

O impacto da cirurgia em gliomas de borboleta – Um estudo real de biópsia versus ressecção cirúrgica

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Abstract

Introduction Although the extent of resection affects the overall survival of patients with gliomas, cytoreduction in patients with butterfly gliomas (BGs) remains controversial. Contemporary studies suggest that wide removal is feasible, but there is a lack of controlled, randomized, multicenter studies on the subject. The aim of the present study was to evaluate the impact of maximal safe resection (MSR) as a primary treatment strategy in patients with BG.

Methods A total of 30 consecutive patients, primarily treated with neurosurgery, were categorized into group A, in whom MSR was $\geq$ 50%, and group B, in whom MSR was $<$ 50% (biopsy). The groups were studied and compared in terms of clinical and epidemiological characteristics, functionality, survival time (ST), and progression-free survival (PFS).

Results The results were analyzed through descriptive and inferential statistics. The most frequent tumor was *IDH1*-wild type glioblastoma, Grade 4 according to the World Health Organization (WHO) classification. Most patients (80%) had Karnofsky Performance Status (KPS) $<$ 70%; however, there was no significant worsening in functionality associated with the interventions. Wider resections, i.e., those performed in group A, were associated with better Kaplan-Meier curves and ST compared with group B (68.35 versus 17.32 weeks respectively; $p = 0.014$). The PFS was also longer in group A compared to group B (57.70 versus 4.77 weeks, respectively; $p = 0.012$). In the multivariate analysis, resections $>$ 50% were associated with reduced risk of recurrence (hazard ratio [HR] = 0.20; 95% confidence interval [95%CI] = 0.06–0.67; $p = 0.009$). The complication rates and functional decline were similar between groups.

Keywords
- butterfly glioma
- biopsy
- surgical resection
- survival
- progression-free survival

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Conclusion Surgical resections > 50% in patients with BG improved ST and PFS without a significant increase in morbidity or dysfunction.

Resumo

Introdução Embora a extensão da ressecção afetar a sobrevida geral dos pacientes com gliomas, a citorredução em pacientes com gliomas em asa de borboleta (GABs) permanece controversa. Apesar de estudos contemporâneos sugerirem que a remoção ampla é viável neste contexto, ainda faltam estudos controlados, randomizados e multicêntricos sobre o assunto. O objetivo deste estudo foi avaliar o impacto da máxima ressecção segura (MRS) como uma estratégia de tratamento primário em pacientes com GAB.

Métodos Ao todo, 30 pacientes consecutivos, tratados primariamente com neurocirurgia, foram categorizados como o grupo A, no qual a MRS foi ≥ 50%, e no grupo B, no qual a MRS foi < 50% (biópsia). Os grupos foram estudados e comparados quanto às características clínicas, epidemiológicas, funcionalidade, tempo de sobrevida (TS) e sobrevida livre de progressão (SLP).

Resultados Os resultados foram analisados por meio de técnicas de estatística descritiva e inferencial. O tumor mais frequente foi glioblastoma de tipo selvagem do gene *IDH1*, de grau 4 na classificação da Organização Mundial da Saúde (OMS). A maioria dos pacientes (80%) tinha Karnofsky Performance Status (KPS) < 70%, mas não houve piora significativa da funcionalidade associada às intervenções. Ressecções mais amplas, ou seja, as realizadas no grupo A, foram associadas a curvas de Kaplan-Meier e TS melhores em comparação com o grupo B (68,35 semanas *versus* 17,32 semanas, respectivamente; $p = 0{,}014$). A SLP também foi mais longa neste grupo em comparação com o grupo B (57,70 semanas *versus* 4,77 semanas, respectivamente; $p = 0{,}012$). Na análise multivariada, ressecções > 50% foram associadas a um risco reduzido de recorrência (razão de risco [RR] = 0,20; intervalo de confiança de 95% [IC95%] = 0,06–0,67; $p = 0{,}009$). As taxas de complicações e o declínio funcional foram semelhantes entre os grupos.

Conclusão Em pacientes com GAB, as ressecções cirúrgicas (> 50%) melhoraram o TS e a SLP, sem aumento significativo na morbidade e nas disfunções.

Palavras-chave
- gliomas em asa de borboleta
- biopsia
- ressecção cirúrgica
- sobrevida
- sobrevida livre de progressão

Introduction

Diffuse gliomas rank among the most prevalent tumors of the central nervous system (CNS), with glioblastoma representing the third most common malignant brain tumor in adults (comprising 50.1% of the cases)[1]. A growth pattern that involves both cerebral hemispheres and the corpus callosum, referred to as butterfly glioma (BG), typically correlates with a grim prognosis, abbreviated survival, challenging management, cognitive decline, and swift functional deterioration.[2] Despite GB, World Health Organization (WHO) grade 4, is the histological subtype most frequently associated with this growth pattern, it can also manifest in astrocytomas WHO grade 2, 3, and 4, as well in lymphoproliferative disorders.

The role of cytoreduction as a primary treatment strategy cases of BG is still controversial.[5–18] The involvement of eloquent areas and long fibers of critical association raises concerns about its indication, as it significantly increases patient morbidity and mortality.[5] Currently, improvements in surgical techniques and the growing number of evidence on the positive impact of surgical resection in the treatment of BG make physicians question the benefits of the more conservative management of the patients, including the strategy of biopsy followed by radiotherapy and chemotherapy.[5] The objective of the present study was to evaluate maximal safe resection (MSR) of the tumor used as a primary treatment strategy in a cohort of patients with BG, considering the survival time (ST) and the progression-free survival (PFS). The results were compared with those observed among patients treated in the same period with biopsy or removal of less than 50% of the total tumor volume (TTV). We also assessed the clinical and epidemiological characteristics of these patients, as well as the complications related to the hospital procedures.

Methods

Study Design and Inclusion Criteria

The present study was conducted through a careful retrospective analysis of information from medical records. We considered for inclusion all BG patients primarily treated

with surgical resection who underwent adjuvant therapy (the Stupp protocol) at Instituto do Câncer do Estado de São Paulo Octávio Frias de Oliveira (ICESP) from January 2011 to August 2022.

Exclusion Criteria

We excluded all patients without radiological and histological confirmation of the diagnosis and those with severe diseases that could interfere with the ST, such as other malignant neoplasms, decompensated systemic diseases, and coronavirus disease 2019 (COVID-19).

Ethical Approval

The institutional Teaching and Research Commission and the Ethics Committee approved the study (under CCEP number: 1842/20). All living patients, or their legal representatives, signed the Free and Informed Consent Form to participate in the study.

Procedures

The participants were categorized into 2 groups based on the extent of the tumor removal: group A comprised patients with MSR $\geq$ 50% of the TTV, while group B included patients who underwent biopsy or MSR $<$ 50% of the TTV. The choice of intervention was made during multidisciplinary discussions, considering the oncological and functional prognosis, as well as the impact and feasibility of the procedure. The clinical and epidemiological variables considered relevant included gender, race, age, symptoms, presence of hydrocephalus, involvement of three or more brain lobes (gliomatosis), overall health status, pre- and postoperative functional status, tumor histology, presence of the R132H mutation in the isocitrate dehydrogenase (NADP+) 1 (IDH1) gene (determined through immunohistochemistry), as well as PFS and ST. The general health conditions were evaluated using the classifications of the American Society of Anesthesiologists (ASA) and of the Eastern Cooperative Oncology Group (ECOG), and the functional status, through the Karnofsky Performance Status (KPS). For the statistical analysis, the time between surgery and the first radiological evidence of tumor volume increase was considered as the PFS. ST was defined as the time from surgery to death.

Statistical Analysis

We used the Jamovi (free, open source) and Stata (Statacorp. LLC, College Station, TX, United States) software for statistical analysis. The categorical variables were compared using the Chi-squared test, and they were expressed as absolute and relative frequencies. The normality of the continuous variables was assessed through Shapiro-Wilk tests. The parametric variables were expressed as means and standard deviation values and compared through the student's *t*-test. The non-parametric variables were evaluated using the Mann-Whitney U test. We used the long-rank test to compare survival curves developed through the Kaplan-Meier method. Univariate and multivariate Cox proportional hazards models were used to analyze possible variables associated with the ST. In the statistical analyses, values of $p < 0.05$ were considered significant.

Results

The current study included 30 patients equally distributed between groups A and B. The demographic, clinical, and epidemiological profiles of the sample are presented in ►**Table 1**. The mean age of the patients was 60.54($\pm$11.43) years, with no statistically significant difference between the groups. In group B, there was a predominance of males (80.0%), and, in group A, the rate of male subjects was of 40% ($p = 0.025$).

The most frequent symptoms reported uniformly in both groups, were delirium/mental confusion (76.7%), headache (63.3%), motor alterations (53.3%), and gait alterations (53.3%). Loss of sphincter control and epilepsy were reported by 43.3% and 30% of the patients, respectively. There were no statistically significant differences regarding the presence of hydrocephalus or the pattern of gliomatosis growth at presentation. The groups were similar regarding the most prevalent comorbidities, which included hypertension (33.3%), diabetes mellitus (23.3%), and cardiovascular disease (10%). They were also similar when categorized by functional performance, considering the KPS ($\geq$ 70% and $<$ 70%) and ECOG ($\geq$ 3 and $<$ 3) scales. Despite this, patients in group B were in better general health conditions (ASA $<$ 3) at the time of the intervention ($p = 0.02$).

Malignant gliomas, WHO grades 3 and 4, were predominant and represented 86.7% and 10% of the cases respectively. Only 1 patient (3.3%) was classified as presenting diffuse astrocytoma, WHO grade 2, mutated *IDH1*. The surgical mortality rate (death up to the seventh day of the intervention) was of 0%. In total, 2 patients (13.33 %) from group A and one patient (6.66 %) from group B showed functional deterioration related to the intervention ($p > 0.05$).

Survival Time

The mean ST was higher in group A compared to group B (68.35 vs. 17.32 weeks, respectively; $p = 0.014$), and the statistically significant differences were maintained in the univariate analysis (hazard ratio [HR] = 0.39; 95% confidence interval [95% CI] = 0.18–0.85; $p = 0.018$) and multivariate analysis (HR = 0.22; 95% CI = 0.07–0.69; $p = 0.010$) models used (►**Table 2**). A comparison of the Kaplan-Meier survival curves is shown in ►**Figure 1**.

The patient who achieved the longest survival underwent surgical excision of a glioblastoma, IDH1-wild type, WHO grade 4. In addition to gross total resection, the patient received comprehensive adjuvant therapy following Stupp's protocol. Remarkably, this individual remains alive with a Karnofsky Performance Status of 90 % and has been free of recurrence for 6 years and 7 months of follow-up (►**Figure 2**).

Progression Free-Survival

The mean time until recurrence was 30.23 ($\pm$70.41) weeks. The PFS was significantly higher in group A compared to group B (57.70 versus 4.77 weeks respectively; $p = 0.012$)

Table 1 Clinical and demographical data of the study sample

		All	Group A*	Group B*	*p*-value
Cases: n (%)		30 (100.0)	15 (50.0)	15 (50.0)	
Age in years: mean ± SD		60.54 ± 11.43	58.19 ± 8.73	61.65 ± 13.86	0.619
Sex: n (%)	Male	18 (60.0)	6 (40.0)	12 (80.0)	0.025
	Female	12 (40.0)	9 (60.0)	3 (20.0)	
Comorbidities: n (%)	Arterial hypertension	10 (33.3)	5 (33.3)	5 (33.3)	1.000
	Diabetes mellitus	7 (23.3)	5 (33.3)	2 (13.3)	0.195
	Cardiovascular disease	3 (10.0)	2 (13.3)	1 (6.7)	0.543
	Stroke	2 (6.7)	2 (13.3)	0 (0.0)	0.143
	Smoking	5 (16.6)	3 (20.0)	2 (13.3)	0.510
Symptoms: n (%)	Headache	19 (63.3)	11 (73.3)	8 (53.3)	0.256
	Epilepsy	9 (30.0)	4 (26.7)	5 (33.3)	0.690
	Motor impairment	16 (53.3)	9 (60.0)	7 (46.7)	0.464
	Gait impairment	16 (53.3)	9 (60.0)	7 (46.7)	0.464
	Sensitive impairment	1 (3.3)	1 (6.7)	0 (0.0)	0.309
	Decreased sphincter control	13 (43.3)	7 (46.7)	6 (40.0)	0.713
	Decreased level of consciouness	12 (40.0)	8 (53.3)	4 (26.7)	0.136
	Delirium/Mental confusion	23 (76.7)	13 (86.7)	10 (66.7)	0.195
	Cognitive impairment	14 (46.7)	7 (46.7)	7 (46.7)	1.000
	Visual disturbance	5 (16.7)	3 (20.0)	2 (13.3)	0.624
ECOG: n (%)	≤ 2	12 (40)	6 (40)	6 (40)	1,000
	≥ 3	18 (60)	9 (60)	9 (60)	
KPS: n (%)	≤ 60%	24 (80.0)	11 (73,3)	13 (86,7)	0.361
	≥ 70%	6 (20.0)	4 (26,7)	2 (13,3)	
ASA score: : n (%)	≤ 2	10 (33.3)	8 (53.3)	2 (13.3)	0.020
	≥ 3	20 (66.7)	7 (46,7)	13 (86.7)	
Histology: n (%)	Grade-2 astrocytoma	1 (3.3)	0 (0.0)	1 (6.7)	0.510
	Grade-3 astrocytoma	3 (10.0)	2 (13.3)	1 (6.7)	
	Grade-4 glioblastoma	26 (86.7)	13 (86.7)	13 (86.6)	
***IDH1* mutation: n (%)**	Mutation	1 (3.3)	0 (0.0)	1 (6.7)	0.030
	Non-mutation	16 (53.4)	5 (33.3)	11 (73.3)	
	NOS	13 (43.3)	10 (66.7)	3 (20.0)	
Hydrocephalus: n (%)		13 (43.0)	6 (46.2)	7 (53.8)	0.713
Gliomatosis: n (%)		22 (73.3)	10 (45.5)	12 (54.5)	0.409
Survival in weeks: mean ± SD		42.84 ± 65.16	68.35 ± 29.57	17.32 ± 29.57	0.014
Recurrence in weeks: mean ± SD		30.23 ± 70.41	57.70 ± 93.97	4.77 ± 7.15	0.012

Abbreviations: ASA, American Society of Anesthesiologists physical status classification; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Scale; SD, standard deviation.

and differences in the Kaplan-Meier curves for recurrence are shown in ►**Figure 3**. After 25 weeks of follow-up, all patients in group B, who were treated with biopsy, had already presented recurrence, compared to 60 % of group A. A statistically significant reduction in the risk of recurrence was observed only in group A, both in the univariate (HR = 0.35; 95% CI = 0.15–0.79; $p = 0.011$) and multivariate (HR = 0.20; 95% CI = 0.06–0.67; $p = 0.009$) analyses (►**Table 3**).

Discussion

Butterfly gliomas are commonly characterized by aggressive behavior, unfavorable histological and molecular profiles, short STs, early recurrence, and poor prognosis, regardless of treatment. Nevertheless, many cases require surgical intervention due to rapid progression, for symptom relief, or simply to establish a histological diagnosis. Although

Table 2 Cox regression for the survival time

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Sex (male)	0.65	0.30–1.39	0.262	0.65	0.24–1.73	0.382
Age (< 60 years)	1.73	0.79–3.76	0.168	2.33	0.82–6.62	0.113
ASA score (< 3)	0.95	0.43–2.08	0.890	5.06	1.33–19.29	0.017
KPS (≥ 70%)	0.38	0.14–1.02	0.054	0.63	0.19–2.13	0.460
Surgery	0.39	0.18–0.85	0.018	0.22	0.07–0.69	0.010

Abbreviations: 95%CI, 95% confidence interval; ASA, American Society of Anesthesiologists physical status classification; HR, hazard ratio; KPS, Karnofsky Performance Scale; SD, standard deviation.

Table 3 Cox regression for progression-free survival

	Univariate analysis			Multivariate analysis		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value
Sex (male)	0.54	0.25–1.18	0.121	0.51	0.19–1.40	0.192
Age (< 60 years)	1.94	0.88–4.29	0.100	2.02	0.71–5.75	0.190
ASA score (< 3)	0.63	0.28–1.43	0.274	4.11	1.00–16.93	0.050
KPS (≥ 70%)	0.51	0.19–1.36	0.180	0.74	0.22–2.56	0.638
Surgery	0.35	0.15–0.79	0.011	0.20	0.06–0.67	0.009

Abbreviations: 95%CI, 95% confidence interval; ASA, American Society of Anesthesiologists physical status classification; HR, hazard ratio; KPS, Karnofsky Performance Scale; SD, standard deviation.

historically MSR has been infrequently indicated to treat BG, there are compelling reasons to consider it. Adequate surgical removal, when combined with adjuvant therapies such as radiotherapy and chemotherapy, can substantially extend survival and enhance the quality of life of patients. This is achieved by reducing intracranial pressure, alleviating pressure on the surrounding brain structures, and potentially mitigating neurological symptoms such as headaches, motor and cognitive deficits, and seizures.

Consistent with the existing literature, the current study predominantly featured gliomas classified as WHO grades 3 and 4 of astrocytic origin, with wild type *IDH1* status. Only 1 case was categorized as diffuse astrocytoma, mutant *IDH-1*, WHO grade 2. Despite this, we noted a significant improvement in both ST and PFS among patients in whom surgical resection exceeded 50% of the TTV group A. Our analysis of the clinical and epidemiological profile highlighted the advanced mean age, functional impairment, and overall frailty of the affected population. Surprisingly, 66.7% and 80% of the cases were classified as ASA ≥ 3 and KPS < 70 respectively. Noteworthy comorbidities included hypertension, diabetes mellitus, cardiovascular diseases, and a history of smoking. The most common symptoms reported were headache, epileptic seizures, and frontal and psychiatric manifestations (delirium, motor changes, cognitive impairments, and loss of sphincter control). The demographic profile, combined with the disease's aggressive nature, justifies the apprehension many neurosurgeons experience when managing these cases and opting for more conservative interventions. However, in the present study, the increase in ST and PFS observed in group A was not associated with higher rates of surgical morbidity, mortality, or functional impairment resulting from the intervention. The effect was particularly pronounced in PFS, which was extended by more than 12 times. Notably, surgery emerged as an independent factor, even in statistical models incorporating established factors such as age, IDH1 status, and functional performance. These findings support recent literature suggesting the favorable impact of MSR as a primary treatment modality in such cases.[3–5,9–11,13,15–18]

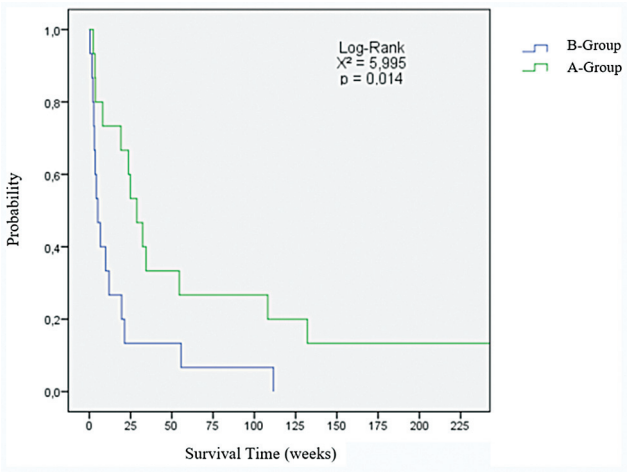

Fig. 1 Kaplan-Meyer analysis of the survival time.

Despite technological advances, established and described techniques for the resection of these tumors, and

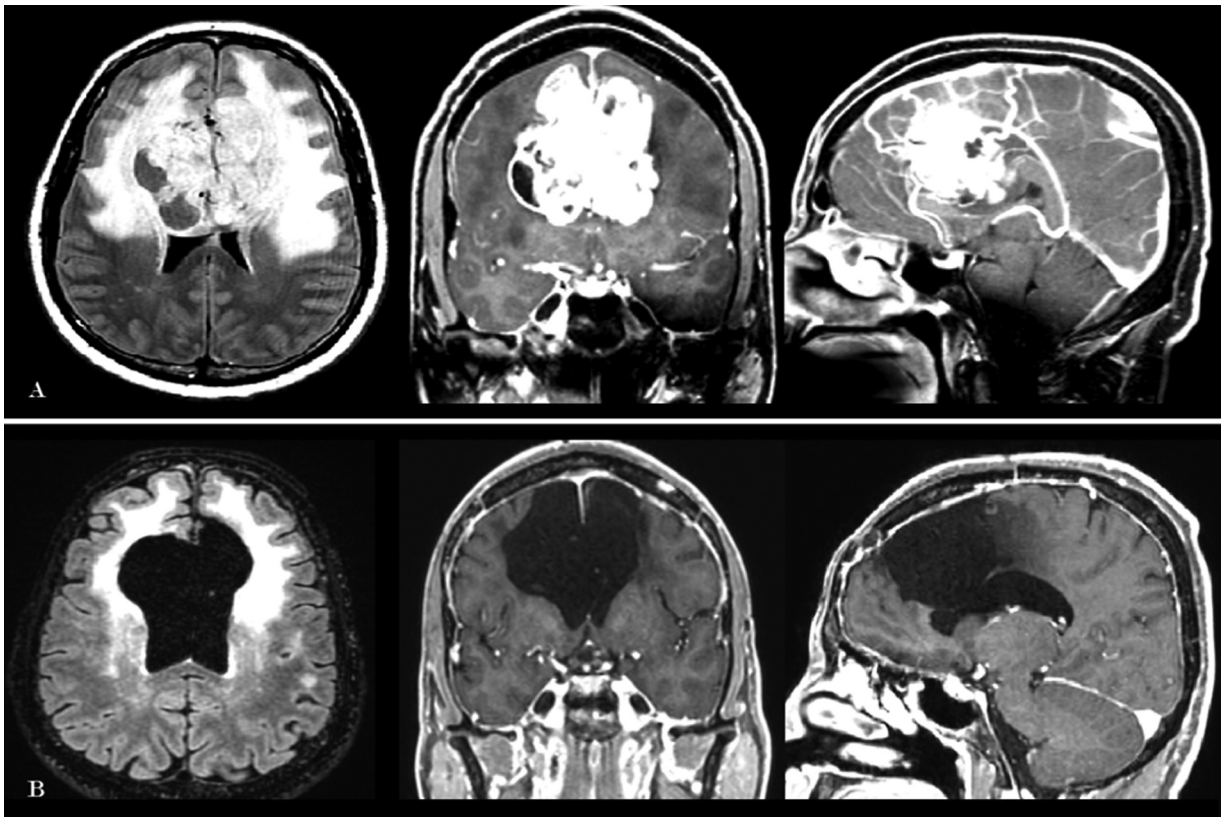

Fig. 2 Illustrative case. Butterfly Glioblastoma, *IDH1*-wild type, WHO grade 4.

along with evidence favorable to this strategy,[4,9,11] surgery is still seldom used in the primary treatment of BG. This may be due to poor results reported in the past and the lack of know-how and expertise among neurosurgeons in this type of intervention. Despite the infiltrative and diffuse character of these tumors, we believe that most of the symptoms, dysfunctions, and mechanisms of death are due to edema, distortion of CNS areas, and fibers.

A recent study[18] found that GBs can increase in volume by an average of 1.1% per day, potentially doubling in size in just 22 days. Analogous to the management of other tumors, as well as well as gliomas affecting different parts of the CNS, we believe that preserving the quality of life in BG patients and reversing or delaying dysfunctions and causes of death may be achieved through more extensive surgical resections. However, definitive conclusions on this matter would require better designed and randomized studies. Yet, the rarity of the disease and ethical considerations pose challenges, potentially rendering such studies unfeasible. Real-world data, such as those presented herein, are vital to support evidence-based practices without depriving functionally sound patients of optimal treatment options or wasting resources on those with poor prognoses. Nevertheless, the current study has notable limitations, including its retrospective design, the single-center design, sample size, molecular data availability, patient inclusion period, and estimation of TTV.

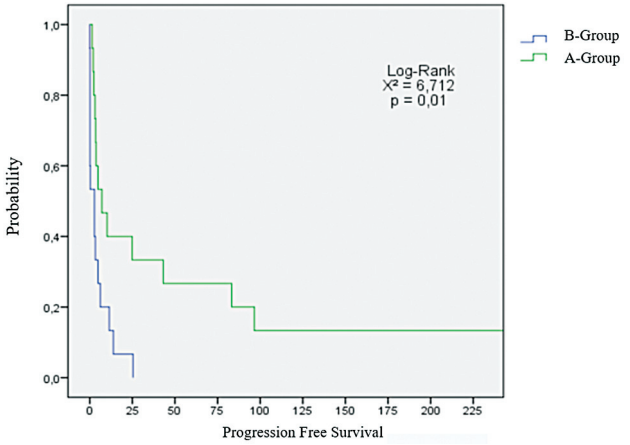

Fig. 3 Kaplan-Meyer analysis of the progression-free survival.

Conclusion

Surgically removing at least 50% of a BG has emerged as a positive independent factor linked to a more favorable outcome in terms of ST and PFS. This improvement was not accompanied by elevated surgical morbidity and mortality rates. However, the present study did not identify specific subgroups that might benefit the most from this approach. These findings align with those of recent research[3–5,9–11,13,15–18] suggesting the superiority of extensive surgical resection over primary management with biopsy alone. Nonetheless, further well-designed, multicenter, randomized studies are still required to reach definitive conclusions.

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

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Visuospatial Changes after Clipping of Anterior Communicating Artery Aneurysms

Alterações visuoespaciais após clipagem de aneurismas da artéria comunicante anterior

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Abstract

Introduction A series of symptoms are commonly seen after anterior communicating artery (ACoA) aneurysm clipping. Previous studies designated it as ACoA syndrome, a condition in which symptoms like amnesia, confabulation, and personality changes are observed. The present study investigates visuospatial impairments associated with ACoA aneurysm rupture followed by subarachnoid hemorrhage (SAH) and clipping procedure.

Methods 31 patients who underwent surgical clipping of the ACoA after SAH were evaluated prospectively at three, six, and twelve months after the surgery. Hooper Visual Organization test (HVOT), Judgment of Line Orientation test (JLOT), and Stroop-I test were used to evaluate visual organization, visual orientation perception, and visual attention, respectively.

Results Regarding the HVOT, the mean score observed in each observation was at three, six, and twelve months, respectively: 20.2 (SD ± 4.4), 21.5 (SD ± 4.7), and 20.9 (SD ± 4.6). The JLOT, in turn, presented the following results at the same respective time frames: 19.0 (SD ± 4.9); 19.7 (SD ± 4.3); 21.2 (SD ± 4.7). Finally, for the Stroop-I test, a similar pattern was found: 18.35 (SD ± 5.8); 18.00 (SD ± 6); 17.00 (SD ± 4.4). Of all the tests above, only Stroop-I test scores did not follow a normal distribution.

Conclusion Visuospatial and visuoperceptual abilities can also present impairments after SAH following ACoA aneurysm rupture and clipping, although it is commonly a

Keywords
- subarachnoid hemorrhage
- anterior communicating artery
- intracranial aneurysm
- visuospatial changes
- visuospatial abilities
- visual impairment

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mild symptom. Therefore, diffuse symptomatology, rather than the stricter ACoA syndrome described in the literature, may be seen. Moreover, positive outcomes are expected twelve months after postoperatively.

Resumo

Introdução Uma série de sintomas é comumente observada após a clipagem de aneurismas da artéria comunicante anterior (ACoA). Estudos anteriores denominaram essa condição como síndrome da ACoA, em que sintomas como amnésia, confabulação e alterações de personalidade são frequentemente observados. O presente estudo investiga os déficits visuoespaciais associados à ruptura de aneurisma da ACoA, seguida por hemorragia subaracnoide (HSA) e clipagem.

Método 31 pacientes que foram submetidos à clipagem cirúrgica da ACoA após HSA foram avaliados prospectivamente aos três, seis e doze meses após a cirurgia. Foram utilizados o Teste de Organização Visual de Hooper (HVOT), o Teste de Julgamento de Orientação de Linhas (JLOT) e o Stroop-I para avaliar, respectivamente, a organização visual, a percepção de orientação visual e a atenção visual.

Resultados Em relação ao HVOT, a pontuação média observada em cada momento foi de três, seis e doze meses, respectivamente: 20,2 (DP ± 4,4), 21,5 (DP ± 4,7) e 20,9 (DP ± 4,6). O JLOT, por sua vez, apresentou os seguintes resultados nos mesmos períodos: 19,0 (DP ± 4,9); 19,7 (DP ± 4,3); 21,2 (DP ± 4,7). Finalmente, para o Stroop-I, foi encontrado um padrão semelhante: 18,35 (DP ± 5,8); 18,00 (DP ± 6); 17,00 (DP ± 4,4). De todos os testes mencionados, apenas os escores do Stroop-I não seguiram uma distribuição normal.

Conclusão Habilidades visuoespaciais e visuoperceptivas também podem apresentar comprometimentos após HSA decorrente da ruptura de aneurisma da ACoA e sua subsequente clipagem, embora sejam comumente sintomas leves. Portanto, uma sintomatologia difusa, em vez da síndrome da ACoA mais restrita descrita na literatura, pode ser observada. Além disso, são esperados desfechos positivos doze meses após o procedimento cirúrgico.

Palavras-chave
- hemorragia subaracnóidea
- artéria comunicante anterior
- aneurisma intracraniano
- alterações visuoespaciais
- habilidades visuoespaciais
- deficiência visual

Introduction

Intracranial aneurysms are present in ~5% of the population.[1] Known risk factors associated with the abnormal dilation of blood vessel walls include advanced age, hypertension, alcoholism, diabetes mellitus, atherosclerosis, family history of the disease, hormonal and ethnic factors, and smoking.[1–3] These factors, directly or indirectly, increase hemodynamic stress on the vessel walls. Arterial hypertension is, in fact, considered one of the main causes of subarachnoid hemorrhage (SAH) resulting from aneurysm rupture, facilitated by the weakening of vessel walls.[1,4] Clinical manifestations are severe and include headache, nausea, vomiting, hemiparesis, and altered consciousness.[5]

The system of vessels formed by the anterior communicating artery (ACoA) and its perforating branches is the most prone to the development and rupture of intracranial aneurysms, causing aneurysmal subarachnoid hemorrhage (SAH).[6–9] It is estimated that 18% of aneurysms are located in this system, and women are more likely to develop them.[5] Etiological factors include trauma, infections, or congenital defects.[10,11] The bifurcations and taperings typical of the vessels in this system are morphological variables associated with aneurysm development.[5]

Anatomically, the ACoA is a small vessel located in the anterior portion of the Circle of Willis, which is responsible for most of the blood supply to the brain. The ACoA connects the two anterior cerebral arteries, and several smaller arteries (called perforators) project from it, classified according to the brain regions they supply (e.g., subcallosal, hypothalamic, and chiasmatic). Cortical and subcortical structures relevant to cognition, including the fornix, cingulate gyrus, and basal forebrain, are supplied by the perforators,[12,13] which explains the cognitive deficits found in nearly 50% of patients following vascular accidents in this region.[14–18]

In addition to neurological damage, the rupture is also associated with severe neuropsychological and psychiatric repercussions. These impairments may result from the brain insult caused by the aneurysm rupture, the pathophysiological consequences of the hemorrhage (e.g., blood toxicity, brain edema, ischemic lesions or infarction typically associated with vasospasm, increased intracranial pressure due to bleeding, and hydrocephalus), and/or iatrogenic effects (e.g., side effects of anesthesia and unavoidable surgical damage to areas adjacent to the aneurysm, including perforators, the rectus gyrus, and limbic structures, among others). Iatrogenic effects may result either from malpractice or the necessity of accessing the frontobasal region.[15,17]

Vasospasm, a phenomenon characterized by the narrowing of blood vessels, typically occurs around five days after the hemorrhagic event[19,20] and has been identified as an important predictor of long-term cognitive deficits.[21] More recent studies, however, suggest that although vasospasm is common, it does not seem to have a significantly strong association with postoperative cognitive damage, unless it leads to brain tissue death (ischemia followed by infarction).[22]

There is ongoing debate surrounding the two main surgical modalities used to treat aneurysms—embolization and clipping—regarding the cognitive risks associated with each. Evidence suggests that patients undergoing the latter may be more prone to cognitive sequelae, mainly due to the higher risk of structural brain damage during the procedure.[9,11] It has been suggested that cognitive sequelae may depend more on the characteristics of the aneurysm (e.g., location and volume of the aneurysm sac) than on the type of treatment used.[20]

Neurocognitive domains commonly affected by the disease and/or treatment seem to result from lesions in respective neuroanatomical regions (mainly front-frontotemporal), although this association is not always clear or direct. These include domains of memory, language, executive functions (EF), and personality changes.[23–25] Confabulation and its rarer variant, fabulism, may also be observed following ACoA hemorrhage.[10]

The pattern of symptoms triggered by aneurysm rupture and possibly exacerbated by surgical treatment has been termed "ACoA syndrome"[26–28]. However, there is no consensus on the accuracy of this entity due to the distinct patterns of deficits found in different studies, both in terms of the cognitive domains affected, their severity, and the transience or permanence of the sequelae.[18]

Recent studies have increasingly emphasized the decline in patients' performance in attention tasks (focused, divided, and alternating) compared with healthy controls.[9] It is acknowledged that, as an "input function," attention impairment is expected to secondarily affect other cognitive domains. Lezak[29] asserts that the quality of attentional focus is a prerequisite for good performance in various neuropsychological tests. Although not always detected by standardized tests, attentional decline is reported by patients and their families.[18]

Deficits in domains associated with posterior brain regions, particularly visual processing (VP), are less commonly reported. VP depends on highly specialized neural networks in different cortical and subcortical pathways responsible for its subcomponents, namely visuospatial (VSE), visuoperceptive (VPE), and visuoconstructive (VCE) abilities. VSE, associated with the dorsal stream (occipitoparietal pathway), refers to the ability to judge the orientation and position of visual stimuli, as well as topographical orientation. VPE, associated with the ventral stream (occipitotemporal pathway), refers to the ability to identify or recognize the identity or nature of visually presented stimuli (the ability to discern what something is or what it is for). Finally, VCE, also associated with the dorsal stream, represents the interaction between visual and motor domains, allowing tasks such as graphomotor execution (e.g., copying figures) or constructive tasks (e.g., assembling blocks based on diagrams or models).[30] Vascular accidents are among the main etiological factors for disturbances in these functions, which include visual agnosias, hemispatial neglect, difficulties navigating familiar environments, constructive disabilities, and other rarer, debilitating, and usually chronic conditions.[31]

One of the few studies that extensively evaluated the cognitive profile of these patients[32] found no significant differences in visuospatial task performance between the group of operated patients and healthy controls. The same was true when comparing the performance of patients treated with clipping to those treated with embolization.[32] Two decades earlier, the same author described the neuropsychological profile of five patients with "ACoA syndrome," none of whom showed significant visuospatial impairments.[27] Diamond's[33] encyclopedic review also pointed to the absence or mild impairment of VSE associated with ACoA aneurysms.

Given the discussion around the involvement of higher visual processing aspects, particularly VSE, this study aims to investigate and discuss the potential impact on visual and visuospatial abilities in a group of 31 patients who underwent surgical clipping to repair SAH secondary to ACoA aneurysm rupture. The patients' performance was analyzed using two neuropsychological tests (line judgment and Hooper) at three points over 12 months. Theoretical considerations about prognostic variables will also be addressed.

Method

This is a prospective study in which 31 patients who underwent surgical clipping for repair of SAH secondary to ACoA aneurysm rupture were evaluated between 2006 and 2010 at the vascular neurosurgery outpatient clinic of the Hospital das Clínicas, Faculty of Medicine, University of São Paulo (HCFMUSP). This project was approved by the ethics committee under no. 0272/10.

The patients, consisting of 13 women and 18 men aged between 20 and 75 years, underwent cognitive evaluation using the Hooper Test, Line Judgment Test, and Stroop Test at three-time points: 3, 6, and 12 months after surgery. Illiterate patients had multiple aneurysms, or had comorbidities affecting the brain were excluded from this study.

To assess visual and visuospatial functions, the Hooper Visual Organization Test (VOT), which evaluates visuospatial ability and was originally designed for assessing adults with neurological damage, was used. It consists of 30 figures of common objects, drawn on cards and cut into two or more parts, forming a puzzle. The figures are presented individually, and the patient is asked to identify and name the object shown on each card.[34] The Judgment of Line Orientation Test (JLO)[35] was also used to assess visuospatial orientation, emphasizing visual perception. It consists of 30 items presented in increasing order of difficulty and evaluates the ability to visually identify the angular positions of 11 lines arranged in a semicircle (0° to 180°).[34]

Visual attention was investigated using the Stroop Test to exclude attentional deficits as a primary cause of other potential deficits. The Stroop Test assesses sustained attention, selective attention, and cognitive flexibility.[29] Visual attention was evaluated using the first card, which measures sustained visual attention. The patient was asked to name the colors of 24 colored rectangles. The time taken to complete each task was timed, and both correct and incorrect responses were recorded.[36]

Descriptive statistical analyses were performed for age, gender, and education. The Kolmogorov-Smirnov test was used to determine the normality of the distribution (Gaussian curve), aiding in the choice of statistical tests for subsequent analyses. The parametric ANOVA (Analysis of Variance) test for repeated measures was applied to the Hooper Test and Line Judgment Test scores. For the Stroop Test, the nonparametric Friedman test was used. Multiple comparisons using Tukey's test were conducted to examine differences between the time points (2×2 comparisons).

Results

The present sample included $N = 31$ patients who underwent surgical clipping for the treatment of ruptured ACoA aneurysms. As shown in ►**Table 1**, there was a variation in age (mean 47.4 years, SD ± 11.4), with 58.1% of the sample being male and 41.9% female. The mean level of education for these patients was 6.9 years (SD ± 3.7).

►**Table 2** presents the results of the normality test for numerical variables to determine the appropriate statistical test for each. The Kolmogorov-Smirnov normality test was applied.

►**Table 3** presents the statistical analyses, with the time between surgery and the three neuropsychological evaluations being 3, 6, and 12 months. Performance on the visuoperceptive Hooper Test followed a normal distribution, with mean scores of 20.2 (SD ± 4.4), 21.5 (SD ± 4.7), and 20.9 (SD ± 4.6) for the respective periods, with a significant difference observed between 3 and 6 months.

Performance on the visuospatial Benton Line Judgment Test also followed a normal distribution, with mean scores of 19 (SD ± 4.9), 19.7 (SD ± 4.3), and 21.2 (SD ± 4.7) for the respective periods, with a statistically significant difference observed between the results at 3 and 12 months.

►**Table 4** shows that Stroop-I scores did not follow a normal distribution, and no significant difference was observed across the three-time points of the study. The sample's mean scores were 18.35 (SD ± 5.82), 19.06 (SD ± 5.94), and 18.3 (SD ± 4.39). Based on the sample's demographic profile and the reference values from the test manual, the mean reference values from the manual for individuals aged 40 to 49 years and 50 to 59 years with 5 to 8 years of education are 19.12 and 18.25, respectively. The average performance on Stroop-I suggests that the deficient performance in visual domains is not secondary to attentional impairment, a domain that does not appear to be compromised in these patients.

Table 1 Descriptive statistics of Age, Years of Schooling, and Sex

	AGE	YEARS OF SCHOOLING
Mean	47,4	6,9
Median	48,0	5,0
Minimum	20	3
Maximum	75	15
Standard deviation	11,4	3,7
n	31	31
Sex	**N**	**%**
F	13	41,9
M	18	58,1
Total	31	100,0

Table 2 Normality test results

	Kolmogorov-Smirnov		
	Statistic	df	Sig. (p)
Hooper 3M	0,078	31	0,200
Hooper 6M	0,104	31	0,200
Hooper 12M	0,089	31	0,200
Judgment of Line 3M	0,111	31	0,200
Judgment of Line 6M	0,097	31	0,200
Judgment of Line12M	0,134	31	0,164
Stroop 3M	0,205	31	0,002
Stroop 6M	0,149	31	0,079
Stroop 12M	0,162	31	0,037

Discussion

The neuropsychological profile of patients undergoing surgery for the treatment of SAH due to ACoA aneurysm rupture has been sparsely investigated for several decades, with most studies reporting that cognition is impacted either by the disease or by the surgical treatment, which, depending on the type, may be invasive. The first recorded changes included focal declines in memory functions (particularly delayed recall), executive functions, awareness (confabulation), and behavioral changes (personality alterations), a condition that became known as "ACoA syndrome"[26,27].

The refinement of neuropsychological (NP) methods and instruments has led to more sensitive and accurate investigations of cognition, making it possible to identify impairments in domains that were previously undetected. Attention and executive functions (EF), for instance, were not initially included among these impairments.[10,26] However, more recent studies have revealed a different scenario, with findings showing that patients perform worse on attention tasks compared with healthy controls.[9,18] In our study, the performance classified as average by patients on focused and selective attention tasks (Stroop) in the three postoperative NP assessments suggests the absence of impairment in this domain.

Tabela 3 Comparativos entre 3 momentos: 3 meses, 6 meses e 12 meses segundo as 3 variáveis numéricas de interesse: Hooper, Julgamento de linhas

		3 months	6 months	12 months	Repeated Measures ANOVA or Friedman Test (p)	Multiple 2 × 2 Comparisons	Result
Hooper	Mean	20,2	21,5	20,9		3m × 6m - $p = 0{,}043^*$	3m < 6m
	Median	20,5	22,0	21,5	$0{,}023^*$	3m × 12m - $p = 0{,}496$	3m = 12m
	Standard deviation	4,4	4,7	4,6		6m × 12m - $p = 0{,}343$	6m = 12m
	n	31	31	31			
Judgment of Line	Mean	19,0	19,7	21,2		3m × 6m - $p = 0{,}747$	
	Median	19,0	20,0	22,0	$0{,}002^*$	3m × 12m - $p = 0{,}007^*$	3m = 6m < 12m
	Standard deviation	4,9	4,3	4,7		6m × 12m - $p = 0{,}053$	
	n	31	31	31			

Table 4 Comparisons across 3 time points: 3 months, 6 months, and 12 months for the 3 numerical variables of interest: Stroop

		3 months	6 months	12 months	Friedman Test (p)	Result
Stroop	Mean	18,35	19,06	18,03		
	Median	17,00	18,00	17,00	0,738	3m = 6m = 12m
	Standard deviation	5,823	5,944	4,385		
	n	31	31	31		

On the other hand, our results showed impacts on EF, a rarely reported finding in the literature. Despite the somewhat hierarchical relationship between attention and other cognitive domains, our data suggest that EF was not impacted secondarily by attention, which was preserved. Neural networks more closely related to visuospatial functioning may have been affected by the SAH and treatment.

In Beeckman et al.'s recent study,[9] 35 operated patients and 20 healthy controls were evaluated on tasks of attention (sustained, divided, and alternating), memory (auditory-verbal and visuospatial), executive functions (verbal fluency, abstract reasoning, planning, and problem-solving), and visuospatial functions (visuospatial judgment and visuospatial construction). The authors noted significantly worse performance of patients on sustained, divided, and alternating attention tasks, but not on visuospatial functions. Regarding EF and memory, their findings confirmed previous studies, with impairments in these domains being cardinal signs of "ACoA syndrome." However, memory impairment was more severe than previously reported, with declines identified in both immediate and delayed recall tasks, as well as in tasks of both auditory-verbal and visual nature. Previous studies, such as those by DeLuca[26] and Ravnik et al.,[18] had reported relative preservation of short-term memory systems for this group of patients, with greater impact on long-term systems.

Beeckman et al.[9] argued that such discrepancies stem from methodological issues. According to the authors, some biases may have compromised the identification of other affected domains in previous studies, such as the absence of more sensitive instruments for assessing skills like visual and visuospatial abilities. Therefore, we recommend the adoption of diverse and specific instruments for these functions in future studies with this patient group, as our findings suggest alterations in these functions. It is worth noting that we were unable to investigate these functions in greater depth in our study due to the research design, which involved adopting the institution's NP protocol. Indeed, the initial aim of the group was to conduct a more global investigation of cognition based on literature findings pointing to "ACoA syndrome" rather than analyzing specific functions or domains. For this same reason, it was also not possible to investigate more deeply some physiological variables that have been generically suggested as possible causes or aggravators of cognitive impairments.

Regarding EF, Beeckman et al.,[9] as mentioned above, did not detect a decline in these patients. Our results suggest otherwise. In the instruments dedicated to evaluating visual synthesis ability (Hooper test) and visuospatial orientation and perception (line judgment), many patients scored below the expected age average. In the Hooper, the mean score of our group was 20.2 (SD ± 4.4), 21.5 (SD ± 4.7), and 20.9 (SD ± 4.6) in assessments conducted three, six, and twelve months after surgery. The instrument's manual establishes, for score ranges of 16–18, 19–20, and 21–22, high, moderate, and low deficit probabilities, respectively. Considering the SD, it can be observed that some patients remained in the most severe classification range even after the longer postoperative period.

In the case of line judgment, the mean score of our group was 19 (SD ± 4.9), 19.7 (SD ± 4.3), and 21.2 (SD ± 4.7), under

the same temporal conditions mentioned above. The best possible score of 25.9 (i.e., 21.2 + 4.7) corresponds, according to the instrument manual, to the 56th percentile. Score ranges of 23–24, 21–22, and 19–20 correspond to the 40th, 22nd, and 9th percentiles, respectively.

Statistically, a decline followed by improvement in average performance can be observed in both the visual synthesis test (Hooper) particularly in the second evaluation, six months after surgery—and the visuoperceptive test (line judgment), especially in the third evaluation, twelve months after surgery, evidencing the expected transitory nature of this sequela. The improvement in both tests allows us to conclude, first, that the impacted function resulted from the cerebrovascular event and/or treatment, second, that it was not secondary to any possible attentional impairment (whose performance, as reiterated, remained constant and within average throughout the period), and third, that this sequela tends to present a good prognosis within a year after the clipping operation.

The line judgment test was also used by Beeckmans et al.[9] and DeLuca.[26] The average score obtained by Beeckmans' 19 patients, evaluated three months after surgery, was higher than that obtained by our 31 patients evaluated 12 months post-surgery (24.4 × 21.2). DeLuca's patients tested a few days post-operation, also performed better than those in our sample (24.6 × 21.2).

It is noted that visuospatial functioning impairments are not always identified by studies, either through testing or by the subjective reports of patients or their caregivers. Likely, this domain is not significantly affected, at least in many cases, to the point of guaranteeing its detection, nor does it impact patients' functionality in everyday tasks requiring such skills, a hypothesis that could be explored in future research.

There has been a debate about whether the pattern of post-surgical cognitive sequelae manifested by SAH patients in the ACoA follows a focal or diffuse logic. DeLuca[26] found evidence supporting the former hypothesis, noting, in one sample, the preservation of global IQ but impaired performance on delayed recall and executive functioning tasks (constituting the "ACoA syndrome"). His study compared the performance of 11 SAH patients in the ACoA (experimental group) with that of 13 controls who had SAH in other vessels. Relative to the control group, the experimental group exhibited worse performance limited to delayed recall tasks (e.g., logical memory test) and EF (e.g., persevering errors on the Wisconsin test). On the other hand, the experimental group performed better on attentional and visuospatial tasks and had higher IQs than the controls. The author suggested that focal damage might be associated with focal lesions in anterior brain regions (e.g., basal forebrain).

Similarly, Ravnik et al.[18] found that, regarding the process of memory and learning, patients with SAH in the ACoA experience more difficulties in certain stages rather than exhibiting a global decline in this domain. In their case, greater impairment was observed in the recall stage than in the ability to store information (suggesting a possible overlap of executive functioning, necessary for the ability to retrieve content from long-term memory systems). Both DeLuca[26] and Ravnik et al.[18] suggest that the disruption of connections between frontal and limbic areas due to lesions in perforating branches of the ACoA accounts for the reduced recall ability, while the limbic structures traditionally associated with memory are preserved.

The fact that our results revealed impairments in functions less related to anterior regions, such as visual processing skills (e.g., EF and visual synthesis ability), may be evidence of the second hypothesis (i.e., a diffuse pattern of cognitive damage). It is likely that, due to the association between cognition and physiological phenomena (e.g., vasospasm, blood toxicity, neuroinflammation, brain edema), and not only the disruption of the connection between frontal and limbic areas, the brain's lesions are not confined to specific areas but rather affect the entire brain. Some studies that concluded in favor of the diffuse hypothesis were cited by Ravnik et al.,[18] demonstrating that the debate remains unresolved. We reiterate that, due to research design issues, our study did not include the analysis of surgical or physiological variables.

Ravnik et al.[18] suggested that blood toxicity in contact with parenchyma and surgical treatment are factors that can generate cognitive impacts from a more localized perspective (EF and verbal and visual recall) but recognized studies that showed more diffuse impairments. The pharmacotoxic effects of anesthesia may also account for the diffuse cognitive decline in these patients. The effects of anesthesia on cognition have been gaining relevance in recent years, although still at an early stage.

To our knowledge, no specific studies have investigated anesthetic side effects as a potential risk factor for cognitive decline in this patient population. However, Ancelin et al.[37] reported impairment of various cognitive functions, including EF, in patients undergoing orthopedic surgeries. According to them, neuronal changes related to aging can be exacerbated by the pharmacotoxic effects of anesthetic substances. Such substances could, for example, promote the acceleration of mild neurocognitive disorders toward forms of dementia. Furthermore, they noted that visuospatial functioning is a particularly vulnerable aspect of cognition in normal aging, in addition to being a hallmark of vascular-type neurocognitive disorder. In this sense, anesthesia could initiate or accelerate subcortical vascular lesions, culminating in more permanent declines, especially in visuospatial functions. If this conclusion applies to orthopedic patients, it is highly likely that it also applies to neurological patients.

Neuroinflammatory effects may also account for part of the postoperative cognitive decline. According to Saxena & Maze,[37] natural defensive reactions of the body are triggered by tissue injury or infections, a phenomenon involving a complex interaction between the immune system and the brain. This is an essential organic response for the body's self-repair, but it can, under certain conditions (e.g., advanced age, low cognitive reserve, insulin resistance, obesity), produce deleterious effects, including on cognition, by favoring excessive inflammatory responses. One of the reasons for cognitive damage, according to the authors, is that inflammatory processes can

impact synaptic plasticity, which underpins cognitive processes such as learning and memory. Although the authors referred only to memory components, it is possible that others, such as EF, are also impacted by chronic neuroinflammatory states.

It is worth noting that tissue damage is invariably inevitable during the treatment of ruptured aneurysms through the clipping method. Depending on clinical variables, more invasive methods may be necessary, increasing the extent of lesions, the inflammatory response, and possibly the cognitive sequelae. However, some authors, such as Hadjivassiliou et al.[38] concluded that the cognitive sequelae exhibited after treatment are more associated with complications from SAH, i.e., the cerebrovascular disease, than with the chosen treatment modality. In any case, it is recommended that future research investigate the association between neuroinflammatory aspects and cognitive deficits in patients operated on for SAH in the ACoA.

Surgical resection of a small portion of the gyrus rectus, for example, may be necessary in some cases. This surgical maneuver aims to facilitate access and visualization of the frontobasal region, where the ACoA and its perforating branches are located. Some studies assume that it is a safe technique from the perspective of cognitive sequelae.[17] Joo et al.[17] investigated this hypothesis based on cognitive screening conducted in a group of 39 patients, 15 and 44 days after surgery. Although they only used the Mini-Mental State Examination, the authors did not observe significant differences in cognitive performance between the group of patients who had the gyrus rectus resected (~65% of the sample) and the group where this maneuver was not necessary. The researchers observed a slight trend toward better performance by the second group (the "non-resected" patients). During the first evaluation, resected patients showed, on average, poorer performance, especially in verbal and executive domains, with improved scores obtained in the second evaluation.

Another potential risk factor for cognitive sequelae mentioned by some studies is vasospasm. Kreiter et al.[39] investigated predictive factors of cognitive impairment in a group of 113 patients affected by hemorrhagic stroke (not restricted to the ACoA but mostly located in anterior regions) three months after surgery. Overall, the sample's performance was below the population average in eight neuropsychological domains: global mental state, visual memory, verbal memory, reaction time, psychomotor functioning, executive functioning, visuospatial functioning, and language.

Regarding vasospasm, the authors concluded that the phenomenon does not appear to correlate clearly with the cognitive decline observed in these patients, contrary to what had been suggested in earlier studies. According to Kreiter et al.[39] the recent development of medications used in vasospasm management, such as nimodipine, suggests that other sources of infarction or ischemia (e.g., procedural complications) are likely more responsible for cognitive damage than vasospasm itself.

Determining which cognitive functions and to what extent they are potentially impaired by the disease and/or treatment leads to the issue of determining the transience or permanence (or the transience of some and permanence of others) of sequelae, something that remains uncertain.[9] Clarifying this issue could help optimize neuropsychological rehabilitation programs that are more effective for the profile of these patients, suggesting the implementation of predominantly restorative strategies for potentially transient damage or predominantly compensatory strategies for permanent conditions.

Methodological difficulties justify the scarcity of research on patients operated on after a considerably long period following surgery. The present study followed the evolution of 31 patients at three moments (three, six, and twelve months) after surgery. Other studies limited the observation of their respective samples to similar or, occasionally, slightly longer intervals,[9,18,26] which represents a limitation of those studies.

Some studies, however, observed the evolution of patients over a longer period. Nassiri et al.,[9] for example, mapped, albeit generically, the global cognitive functioning and quality of life of 32 of these patients approximately eight years after surgery. Standardized tests were not used. Cognitive complaints (in the domains of memory, perception, and motor functioning) in daily life activities were reported by participants from all three groups. Overall, six (19%), all belonging to the clipping groups, scored in a way that suggested cognitive impairment, with worse performance on the instruments assessing cognition. Eight years after surgery, the patients continued to report cognitive complaints, with better performance in the group of patients treated by embolization.

We emphasize that, although the results of this study found visuospatial impairment, the initial objective of this work was to investigate the different cognitive functions and not only the altered abilities. For this reason, we suggest the conduction of further studies that utilize a greater quantity and diversity of instruments for visuospatial functions, as well as more specific and sensitive tests for attentional abilities.

Our findings directly contribute to the discussion about "ACoA syndrome," particularly concerning visuospatial functions, which have so far been less explored in the literature. The significant improvement in patients' performance on visual orientation and organization tests over 12 months suggests that initially observed deficits may be transient and not necessarily permanent, as suggested in previous studies.[9,26] This reinforces the hypothesis that, although "ACoA syndrome" involves severe neuropsychological impairment, some cognitive functions, especially visuospatial ones, may show progressive recovery over time, opening new perspectives for rehabilitation approaches focused on these specific domains.

Conclusion

We conclude that, indeed, several cognitive functions are impaired by cerebrovascular disease (SAH in ACoA) and by the surgical treatment for its correction. However, contrary to the extensive literature pointing to an "ACoA syndrome"

(memory, executive functions, alterations in consciousness, and personality), we observed that a group of functions anatomically "more distant" from the frontotemporal regions may also be impaired, albeit more subtly, as is the case with visuospatial and visuoperceptual abilities. This impairment is apparently followed by a positive prognosis within a year after surgery, considering the increasing performance of our samples in the tests dedicated to these abilities. By comparing our data with recent, though sparse, studies that have investigated the association between certain physiological phenomena and cognitive impairment, we hypothesize that such factors may have, to some extent, contributed to this decline. It is worth noting that these phenomena (vasospasm, bleeding, anesthetic toxic effects, among others) represent threats to the brain from a diffuse perspective, while the ACoA stroke and its respective treatment are more circumscribed to the frontotemporal region, explaining the heterogeneity of neuropsychological profiles in these patients.

Conflict of Interest
None.

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Prognostic Value of Neutrophil to Lymphocyte Ratio in Cerebral Venous Thrombosis Outcomes: Systematic Review

Valor prognóstico da relação neutrófilo-linfócito nos resultados da trombose venosa cerebral: Revisão sistemática

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Abstract

Introduction The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker that may be associated with the presence and degree of severity of vascular diseases and is a possible predictor of risk and mortality of cerebral venous thrombosis (CVT).
Methods Using PRISMA, the articles were evaluated based on sensitivity, specificity, cut-off, and AUC using the databases PUBMED and BVS. Inclusion criteria of articles were as follows: written in English, in cohort presentation, clinical trial, or control case with the key terms included in the abstract, title, or keywords of the selected articles.
Results A total of 700 articles were analyzed in the databases, obtained through the search string, and evaluated for the exclusion and inclusion criteria previously indicated. Four articles were included in the final analysis. The values of sensitivity (Sen) and specificity (Esp) differed among the articles analyzed, and three of the four articles showed higher specificity. Cut-off and AUC, likewise, differed in most articles, with a lower cut-off value of 2.1 and a higher value of 6.8. The AUC ranged from 0.71–0.77. The simple mean values for Sen and Esp were 62.8% and 78.7%, respectively.
Conclusion The data show that NLR can predict worse outcomes in CVT with moderate values of specificity and sensitivity (Ms Esp 78.7% / Ms Sen 62.8%).

Keywords
- cerebral venous thrombosis
- neutrophil-lymphocyte ratio
- inflammatory marker
- prognosis
- predictor of risk and mortality

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Resumo

Introdução A razão neutrófilo-linfócito (NLR) é um marcador inflamatório que pode estar associado à presença e ao grau de gravidade de doenças vasculares e é um possível preditor de risco e mortalidade de trombose venosa cerebral (TVC).

Métodos Usando o PRISMA, os artigos foram avaliados com base na sensibilidade, especificidade, cut-off e AUC usando os bancos de dados PUBMED e BVS. Os critérios de inclusão dos artigos foram os seguintes: escritos em inglês, em apresentação de coorte, ensaio clínico ou caso controle com os termos-chave incluídos no resumo, título ou Palavras-chave dos artigos selecionados.

Resultados Um total de 700 artigos foram analisados nos bancos de dados, obtidos por meio da sequência de busca e avaliados para os critérios de exclusão e inclusão indicados anteriormente. Quatro artigos foram incluídos na análise final. Os valores de sensibilidade (Sen) e especificidade (Esp) diferiram entre os artigos analisados, e três dos quatro artigos apresentaram maior especificidade. O corte e a AUC, da mesma forma, diferiram na maioria dos artigos, com um valor de corte inferior de 2,1 e um valor superior de 6,8. A AUC variou de 0,71 a 0,77. Os valores médios simples para Sen e Esp foram 62,8% e 78,7%, respectivamente.

Conclusão Os dados mostram que a NLR é capaz de prever um pior resultado na TVC com valores moderados de especificidade e sensibilidade (Ms Esp 78,7% / Ms Sen 62,8%).

Palavras-chave

- trombose venosa cerebral
- razão neutrófilo-linfócito
- marcador inflamatório
- prognóstico
- preditor de risco e mortalidade

Introduction

Cerebral venous thrombosis (CVT) is a rare neurological condition (~1% of cases of stroke) that is related to the aggregation of erythrocytes, fibrin, and platelets in the sinuses or dural veins of the brain and has a high degree of severity in all age groups despite being more common in young female adults.[1–6] CVT cases are estimated at 3–12 cases per million per year.[7]

The clinical signs of this condition vary widely depending on the severity, location, and characteristics of the thrombotic process. The aggravators depend on the patient's age and complications involving the deep or cortical cerebral venous system that increase intracranial pressure, resulting in loss of consciousness.[2] Although the mechanism of CVT is not fully understood, evidence suggests that this condition is related to thrombo-inflammatory processes and risk factors, which include inflammation of the head and face, hypercoagulation, lesions in the vascular walls, and intracranial hypotension.[2,3,6,8–10]

The prognosis of CVT is hindered by a variety of etiologies and clinical manifestations, with outcomes that vary from total recovery to death.[11,12] The diagnosis of CVT is often delayed and takes ~4–7 days after the onset of symptoms.[12] Delay in diagnosis is related to a variety of non-specific manifestations. Patients under the age of 50 years who present with headaches with atypical characteristics, focal neurological deficits, intracranial hypertension, and haemorrhagic infarction should be worked up for a possible diagnosis of CVT.[12,13] Neuroimaging examinations are fundamental to patient prognosis and progress.[12,13] Drug treatment for CVT includes anticoagulation, etiologic treatment, and symptomatic therapy; however, the decline in mortality from CVT cases is mainly due to better diagnosis and earlier anticoagulant treatment.[6]

The neutrophil-to-lymphocyte ratio (NLR) is a prognostic inflammatory marker with a high value that may be associated with the presence and higher degree of severity of vascular diseases, classifying it as a risk and mortality predictor of cardiovascular diseases.[3,14,15] The ease and low cost of performing the blood count is another advantage in the use of NLR as a prognostic predictor of thrombo-inflammatory diseases, cardiac events, ischemic stroke, neoplasms, sepsis, and infectious pathologies.[3,16–23] The NLR integrates information from the innate (nonspecific) and adaptive (specific) compartments of the immune system, categorizing a reliable measure of the body's inflammatory load.[18] Poredoš et al. also indicate a faster NLR in demonstrating the evolution of these diseases.[22]

The NLR was recently postulated as a thrombo-inflammatory marker with a high potential for predicting adverse outcomes and mortality in cases of cerebrovascular diseases, such as CVT.[24–26] Increased NLR is associated with worsening cases of thrombosis and inflammation as well as an indicator of progressing destructive inflammation.[3,6] NLR is also seen as a more stable and viable marker than isolated changes in neutrophil or lymphocyte levels.[6] The combination of the NLR with other markers, such as the platelet-to-lymphocyte ratio (PLR), increases the accuracy in the study of clinical pictures of cerebral venous thrombosis.[27–30]

This study aims to evaluate the prognosis accuracy of higher NLR in patients with CVTBiblioteca virtual.

Methodology

Search for Articles

To conduct this study, following PRISMA guidelines articles and data were collected from the PUBMED and Biblioteca Virtual em Saúde (BVS) platforms using the search string

Table 1 Inclusion and Exclusion criteria of articles presents on the study

Inclusion	Exclusion
1. Article must be written in English	1. Incomplete texts
2. Article must be in cohort presentation, clinical trial, or control case	2. Inadequate follow-up of the patients
3. Key terms must be included in abstract and/or title and/or keywords of the selected articles	3. Not expressing results for the research question
4. Adequate analysis score in the NewCastle Ottawa Score	4. Articles that do not show data on sensitivity, specificity, area under the curve, or cut-off value that involve NLR in the context of CVT

Table 2 NewCastle Ottawa Scale (NOS) scores of the articles in this study

Study analyzed	Score on NewCastle Ottawa Scale (NOS)
Aguiar, D	8
Li, Shen	9
Wang, L	9
Akboga, Y	8

("Neutrophil to Lymphocyte Ratio" OR "Neutrophil-lymphocyte ratio" OR "Neutrophil/lymphocyte ratio" OR "NLR" OR "Inflammation index" OR "Inflammatory markers" OR "Inflammation mediators" OR "inflammatory Status" OR "inflammation prognostic") AND ("cerebral venous thrombosis" OR "venous thrombosis" OR "venous sinus thrombosis" OR "deep cerebral venous thrombosis" OR "deep venous thrombosis" OR "intracranial thrombosis" OR "CVT" OR "VTE" OR " Cerebral sinus venous thrombosis" OR "Cerebral venous and sinus thrombosis" OR "sagittal sinus thrombosis" OR "dural sinus thrombosis" OR "intracranial venous thrombosis" OR "CSVT" deep cerebral venous thrombosis. On the platforms, the filters selected for the search were clinical trials, cohort, and case-control studies between 2010 and 2021. Subsequently, the articles obtained from this search and any relevant references cited in the articles were reviewed by two independent and blinded reviewers, the senior author reviewed discrepancies between them.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are shown in ►**Table 1**.

Quality Assessment

The selected articles were evaluated using the presence or absence of sensitivity, specificity, cut-off, AUC, and time. Articles that did not have values for these variables were excluded at this stage. Bibliographic citations of the included studies were checked by applying crossed references to find another suitable article.

Articles were submitted for analysis using the Newcastle Ottawa Scale (NOS), a tool developed to assess the quality of nonrandomized studies available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. The NOS uses three perspectives to judge the study: the selection of study groups, comparability of the groups, and ascertainment of the exposure or outcome of interest for case-control or cohort studies, respectively. The analysis of the articles presented in this study is shown in ►**Table 2**.

Results

A total of 385 articles were identified in the research, of which 189 were on the PUBMED platform, while 196 were on the BVS network. Of the articles found, 125 were removed as duplicates, and one article, analyzed in its entirety, was likewise removed because it did not contain relevant information for the review. Four of these articles were included using the inclusion criteria described in the methodology. The articles were given a score from the Newcastle-Ottawa Scale (NOS) of 8 for the titles of AGUIAR and AKBOGA and 9 for the articles by Wang and Li, which were considered satisfactory for the analysis of the exposed data (►**Table 2**). The article selection process is described in the flowchart recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses platform (PRISMA flowchart).

PRISMA Flowchart

The selected articles were dated from 2016 to 2020, with an analysis period ranging from 33 months[3] to 71 months.[29] The data found in the included articles are listed in ►**Table 3**.

Table 3 Sensitivity Values (SEN), Specificity (ESP), Area under the curve (AUC), Cut off, Number (N), and Period

Author	Year	N	Period	NLR Cut-off	NRL Sen	NRL Esp	AUC
Aguiar, D	2020	62	48 months	5.1	67%	79%	0.71
Li, Shen	2020	270	71 months	6.8	56.5%	83.3%	0.74
Wang, L	2018	95	36 months	4.2	61.5%	86.6%	0.77
Akboga, Y	2016	277	33 months	2.1	66.3%	66%	0.73

Discussion

Cerebral venous thrombosis is related to more severe cases with late diagnosis, and the evolution of the patients has not been fully elucidated. The NLR can be especially important in this scenario to provide information on the patient's inflammatory condition, which helps in the prognosis of patients.

The main results of the analyzed studies show that Aguiar et al. reported an association between higher baseline levels of NLR and worse functional prognosis at the 90th day in patients with CVT. AKBOGA, which was published in the Journal of the Neurological Sciences, presents similar values of sensitivity and specificity of the NLR and had the lowest cut-off and AUC than those of the other studies. WANG showed an evident difference between specificity and sensitivity among the selected articles. Their paper reported the highest specificity, a cut-off of 4.2, and the highest AUC. Li had the lowest sensitivity, the second highest specificity value, and the highest cut-off. Their AUC was similar to that of the other papers. Finally, AGUIAR presented the highest sensitivity and specificity in the mean values, a cut-off of 5.1, and the lowest AUC. The simple averages of the sensitivity and specificity values were 62.8% and 78.7%, respectively.

Wang et al. revealed that the group with NLR that was higher than the cut-off showed poorer outcomes when compared with patients with good outcomes. The analysis found that the baseline NLR was significantly associated with a high risk of poor outcomes at discharge, suggesting that baseline inflammation could influence and predict the short-term outcomes of CVT and that higher NLRs were significantly and independently related to the presence of CVT.

All articles analyzed showed that the NLR is strongly associated with CVT. Improved results of inflammation biomarkers in gender groups were reported in one of the four studies but were not cited in the others. An important result was the improved effect of NLR on mortality when compared with independent counts of neutrophils or lymphocytes.

Wang L had some significant limitations. As a retrospective study, some data were missing, and the evaluation of the outcome at a fixed time point could not be evaluated. In addition, some patients were lost to follow-up for various reasons; the number of studied inflammatory factors and the study population were too small to obtain an acceptable conclusion. Furthermore, the underlying mechanism of inflammation acting on CVT cannot be precisely explained by this type of clinical study, necessitating further exploration of this aspect. Akboga, Y was a single-center study, and local PLR and NLR values were used for analysis rather than temporal trends.

The analyzed articles provided new data that show the relationship between higher admission NLR and worse prognosis in CVT, which shows that NLR can be useful for the prognosis of CVT when compared with the count of neutrophils and lymphocytes alone.

Our results can be used in clinical practice not alone, but with other factors and the clinicians can make decisions regarding more aggressive therapies or more frequents imagiologic or laboratory follow us for example for ICU discharges, patients with CVT and higher admissions values of NLR should be considered as a risk group for worse outcome (functional outcome).

Conclusion

NLR can predict with moderate accuracy prognosis in patients with CVT, it's a safe, and low-cost tool that can be helpful in clinical practice.

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Conflict of Interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Subdural Empyema, an Intracranial Sinus Complication

Empiema subdural, uma complicação intracraniana sinusal

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Abstract

Subdural empyema is the most common intracranial complication in sinusitis, defined as an infection with purulent collection between the inner surface of the dura mater and the outer surface of the cerebral arachnoid. This condition is underestimated and neglected by physicians due to its low incidence. However, despite its rarity, it is a serious pathology, requiring early diagnosis and therapeutic management. The present work aims to emphasize sinusitis as the primary focus of subdural empyema and the importance of its eradication for treatment.

Scientific articles published in the past 15 years on PubMed, SciELO, and BVS databases were reviewed using the keywords *sinusitis*, *subdural empyema*, and *intracranial complication*, and selected according to the inclusion criteria: case reports and retrospective studies from 2008 to 2023. At last, 16 works were selected. According to the reviewed articles, sinusopathy should not be underestimated, and more attention should be given to clinical signs suggestive of intracranial infections.

In conclusion, despite being uncommon, subdural empyema resulting from sinusitis complications is a neurosurgical emergency that carries considerable morbidity and mortality rates. Therefore, physicians should be aware of its correct treatment. Lastly, it was observed that otorhinolaryngological procedures can be performed to eliminate the primary focus, while neurosurgical interventions can solve this pathology. Thus, it is impossible to deny the importance of new studies with clear analysis regarding the eradication of the primary focus.

Keywords

- subdural empyema
- sinusitis
- intracranial complication

Resumo

O empiema subdural se traduz como a complicação intracraniana mais comum da sinusite, sendo definido como uma infecção cuja coleção purulenta se localiza entre a superfície interna da dura-máter e a superfície externa da aracnoide cerebral. Essa condição é subestimada e negligenciada por médicos, devido a sua baixa incidência.

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Entretanto, apesar de rara, essa patologia é grave e requer um diagnóstico e uma abordagem terapêutica precoce. O objetivo do presente trabalho é reforçar a sinusite como foco primário do empiema subdural e a importância da sua erradicação para o tratamento.

Foram revisados os artigos científicos publicados nos últimos 15 anos nas bases de dados PubMed, SciELO e BVS, usando os descritores: *sinusitis*, *subdural empyema* e *intracranial complication*, e selecionando os estudos de acordo com os critérios de inclusão: relatos de caso e estudos retrospectivos de 2008 a 2023. Por fim, foram selecionados 16 trabalhos. Conforme os artigos estudados, não a sinusopatia não pode ser subestimada e os sinais clínicos sugestivos de infecções intracranianas devem receber mais atenção.

Conclui-se que, apesar de incomum, o empiema subdural advindo de complicações da sinusite é uma emergência neurocirúrgica com morbidade e mortalidade consideráveis. Assim, os médicos devem se atentar ao seu tratamento correto. Por fim, procedimentos otorrinolaringológicos podem ser feitos para erradicar o foco primário, enquanto intervenções neurocirúrgicas podem solucionar essa patologia. Portanto, é inegável a importância de novos estudos com uma análise esclarecedora referente à erradicação do foco primário.

Palavras chaves
- empiema subdural
- sinusite
- complicação intracraniana

Introduction

Sinusitis is a common medical condition from which most patients can recover with proper treatment. However, in rare cases, there are potentially lethal intracranial complications, such as subdural empyema, meningitis, venous sinus thrombosis, intracerebral and epidural abscesses, which develop as a result of the inflammation of frontal, ethmoidal, sphenoidal, and maxillary sinuses.[1–5]

Subdural empyema is the most common complication, and it can be defined as an infection with its purulent collection located between the inner surface of the dura mater and the outer surface of the cerebral arachnoid. Moreover, it should be noted that it is more frequent among male patients younger than 20 years of age.[2,4–11]

The mortality rate can be significantly reduced with antibiotics, and it varies from 4 up to 15%, while morbidity in survivors can reach up to 50% for residual neurological deficits, 15 to 35% for hemiparesis, and 12 to 37,5% for persistent seizures.[2,4–6,12]

It is widely known that subdural empyema is overlooked by physicians due to its low incidence. However, despite its rarity, this pathology is a serious condition and requires early diagnosis and therapeutic management, as sequelae are reported in up to 40% of cases and onset is related to late treatment and the duration of the symptoms prior to diagnosis.[11,13]

Still, delays in diagnosis occur due to the absence of specific signs. Therefore, in cases with clinical suspicion, patients must be evaluated via computerized tomography (CT) or magnetic resonance imaging (MRI) to rule out intracranial infection. Empyema is considered a neurosurgical emergency due to the increase in intracranial pressure in the first 24 to 48 hours, which may lead to coma and death. Thus, physicians must be aware of its risks.[2,5,6]

In summary, this study aims to reaffirm sinusitis as the primary focus of subdural empyema and the importance of its eradication for treatment.

Materials and Methods

A systematic literature review was conducted. Articles were selected from the PubMed, SciELO, and BVS platforms, using the descriptors *sinusitis*, *subdural empyema*, and *intracranial complication*, followed by the Boolean operators "AND" and "OR" to combine keywords. All the references from the eligible studies were also reviewed in search of additional articles.

The inclusion criteria were case reports and retrospective studies from the past 15 years (2008–2023), available in full, were included in this study. We excluded unrelated articles, reviews, meta-analyses, and those without full text available. Following the criteria application, 16 articles remained.

Results

Out of the 16 selected articles (►**Fig. 1**), 5 are retrospective studies, and the other 11 are case reports, which reinforce subdural empyema as a complication of sinusitis. Moreover, they highlight this condition as a neurosurgical emergency and highlight symptoms that raise clinical suspicion of related intracranial complications. Some studies also provide evidence for the recommendation of otolaryngological procedures, since sinusitis is the main focus and must be treated to eradicate the infection (►**Table 1**).

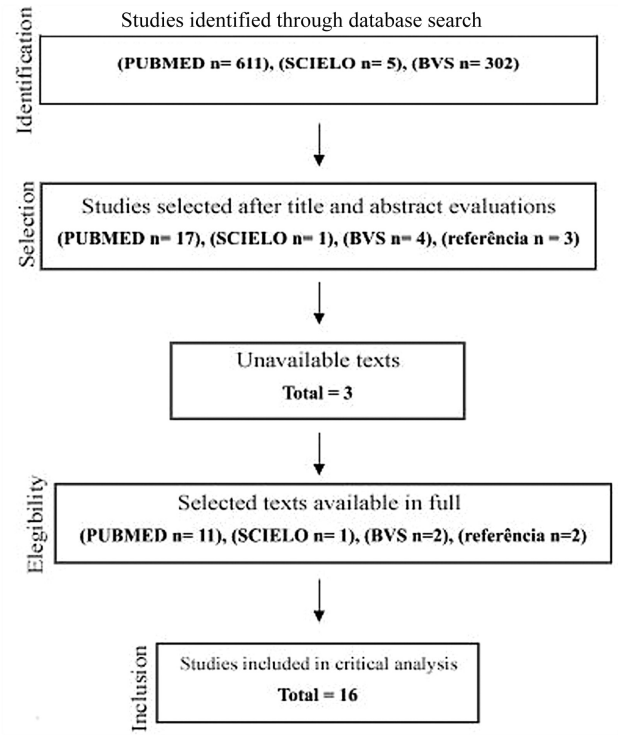

Fig. 1 Study methodology.

Discussion

Sung et al.[1] and Belentani et al.[7] argued that intracranial complications in consequence of rhinosinusitis conditions occur through direct extension due to a defect in the anterior cranial base, or hematogenously through retrograde thrombophlebitis of veins which interlink face and skull sinuses.[1,7]

Aljonas and Watanabe[6] reported a clinical case regarding a 17-year-old male patient diagnosed with rinosinusitis who underwent outpatient, antibiotic treatment. His symptoms regressed temporarily but evolved again after discontinuing medication. Thus, the patient underwent outpatient treatment again. Subsequently, the patient had changes to his clinical condition, such as seizures and decreased levels of consciousness. An MRI scan was performed, leading to clinical suspicion of subdural empyema. However, his condition ultimately led to brain death.[6]

The authors note that the most common symptoms are headaches, altered mental status, seizures, focal deficits, vomit, orbital swelling, fever, rhinorrhea, nasal obstruction, neck stiffness, and Kerning's sign. Moreover, they insist on the need for imaging exams in any case of sinusitis with neurological signs, failure from a previous treatment, or associated orbital cellulitis, to ensure rapid diagnosis and avoid outcomes such as the reported one.[6]

Barroso et al.[2] state that imaging exams are mandatory for patients diagnosed with frontal sinusitis who persistently demonstrate fever, frontal edema, or failure to resolve symptoms, even if their condition lacks neurological signs.[2]

Belentani et al.[7] and Pereira et al.[8] emphasize that subdural empyema diagnosis is based on clinical suspicion. Therefore, physicians must be vigilant in cases that show a symptom evolution with fever, headaches, or neurological manifestations. Lastly, these authors highlight the importance of specific procedures for paranasal sinuses, along with the endoscopic submucosal dissection (ESD), to eradicate the primary focus infection during the same surgical procedure. This also brings the advantage of reducing mortality rates. Similarly, antibiotic treatment associated with otorhinolaryngological, and neurological surgical approaches result in good prognosis.[8]

Rasul et al.[12] conducted a retrospective study regarding 36 patients and demonstrated an increase in the occurrence of sinusitis and related intracranial complications. The cause of this increase, however, remained unclear. Furthermore, in their study, none of the patients who underwent simultaneous otorhinolaryngological procedures needed repeated surgery, emphasizing the importance of controlling the primary focus infection.[12]

According to Hicks et al.,[14] laboratory data such as leukocytosis, polymerase chain reaction (PCR), and elevated sedimentation levels in a sinusitis scenario can be used to raise suspicion of possible intracranial complications. Even though those are nonspecific markers of infection and inflammation, a comparison among 12 patients suggests that individuals diagnosed with uncomplicated sinusitis have lower PCR and sedimentation levels than those with intracranial abscesses. However, the small sample size is one of the study's limitations.[14]

Pereira et al.[8] concluded that sinusitis, when it is not adequately treated, may lead to intracranial complications such as subdural empyema. They also observed that headaches and fever are often found prior to more specific symptoms, such as neck stiffness, dizziness, vomit, seizures, altered consciousness, and focal neurological signs.

Mathon and Korinek[13] emphasize the delay in therapy as the main factor for bad subdural empyema prognosis. They also bring attention to the importance of entry point surgical treatment, especially when draining sinusitis, to increase bacterial isolation and improve the effectiveness of antibiotic therapy.[13]

According to Szyfter et al.,[3] neurological signs associated with intracranial complications have been less frequent in recent years, when compared with the usual symptoms of paranasal sinusitis. They further emphasize that simultaneous treatment of inflammation along with intracranial complications is quite effective.[3]

Similarly, Herrero et al.[11] describe that the therapeutic approach includes not only surgical intervention of empyema but also drainage of the original focus.[11]

Building on other studies, Waseem et al.[4] suggest that subdural empyema is one of the most common complications of sinusitis and that the similarity of its symptoms with those of sinusitis can make it difficult to differentiate. The authors also noted that acute or progressive headaches are the most important indicator of intracranial complications. They further report that, despite antibiotic treatment, infections can still progress rapidly and might require surgical drainage, which is the most important factor in determining a favorable outcome.[4]

Table 1 Summary of selected articles

Author (year)	Title	Type of study	Sample	Points relevant to each study
Aljonas and Watanabe (2018)[6]	Subdural empyema following rhinosinusitis condition – case report	Case report	It reports a case regarding a 17-year-old male patient, diagnosed with rhinosinusitis. It evolved, however, to an SDE. The patient received antibiotic therapy treatment, but his condition ultimately led to death.	Complications of rhinosinusitis may come from acute or chronic infections. Although they occur more frequently in children, these infections may also impair adult patients. Among those of nasosinusal origin, SDE, cerebral, and extradural abscesses, as well as meningitis are mentioned as the most common. Treatment for empyemas is a neurosurgical emergency (burr holes or craniotomy) due to how quickly it can lead to coma or death as a consequence of the increase in intracranial pressure in the first 24 to 48 hours.
Sung et al. (2018)[1]	Bilateral subdural empyemas with meningitis secondary to acute barosinusitis	Case report	Healthy, immunocompetent 30-year-old man developed bilateral SDEs secondary to barosinusitis succeeding a plane trip abroad.	Intracranial complications of acute rhinosinusitis are not common, but may lead to extreme consequences, such as neurological morbidity or death.
Rasul et al. (2022)[12]	The Case for Early Antibiotic Commencement and Source Control in Pediatric Subdural Empyema: A Single-Centre Retrospective Case Series	Retrospective cohort study	Every patient admitted to their unit with a diagnosis of SDE over an 11-year period. A total of 36 patients received medical treatment throughout the inclusion period.	The contemporary series highlights some of the important changes regarding presentation and management of SDE over time. First, bimodal age distribution is in accordance with prior observations, with peaks in infancy, secondary to meningitis, and in older children, secondary to sinusitis or otitis media.
Belentani et al. (2008)[7]	Subdural Empyema: Complication of Acute Rhinosinusitis	Case report	13-year-old male patient.	SDE as an intracranial complication due to sinus disease, despite being infrequent, is still a reality. It is more common among male patients under 20-years-old, and presents considerable morbidity and lethality. It must be faced as a matter of urgency.
Barroso et al. (2019)[2]	Recurrent subdural empyema secondary to bacterial frontal sinusitis in an immunocompetent teenager: case report	Case report	16-year-old immunocompetent patient, with no associated comorbidities, who suffered an aggressive evolution to SDE from acute sinusitis. Urgent clinical-surgical approach was necessary.	Morbidity in SDE may reach 50% of the cases for residual neurological deficits, 15 to 35% for hemiparesis, and 12 to 37,5% for persistent seizures. In this case, the clinical picture had a satisfactory evolution, with no sequelae.
Hicks et al. (2011)[14]	Identifying and managing intracranial complications of sinusitis in children: a retrospective series	Retrospective cohort study	Every underage patient admitted to the Children's Hospital between January 1st, 2001, and December 31, 2009, with a diagnosis of sinusitis and intracranial suppuration or CVST.	Findings suggest that acute sinusitis, in combination with severe intractable headache, various degrees of altered level of consciousness, focal neurological deficits, and/or meningeal irritation signs, should raise clinical suspicion for potential sinusitis intracranial complications.
Pereira et al. (2018)[8]	Subdural empyema as a consequence of sinus diseases: considerations on 11 cases	Retrospective cohort study	11 cases of sinogenic SDE treated from January 1994 to August 1995 at the Department of Neurosurgery and Infectology from João Alves Filho Hospital (Aracaju, SE, Brazil) were studied.	It is worth noting the importance of conducting the specific procedure for the paranasal sinuses simultaneously to the SDE treatment. This approach aims to eradicate the infection's primary focus during the same surgical procedure, reducing the mortality rate.
Nicoli et al. (2016)[15]	Intracranial Suppurative Complications of Sinusitis	Retrospective cohort study	6 patients diagnosed with intracranial infection related to sinusitis; 4 patients with epidural abscess;	This study highlights the important clinical finding that patients with epidural abscess or SDE related to sinusitis usually present

Table 1 (*Continued*)

Author (year)	Title	Type of study	Sample	Points relevant to each study
			1 patient with both epidural abscess and SDE; 1 patient with SDE.	signs of elevated intracranial pressure instead of ordinary signs of sinusitis.
Gorman et al. (2018)[16]	Subdural empyema	Case report	69-year-old female patient on long-term immunosuppressive therapy for liver transplantation.	SDE is typically caused by prior neurosurgical procedure, sinusitis, otitis media, mastoiditis or meningitis. Its imaging characteristics may look subtle compared with its clinical severity. Thus, a high index of suspicion for diagnosis is required.
de Albuquerque Freitas et al. (2010)[9]	Intracranial complications of rhinosinusitis	Case report	15-year-old male patient, previously healthy, admitted to Risoleta Tolentino Neves Hospital in Belo Horizonte, MG, Brazil.	IEA and SDE are rare but highly lethal intracranial complications of sinusitis. They must be faced as a matter of urgency. In cases with clinical suspicion, CT is still the first exam in diagnostic investigation.
Mathon & Korinek (2018)[13]	Subdural empyema: an underestimated neurosurgical emergency	Case report	The study describes the clinical cases of three patients, aged 17, 21, and a 16-years.	SDE is an absolute neurosurgical emergency. Any delay in diagnostic and/or therapeutic management exposes the patient to a higher risk of death or neurological sequelae.
Szyfter et al. (2018)[3]	Simultaneous treatment of intracranial complications of paranasal sinusitis	Retrospective cohort	51 patients with intracranial complications of sinusitis, treated in the Department of Otorhinolaryngology and Laryngeal Oncology at the Poznán University of Medical Sciences from 1964 to 2016.	The most common intracranial complications of sinusitis develop as a result of inflammation of the frontal sinuses, ethmoid cells, sphenoid sinus and, less frequently, the maxillary sinuses.
Shen et al. (2018)[10]	Interhemispheric Subdural Empyema Secondary to Sinusitis in an Adolescent Girl	Case report	13-year-old female patient.	The most common cause of SDE is sinusitis, which represents 15% of hospitalized patients.
Varas et al. (2011)[11]	Subdural empyema secondary to sinusitis. A pediatric case report	Case report	9-year-old male patient.	For early diagnosis, it is important to search for any neurological complications in sinusitis cases with a negative clinical course. In view of clinical suspicion, imaging diagnosis is necessary to rule out complications.
Waseem et al. (2008)[4]	Subdural empyema complicating sinusitis	Case report	A case of sinusitis causing SDE in an immunocompetent, healthy teenage patient.	Despite improvements in antibiotic therapies, sinusitis still carries a risk of serious and potentially fatal complications. Physicians must consider SDE or brain abscess when evaluating a patient with severe headaches, especially if there is a recent history of sinusitis or ear infection.
Bruner (2012)[5]	Subdural empyema presenting with seizure, confusion, and focal weakness	Case report	16-year-old male patient.	Emergency neurosurgical consultation is essential, because surgical intervention (burr hole or craniotomy) is necessary in most cases to provide the best opportunity for neurological recovery. Similarly, otorhinolaryngological consultations are recommended because FESS can assist with drainage and recovery.

Abbreviations: CT, computed tomography, CVST, cerebral venous sinus thrombosis; FESS, functional endoscopic sinus surgery; IEA, intracranial epidural abscess; SDE, subdural empyema.

Contrary to other studies, Nicoli et al.[15] say that patients with intracranial complications related to sinusitis often present signs of elevated intracranial pressure rather than usual sinusitis signs. Moreover, in accordance with other studies, they advise drainage of both the source of infection and the intracranial suppuration, in combination with antibiotic therapy, to limit morbidity, mortality, and recurrence. In addition, these authors emphasize the need for multidisciplinary management by neurosurgeons and otorhinolaryngologists.[15]

According to Bruner et al.,[5] complications historically occurred secondary to middle ear infection, but currently are more frequent as a consequence of bacterial sinusitis. The authors also highlight that otolaryngological and emergency neurosurgical consultations are essential, since a functional endoscopic sinus surgery (FESS) can assist in drainage and recovery.[5]

In summary, sinusitis is the most common cause of subdural empyema, and the aforementioned articles reinforce the need to raise suspicion for intracranial complications whenever there is a poor clinical course, to obtain better therapeutic response and to reduce the risk of morbidity and mortality.

Additionally, sinus disease ought not to be underestimated, and physicians should pay attention to clinical signs suggestive of intracranial infections, as subdural empyema is a neurosurgical emergency that requires rapid recognition for appropriate intervention. With the analyzed data, it becomes evident there is a great diversity of symptoms, so imaging tests should be performed in cases with headaches, fever, or if the treatment fails, even if they show no neurological signs.

Furthermore, it has been observed that antibiotic therapy shows better results and prognosis when associated with otorhinolaryngological and neurological surgical approach, since these contribute to the eradication of the primary focus. For this reason, Rasul et al.[12] reported no repeated surgeries among their 36 patients, all of whom underwent these simultaneous procedures. Therefore, we emphasize the importance of further research addressing this topic and thoroughly examining the relationship between both interventions.

This work presents some limitations, as it did not address empyema treatment, except for surgical intervention simultaneous to otorhinolaryngological treatment to eradicate the primary focus. Furthermore, there were few studies on the relationship between both interventions. Finally, most of the included studies are case reports, so the final sample size is considerably small. There is a scarcity of studies measuring the neglect from both doctors and patients regarding sinusitis.

Despite this limitation, the present study reinforced sinusitis as the primary focus of empyema to raise awareness regarding this matter and highlighted the main symptoms that lead to early diagnosis. Finally, we discussed otorhinolaryngological treatments aimed at eradicating sinusitis being managed simultaneously to surgical intervention.

Conclusion

In light of this discussion, we can conclude that sinusitis is indeed one of the primaries focuses of subdural empyema. However, its treatment is still neglected. Despite being infrequent, subdural empyema resulting from sinusitis complications is a neurosurgical emergency with significant morbidity and mortality rates. This should be enough to encourage careful monitoring of patients diagnosed with sinusitis.

Additionally, we discussed how otorhinolaryngological procedures can eradicate the primary focus, and neurosurgical interventions may be conducted to resolve subdural empyema. However, there is limited data regarding these approaches, preventing a comprehensive and widespread understanding of the subject. Thus, a larger sample of patients would provide more precise information on how to prevent and treat this condition.

Furthermore, the importance of new studies providing a clear analysis of these issues cannot be denied.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Immunomediated Encephalitis: New Diagnoses on the Neurology–Psychiatry Interface

Encefalite imunomediada: Novos diagnósticos na interface neurologia–psiquiatria

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Abstract

Immune-mediated encephalitis is a real diagnostic challenge. Initially, patients present with subacute behavioral alterations, evolving over months, being attributed to purely psychiatric mechanisms, as well as neurological symptoms that often go unnoticed by professionals who are not neurologists. The etiologies behind these diseases are represented by paraneoplastic syndromes (including occult tumors) as well as viral infections, in both cases constituting true immunological triggers with exposure of antigens that will lead to a cross-immunological response directed at healthy structures of the nervous system. In the current review, we present the different clinical scenarios which differ based on antibodies against membrane receptors described so far, emphasizing the relevance of an early diagnosis for a smaller impact on prognosis.

Keywords
- encephalitis
- autoimmune encephalitis
- antibody-mediated encephalitis
- limbic encephalitis

Resumo

As encefalites imunomediadas constituem-se em um verdadeiro desafio diagnóstico. Inicialmente, os pacientes apresentam alterações comportamentais de caráter subagudo, com meses de evolução, sendo atribuídos a mecanismos puramente psiquiátricos, bem como sintomas neurológicos que passam muitas vezes despercebidos por profissionais não neurologistas. As etiologias por trás destas doenças são representadas por síndromes paraneoplásicas (incluindo tumores ocultos) bem como por infecções virais, em ambos os casos constituindo verdadeiros gatilhos imunológicos com exposição de antígenos que desencadeará uma resposta imunológica cruzada direcionada a estruturas saudáveis do sistema nervoso. Nesta revisão, apresentamos os diversos cenários clínicos diferenciados pelos anticorpos contra receptores de membrana descritos até o momento, enfatizando a relevância de um diagnóstico precoce para um menor impacto nos prognósticos.

Palavras-chave
- encefalite
- encefalites autoimune
- encefalite mediada por anticorpos
- encefalite límbica

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Introduction

Immune-mediated encephalitis constitutes a group of acute/subacute diseases that present antibodies directed against neuronal structures, clinically translating into psychiatric alterations, such as behavioral alterations. These antibodies can be directed against the neuronal plasma membrane, membrane receptors, ion channels, synaptic proteins, and intracellular structures, the latter of which are onconeural antibodies.[1,2]

Immune-mediated encephalitis is considered the most common form of noninfectious encephalitis, with anti-N-methyl-D-aspartate (anti-NMDA) antibodies being the most studied. Theoretically, any age can be affected, with some antibodies being more frequent in children and young adults.

The clinical expression of these diseases may include behavioral changes, psychosis, seizures, cognitive impairment, amnesia, movement disorders, dysautonomia, and lowered level of consciousness. Unlike other autoimmune diseases, there are many cases with no systemic manifestations other than dysautonomia, thus revealing the disease's behavior is more directed against structures of the nervous system. Among the triggers for this encephalitis, we must consider paraneoplastic conditions (cancers), as well as viral infections, which expose antigens that trigger activation of the immune system.[2,3]

Objective

The objective of the present study is to present the current knowledge about the pathophysiology of immune-mediated encephalitis, with emphasis on its main clinical presentations, mechanisms, and the need for diagnosis and prompt therapeutic implementation.

Methods

The Latin American and Caribbean Literature in Health Sciences (LILACS) and National Library of Medicine (PubMed) databases were searched during November and December 2020, using the following descriptors: *encephalitis*, *antibody encephalitis*, *autoimmune encephalitis*, *antibody-mediated encephalitis*, and *limbic encephalitis*.

Development

The estimated annual incidence of all types of encephalitis is of around 5 to 8 cases per 100 thousand inhabitants, half of which are individuals younger than 30 years of age.[4] Diagnoses of immune-mediated encephalitis emerged in the 1980s, referring to patients with neurological manifestations in the presence of cancer, thus constituting paraneoplastic syndromes.[5]

In immune-mediated encephalitis, antibodies are directed against extracellular protein epitopes, present on the cell surface; another possible mechanism of aggression are antibodies directed against intracellular protein antigens (also called onconeural), activating a Th1 cell response mechanism (involving $CD8^+$ T cells, complement system, and *natural killer cells*), typically coursing with neuronal dysfunction, synaptic impairment, and even neuronal death. The presence of the antibody can result in receptor blockade (anti-gamma-aminobutyric acid receptor B [anti-$GABA_B$]), receptor internalization (anti-NMDA) or interference in synaptic protein interaction.[6–8]

Two of the potential triggers for immune-mediated encephalitis are cancer and viral infections. Tumors that express nervous tissue or neuronal proteins promote epitope exposure to antigen-presenting cells, thus initiating an autoimmune response.[1] Encephalitis caused by herpes simplex is also a potential trigger for the anti-NMDA type, as it exposes neuronal surface protein epitopes. Typically, encephalitis with antibodies directed against neuronal membranes has a better prognosis with a greater response to immunosuppression.[9]

There are four different laboratory techniques used for the detection of antibodies against cell surface antigens: cell-based assay (CBA) with HEK293 cells; tissue-based assay (TBA) through indirect immunohistochemistry or indirect immunofluorescence; and culture of rat hippocampal neurons. Tests for the detection of antibodies should be performed both in cerebrospinal fluid (CSF) and in serum. There are some reasons for this indication:

1. In some syndromes, such as anti-NMDA, the antibodies can only be found in the CSF, while in others, such as anti-leucine-rich glioma-inactivated protein 1 (anti-LGI1), only in the serum;
2. Some patients may have the presence of different antibody spectra in the CSF and in the serum (anti-NMDA in the CSF and in the serum associated with anti-gamma-aminobutyric acid receptor A [anti-$GABA_A$] only in the serum), in this case, the antibody present in the CSF will define the clinical syndrome gift;
3. The CSF antibody titers will have better clinical correlation with the syndrome in question; and
4. Serum-only tests may result in more false positives.

Recently, anti-NMDA immunoglobulin M (IgM) and immunoglobulin A (IgA) antibodies were found in schizophrenic patients, patients with Creutzfeldt-Jakob, parkinsonian, and depressive patients, in addition to normal individuals. However, they were absent in the cerebrospinal fluid of these individuals. It is important to emphasize that negative results for antibody dosage do not exclude the diagnostic possibility, the use of corticosteroids may interfere with the test results.[10]

Clinical Syndromes

In recent decades, several antibodies have been identified, explaining, at least in part, some clinical presentations initially attributed to purely behavioral (psychiatric) conditions, thus revealing their hitherto unknown immune-mediated substrate (►**Fig. 1**).

The anti-NMDA was first described in 2007 in a group of 12 patients, 11 of whom had ovarian teratoma.[11] Found in

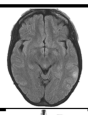
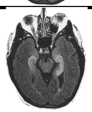
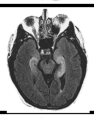
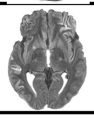
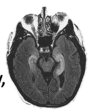
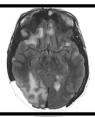
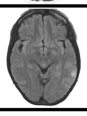
ANTIBODY	CLINICAL FEATURES / MRI		In Vitro MECHANISM	IMUNOGLOBULIN CLASS	NEOPLASM ASSOCIATION
Anti-NMDA	Seizures, choreoathetosis, psychiatric symptons; MRI: unspecific lesions		Receptor internalization; Excitatory synaptic dysfunction	IgG1	Ovarian Teratoma Testicular Teratoma Oat Cells
Anti-LGI1	Focal seizures with braquiofacial dystonia, hyponatremia e amnesia; MRI: temporal lobe hypersignal		Inhibition of LGI1 interaction with proteins ADAM22 and ADAM23; AMPA reduction	IgG4	Tymoma
Anti-$GABA_B$	Seizures, *Status Epilepticus*; Opsoclonus-Mioclonus; Amnesia, mental confusion; MRI: temporal lobe hypersignal		GABA receptor blockade	IgG1	Oat Cells
Anti-AMPA	Amnesia, mental confusion, psychiatric disorders; MRI: temporal lobe hypersignal		AMPA receptor internalization	IgG1	Oat Cells Tymoma Breast Cancer
Anti-$CASPR_2$	Amnesia, insonia, ataxia, disautonomic features, Morvan's syndrome, neurophatic pain, peripheral nerve hyperexcitability, MRI: temporal lobe hypersignal		Gefirina protein alterations (inhibitory synapses)	IgG4	Variable according clinical features Morvan's Syndrome: Tymoma
Anti-$GABA_A$	Seizures, *Status Epilepticus*, comportamental alterations; MRI: FLAIR cortical and subcortical (>2 areas) hypersignal		$GABA_A$ density reduction	IgG1	Tymoma
Anti-DPPX	Mental confusion, diarrhea, weight loss, hyperekplexia, *Stiff-Person Spectrum*; MRI: unspecific lesion		DPPX and Kv4.2 density reduction	IgG4	B Cell Neoplasm
Anti-$mGluR_5$	Ophelia's Syndrome MRI: normal / unspecific lesion		mGluR5 density reduction	IgG1	Hodgkin's Lymphoma

Fig. 1 Overview of some immune-mediated encephalitis, immune mechanism of injury, clinical and radiological presentation as well as possible correlations with neoplasms. Note: modified from Dalmau et al..[1]

patients with a mean age ranging from 12 to 45 years, this type of encephalitis is strongly related to the presence of ovarian teratoma ($\sim$ 94% of cases), extraovarian teratoma (2%), and other tumors. The herpes simplex virus type 1 also has a strong correlation with the disease, often revealing itself months or years after the presentation of herpetic encephalitis. In these cases, in younger individuals, it often appears as behavioral changes (insomnia, irritability, restlessness, and reduced verbal fluency) and movement disorders (dystonia, chorea, or choreoathetosis), while in older individuals it appears more commonly in the form of psychiatric symptoms (hallucinations, delusions, psychosis, agitation, and catatonia) and epileptic seizures.

Approximately 70% of patients may have nonspecific prodromal symptoms such as fever, headache, nausea, vomiting, diarrhea, and flu-like symptoms. In an earlier phase of encephalitis, the patient typically presents behavioral changes, psychosis, hallucinations, and memory deficit progressing to catatonia and mutism, accompanied by lowered level of consciousness and autonomic instability. Patients with anti-NMDA encephalitis are more sensitive to neuroleptics, so it is important to avoid the administration of these medications under the risk of neuroleptic malignant syndrome. Epileptic conditions may also be present, including the form of status epilepticus with electroencephalogram showing a characteristic extreme delta brush pattern, which can be found in up to 30% of cases.

Neuroimaging with magnetic resonance imaging (MRI) only reveals nonspecific alterations in approximately 35% of cases, in the form of hyperintense lesions affecting the gray and white matter of the cortical, subcortical, and cerebellar areas. The scans revealing changes in the basal ganglia and brainstem allow an important differential diagnosis: anti-D_2 encephalitis (parkinsonism, dystonia, and psychiatric symptoms), as shown in ►**Fig. 2A**. Hyperintensity of the claustrum can also be observed in the cases that course with refractory status epilepticus (new-onset refractory status epilepticus, NORSE), which may be associated with a recent history of fever (febrile infection-related epilepsy syndrome, FIRES) associated with anti-NMDA encephalitis, as shown in ►**Fig. 2B**. Some diagnostic criteria have been proposed for this type of encephalitis (►**Table 1**).[1]

Furthermore, anti-NMDA encephalitis may have an overlapping syndrome, such as multiple sclerosis, or neuromyelitis optica (NMO) represented by anti-aquaporin 4 antibody against myelin oligodendrocyte glycoprotein (anti-MOG), and antibody against the glial fibrillary acidic protein (anti-GFAP).[1,2]

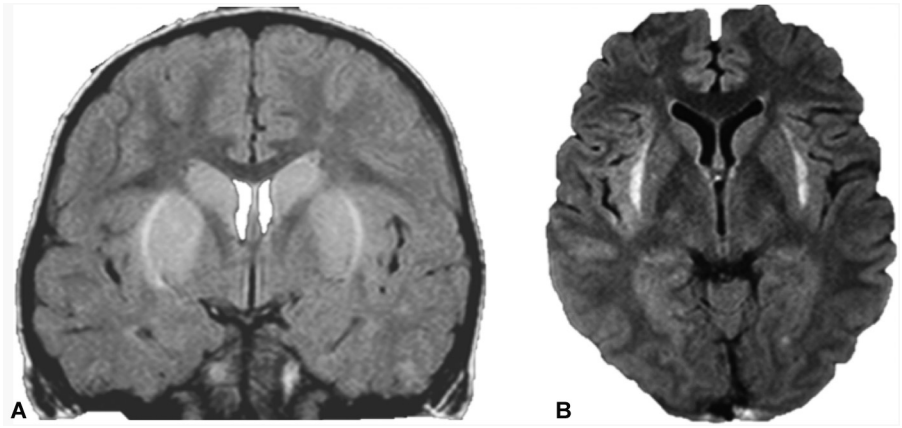


Fig. 2 (**A**) Neuroimaging of encephalitis mediated by anti-D_2 antibodies, with hypersignal in the subcortical structures of the basal ganglia (putamen, caudate, claustrum and globus pallidus) and brainstem, an important differential diagnosis of anti-N-methyl-D-aspartate (anti-NMDA) encephalitis. (**B**) Bilateral claustrum sign observed in new-onset refractory status epilepticus (NORSE).

Limbic Encephalitis and Related Antibodies

The criteria that define limbic encephalitis include the presence of four conditions: 1) subacute presentation (rapid progression in the last 3 months) of working memory deficit, seizures, or psychiatric symptoms (behavioral changes); 2) bilateral mesial temporal lobe abnormalities observed on T2-weighted MRI scans and fluid-attenuated inversion recovery (FLAIR) sequences; 3) Temporal lobe epileptic changes on electroencephalograms (EEGs) or CSF pleocytosis; 4) exclusion of more likely diagnoses.

Anti-LGI1 encephalitis: it was formerly called anti-voltage-gated potassium channel (anti-VGKC) antibody-associated encephalitis, but anti-LGI1 is now recognized as a synaptic protein that participates in the interaction between two other synaptic interaction complexes called ADAM22 and ADAM23, involving potassium channels and the α-amino 3-hydroxy 5-methyl 4-isoxazole propionate (AMPA) receptor. The functional impairment of this LGI-1 protein promotes symptoms attributed to limbic encephalitis, temporal lobe epilepsy, and hyponatremia. About 50% of patients have epilepsy with faciobrachial dystonia, which may, in some cases, also involve the lower limbs. They are rarely correlated with paraneoplastic conditions.[12,13]

Anti-$GABA_B$ encephalitis is characterized by cognitive symptoms associated with status epilepticus. There are descriptions of saccadic intrusions without an intersaccadic interval, such as opsoclonus-myoclonus and ataxia. There is an important association between the presence of these antibodies and oat-cell lung cancers (small cells).[14]

Anti-AMPA encephalitis: AMPA is a glutamatergic receptor, and the presence of its antibodies is related to the presence of seizures, amnesia and psychosis. The literatures describes cases of movement disorders as well as sleep disorders.[15] In approximately 64% of the cases, there is a correlation with the paraneoplastic syndrome in the presence of thymomas, breast and lung cancers, and ovarian teratoma.[15]

Anti-contactin-associated protein-like 2 ($CASPR_2$) encephalitis: like anti-LGI1 encephalitis, it was initially considered to

Table 1 Diagnostic criteria for immune-mediated encephalitis caused by anti-NMDA antibodies

Probable anti-NMDA encephalitis (ALL 3 criteria are required)
Period of symptoms < 3 months associated with at least 4/6 of the following:
a) Psychiatric symptoms with cognitive dysfunction
b) Language dysfunction (verbal reduction, mutism, pressure to speak)
c) Seizures
d) Movement disorder (dystonia, dyskinesia, rigidity)
e) Lowering of the level of consciousness
f) Autonomic dysfunction with central hypoventilation
At least ONE laboratory alteration:
a) EEG extreme delta brush OR focal or diffuse slowing or disorganized activity OR epileptic activity
b) CSF with pleocytosis or presence of oligoclonal bands
Exclusion other diseases
a) Ovarian teratoma corroborates the diagnosis
b) Anti-NMDA antibody against the N1 fraction confirms the disease

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalogram; NMDA, N-methyl-D-aspartate.

belong to the group of anti-VGKC encephalitides. Currently, it is identified as a juxtaparanodal adhesion molecule that interacts with contactin 2 and the cytoskeleton, interfering with the synaptic interaction of myelinated axons. The presence of these anti-$CASPR_2$ antibodies is associated with peripheral nerve hyperexcitability, clinically represented by myokymia, fasciculations, and cramps.[16] Dysautonomia and insomnia (*Agrypnia excitata*) are also described, in addition to Morvan's syndrome. The presence of paraneoplastic syndrome should be considered, as it is associated with thymomas, lung cancer, and endometrial carcinoma.[17]

Anti-$GABA_A$ encephalitis: GABA is the main inhibitory neurotransmitter in the nervous system. The presence of antibodies directed against this receptor was described in 2014.[18] Clinically, there is a description of rapidly progressive encephalopathy with cognitive alterations, refractory seizures, and multifocal lesions on MRI. The CSF exam reveals lymphocytic pleocytosis with or without the presence of oligoclonal bands. Paraneoplastic association is not common, however, thymomas should be investigated. There may be overlapping of autoimmune diseases, such as thyroiditis and myasthenia gravis.[19]

Anti-dipeptidyl-peptidase-like protein 6 (anti-DPPX) encephalitis: DPPX is a subunit of potassium channels (Kv4.2) expressed in the hippocampus, cerebellum, striatum, and myenteric plexuses. Patients who develop antibodies directed to DPPX may present with neuropsychiatric symptoms, such as mental agitation, confusion, myoclonus, tremors, startles (*startle*), convulsions, diarrhea, and presentation patterns compatible with stiff-person syndrome. Other symptoms are described, including dysautonomia, thermodysregulation, diaphoresis, sleep disturbances, and urinary symptoms. Classically, the CSF will show hyperproteinorrachia associated with pleocytosis; however, a normal evaluation as well as MRI do not rule out the presence of anti-DPPX encephalitis.[20,21]

Anti-glycine and anti-glutamic acid decarboxylase (anti-GAD) encephalitis: glycine receptors are chloride channels responsible for inhibitory neurotransmissions through the hyperpolarization of nerve cells. The presence of antiglycine antibodies has been described in patients with progressive encephalomyelitis with rigidity and myoclonus (PERM), within the spectrum of stiff-person syndrome. Also associated with cerebellar ataxias are anti-GAD encephalitis and demyelinating diseases, such as multiple sclerosis and optic neuromyelitis spectrum disorders. Despite the little correlation with paraneoplastic syndromes, there are descriptions of thymomas, small cell lung cancer, and chronic lymphocytic leukemias.[22,23] Glutamic acid decarboxylase is an enzyme responsible for catalyzing the conversion of glutamic acid to GABA. Some autoimmune diseases, such as diabetes mellitus, have the presence of antibodies directed to GAD. The main neurological diseases associated with the presence of anti-GAD are stiff-person syndrome, cerebellar ataxias (slow progression associated with downbeat-type nystagmus and eye movement disorders), epilepsy (temporal lobe and status epilepticus), and limbic encephalitis. Anti-GAD is rarely associated with paraneoplastic syndromes, but its presence concomitantly with limbic encephalitis increases the risk of paraneoplastic syndrome by 10 times.[24]

Anti-IgLON5 encephalitis: the fifth member of the neuronal cell adhesion molecule family (IgLON) belongs to the immunoglobulin superfamily. The presence of antibodies directed to IgLON5 manifests itself clinically with changes in rapid eye movement (REM) and non-REM sleep, central hypoventilation, obstructive sleep apnea, stridor, chorea, gait instability, dementia, dysarthria, dysphagia, dysautonomia, and supranuclear gaze palsy resembling the classic tauopathies. Post-mortem studies reveal neuronal deposits of hyperphosphorylated Tau protein involving the brainstem tegmentum and hypothalamus.[25,26]

Anti-glutamate encephalitis: type-1 and type-5 metabotropic glutamate receptors (mGluR1 and mGluR5) are G protein-coupled and very similar, structurally. These receptors are involved with excitatory synapses in the nervous system. Patients with antibodies directed at mGluR1 receptors develop subacute cerebellar ataxia, dysgeusia, paranoia, diplopia, and cognitive deficits. Prostate adenocarcinomas as well as hematological cancer seem to have an important correlation with anti-mGluR1.[27] The presence of anti-mGluR5, on the other hand, appears in the form of encephalitis attributed to Ophelia's syndrome, consisting of amnesia, psychosis, and Hodgkin's lymphoma.[28]

Clinical Management and Perspectives

The current recommendation for the management of immune-mediated encephalitis is based on expert opinion and case series. Immunotherapy associated with removal of the immune trigger (diagnosis and treatment of cancers) is advocated. The early approach correlates directly with the prognosis. Most encephalitis occurs within the blood-brain barrier, which largely limits the success of plasmapheresis, as well as immunoglobulins. Even so, in practice, those are the two main options for treatment, along with corticosteroids. In the absence of response, we still have rituximab and cyclophosphamide as alternatives. Spontaneous recovery is very unlikely, and once the diagnostic hypothesis has been established, treatment should be initiated. There are some cases of recurrence, after immunosuppression is completed.[29]

It is also worth noting that, for those antibodies with a strong correlation with neoplasms, a complete screening is recommended (including tumor markers, mammography, testicular ultrasonography, imaging tests of the chest and abdomen, and scintigraphy). Patients must follow neoplastic screening protocols for at least 5 years.[30]

The discovery of antibodies that cause encephalitis has broken paradigms between neurology and psychiatry over the last 10 to 15 years. Patterns of behavioral changes that are poorly explained by isolated psychiatric illnesses or even refractory to their approaches could have an immune-mediated neurological substrate. In the near future, we should seek better diagnostic tools, including more sensitive and specific biomarkers, as well as functional neuroimaging techniques.

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

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Lumbosacral Paraspinal Intramuscular Myxoma: Case Report and a Brief Literature Review

Mixoma Intramuscular Paraespinhal Lombossacral: Relato de caso e uma breve revisão da literatura

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Abstract

Myxoma is a tumor of mesenchymal origin with a slow-growing behavior and an unknown etiology, occurring in a variety of locations. It mostly affects the heart's chambers, but large skeletal muscles may also harbor these neoplasms (i.e., intramuscular myxoma [IM]) at a lower frequency. Lumbosacral paraspinal IM is very rare, and only five cases have been reported worldwide, with none in the Brazilian population. We present the first Brazilian case: a 38-year-old woman complaining of increased volume and pain in the right lumbosacral region in the last two months without radiculopathy and without focal neurological deficits. Imaging showed a large paraspinal lumbosacral tumor from the second lumbar vertebra to the second sacral segment. This was completely removed by a posterior approach. Histopathological revealed an intramuscular myxoma. Surveillance imaging for four months after surgery revealed no recurrence and the patient was doing well. Literature on the topic was reviewed.

Keywords
- myxoma
- spine
- intramuscular
- report

Resumo

Mixoma é um tumor de origem mesenquimal com comportamento de crescimento lento e de etiologia desconhecida, ocorrendo em uma variedade de localidades. Afeta principalmente as câmaras cardíacas, mas grandes músculos esqueléticos também podem abrigar estas lesões (mixoma intramuscular [MI]). O MI paraespinhal lombossacro é bastante raro e apenas cinco casos foram relatados ao redor do mundo, nenhum no Brasil. Apresentamos o primeiro caso brasileiro: uma mulher de 38 anos com queixa de 2 meses de aumento de volume e dor na região lombossacra direita, sem

Palavras-chave
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- coluna vertebral
- intramuscular
- relato

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radiculopatia e sem déficits neurológicos. Imagem demonstrou um grande tumor paraespinhal lombossacro desde a segunda vértebra lombar até o segundo segmento sacral. A lesão foi completamente removida por um acesso posterior. A histopatologia demonstrou mixoma intramuscular. O seguimento com imagem quatro meses após a cirurgia não revelou recorrência e a paciente apresentava boa evolução. A literatura sobre o assunto foi revisada.

Introduction

Myxoma is a tumor of mesenchymal origin with a slow-growing behavior and an unknown etiology, occurring in a variety of locations. The striated muscle is a rare site (i.e., intramuscular myxoma [IM]), with an estimated incidence of 0,1 to 0,13 per 100.000 individuals.[1] Adults at 40–70 years of age are most affected, with a female predominance.[2] No race predilection nor hereditary pattern were identified.[3] This paper describes the first case of an intramuscular myxoma of the lumbosacral paraspinal muscle in a Brazilian population. The patient provided written consent.

Case History

A 38-year-old woman arrived at our outpatient clinic complaining of increased volume and pain in the right lumbosacral paraspinal region for two months without radiculopathy and with no focal neurological deficits. Past medical history included bariatric surgery nine years before. The physical examination showed a massive, hardened tumor, painless to palpation. A CT scan showed a hypodense formation in the right paraspinal region remodeling of the adjacent bonny structures with no sign of bone infiltration (►**Fig. 1**). An MRI showed a cystic-like lesion in the right paraspinal musculature topography, hypointense on T1 sequence and hyperintense on T2, exhibiting fine internal septations of regular contours and well-defined limits, exerting mass effect. It extended from the disc level L2-L3 to the height of the second sacral segment (S2), measuring ~12,2 × 6,6 × 6,0 cm (►**Fig. 1**). A posterior approach was performed with a paramedian incision, dissecting the layers by planes with visualization of a large tumor and a small portion insinuating to the right L5 foramen, which was also removed. A total gross resection was achieved (►**Fig. 2**). The histopathological exam showed a nodular, partially capsulated, poorly cellular stromal neoplasm. It was composed of spindle cells and stellate cells with inconspicuous cytoplasm and oval hyperchromatic nuclei with low pleomorphism embedded in a rich myxoid matrix with sparse connective fibers, corresponding to an intramuscular myxoma (►**Fig. 3**). Follow-up MRI after four months documented no evident residual or recurrent tumor (►**Fig. 4**). The patient was asymptomatic and returned to her routine life.

Discussion

In 1863, Virchow introduced the term Myxoma to describe a tumor that histologically resembles the umbilical cord.[1,2,4] Only in 1948 histological criteria were established for its diagnosis, by Stout in 1948, who stated that myxoma is a true mesenchymal neoplasm composed of undifferentiated star cells in a myxoid stroma with delicate reticulin fibers.[1] In 1965, Erzinger and Weiss classified IM as a distinct subtype.[1] IM usually arises as a single lesion, although they can be seen as multiple lesions associated with fibrous bone dysplasia, Mazabraud syndrome, or as part of McCune-Albright syndrome (characterized by polyostotic fibrous dysplasia, café-aú-lait spots, and endocrine hyperfunction).[1] Although presumptive diagnosis can be yielded from clinical and imaging findings, the definitive diagnosis requires anatomopathological evaluation.[5]

Paraspinal IM presents as a solitary painless mass in the dorsal region. Current imaging techniques for IM workup include ultrasound (USG), computed tomography (CT), and magnetic resonance (MR). On USG, IM appears as a hypoechoic lesion with a well-defined margin. Anechoic cystic foci may be

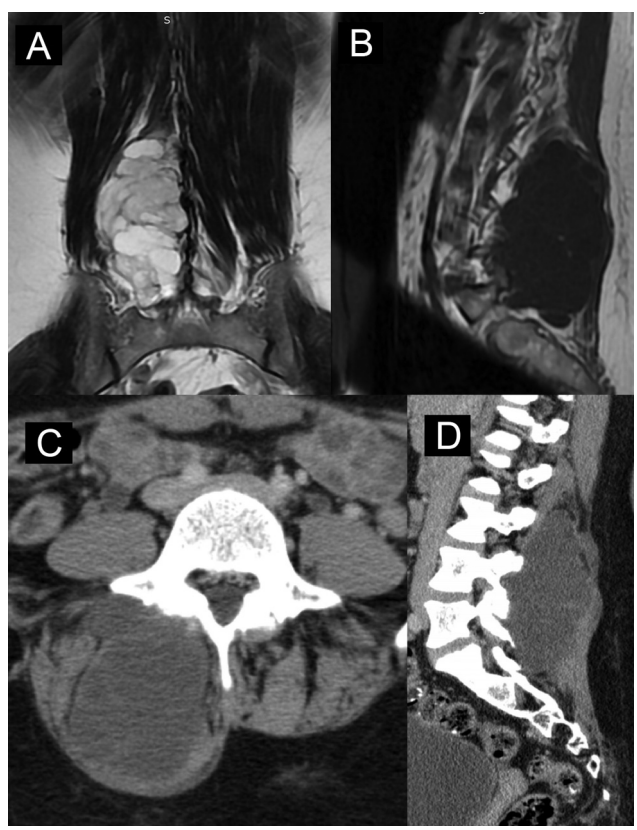

Fig. 1 Lumbosacral spine: (A) T2-weighted MRI coronal view with hyperintense multilobulated paraspinal tumor. (B) sagittal view shows hypointense tumor on T1-weighted MRI. (C) axial and (D) sagittal CT scans demonstrate a low-density mass, with remodeling of adjacent bony structures.

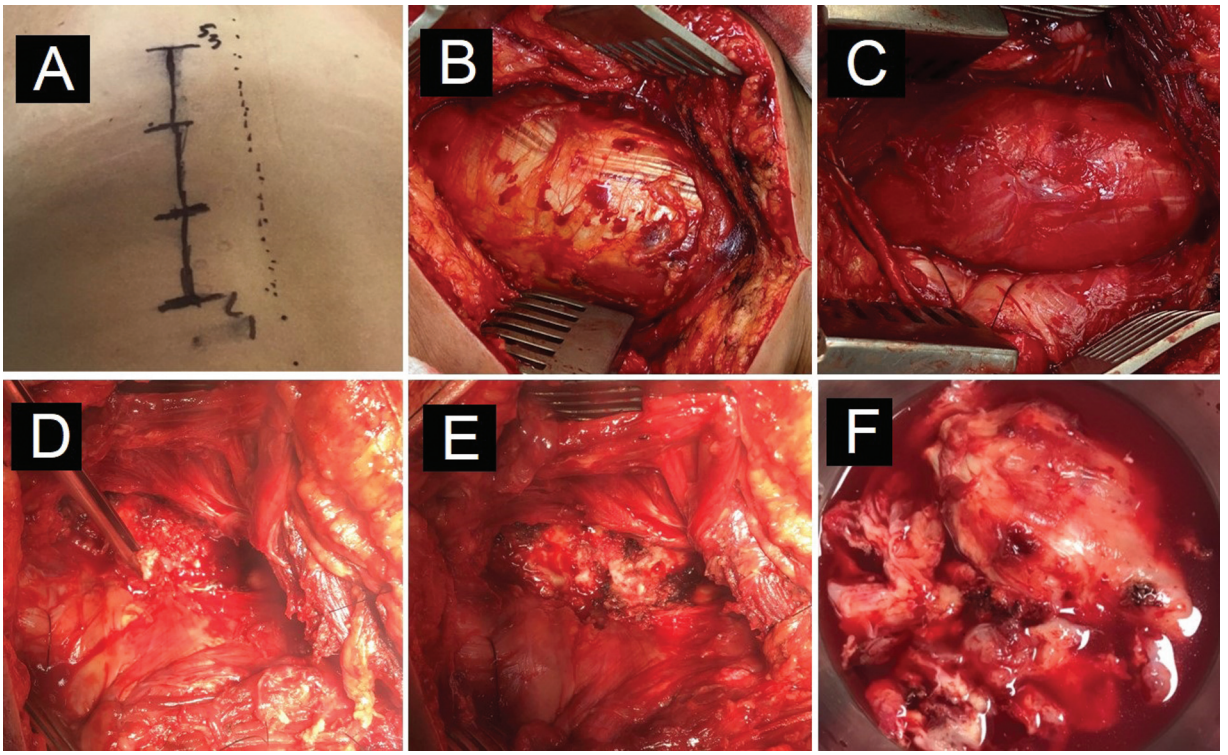

Fig. 2 (A) Incision line. (B) paravertebral musculature containing an evident tumor mass. (C) Lumbosacral tumor in its entirety. (D) Removal of the tumor that extended into the vertebral foramen. (E) Tumor bed. (F) Tumor fragments.

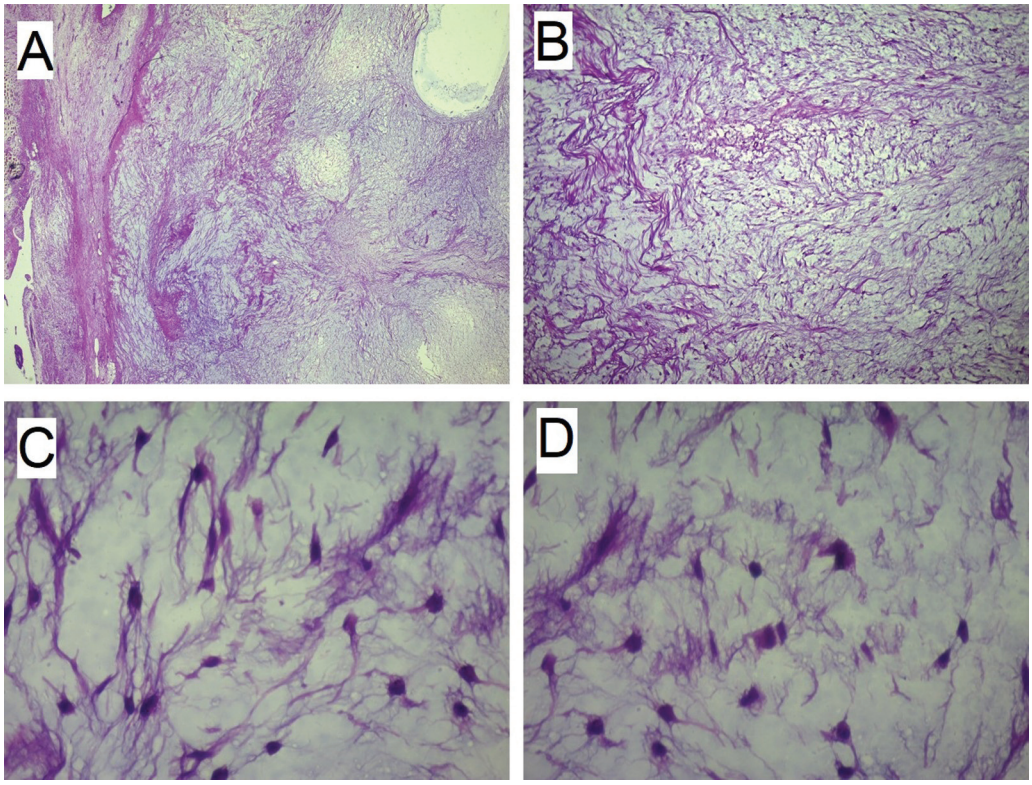

Fig. 3 (A) Nodular, poorly cellular stromal neoplasm (HE, 20x); (B) cells embedded in a rich myxoid matrix with sparse connective fibers (HE, 100x); (C) and (D) spindle cells and stellate cells in a rich myxoid matrix (HE, 600x).

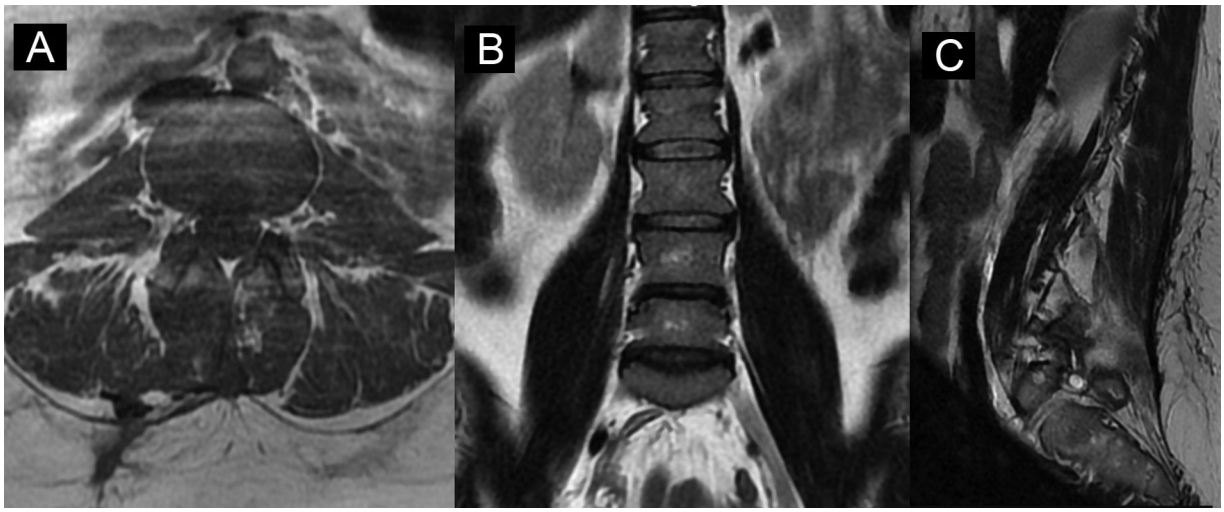

Fig. 4 Lumbar postoperative spine MRI: (A) axial, (B) coronal and (C) sagittal reconstructions show total removal of the tumor.

present.[6] Intramuscular myxomas tend to show similar imaging patterns in both CT and MR which include the intramuscular localization, edges of the tumor with similar aspect to the bone marrow, and high water content. Thus, it is hypodense in CT, whereas, in MRI, it presents as a lesion hypointense in T1 and hyperintense in T2.[7] Additionally, it may appear as a well-defined ovoid (65%), lobulated (30%), or spherical lesion (5%), with fluid-like signal intensity and a peritumoral fat rim on T1-weighted MR images, and present with an increased signal in the adjacent muscle on T2-weighted or fluid-sensitive MR sequences.[7] The latter two features have not been previously emphasized and are the most reliable radiologic features for differentiating intramuscular myxoma from other myxoid soft-tissue lesions.[7]

Differential diagnoses include more aggressive neoplasms such as angiomyxoma, myxoid neurofibroma, low-grade fibromyxoid sarcoma, myxoid liposarcoma (ML), cellular myxoma, juxta-articular myxoma, and nodular fasciitis.[2] IM is of particular interest to radiologists because it may have imaging features similar to other myxoid lesions, especially the ML, which makes their imaging differentiation often challenging.[7] For example, in cases with a predominantly myxoid morphology (cystic appearance) and intramuscular location, ML may strikingly resemble an IM in the image.[7] These similarities extend to the gross and histological appearances as well, and differentiating between the two may also be difficult.[7] The correct diagnosis is of utmost importance as IM has a benign clinical course, with no tendency to recur or metastasize, whereas other neoplasms may require adjuvant treatment and carry a worse prognosis.[7–9] At last, neurogenic tumors should be considered, as these are intermuscular, which may be confounded for an intramuscular lesion. Nonetheless, they often show an entering and exiting nerve on imaging, and with the "target sign" on T2-weighted MR imaging.[10]

The treatment of choice for IM is surgical excision. Throughout the literature, there were no reports of their metastatic spread or malignant transformation, although local recurrence/progression is possible when the surgical procedure consists of enucleation or incomplete resection.[1,4] Therefore, wide excision with clear margins is recommended.[3,10]

Conclusion

In conclusion, IM of the lumbosacral paraspinal muscle is a rare entity and, up to this date, no cases have been reported on the Brazilian population. It must be part of the differential diagnosis of paraspinal tumors. The precise diagnosis may be challenging due to radiological/histological similarity to other entities, especially soft tissue sarcoma, but it is of utmost importance to define management.

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Conflicts of Interest

The authors disclose no conflicts of interest.

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A Rare Case of Partial Cauda Equina Syndrome Following Decompression for Spinal Stenosis: An Illustrative Case

Um caso raro de síndrome da cauda equina parcial após descompressão para estenose espinhal: Um caso ilustrativo

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Abstract

Cauda equina syndrome (CES) is a rare and critical complication of lumbar disc herniation with a reported incidence between 0.08 and 0.5%. Whether CES occurs because of compression from disc herniation or as a complication of surgery, surgical decompression remains the mainstay of management of CES. In cases of partial CES, without motor symptoms, conservative management may also be considered.

We describe a rare case of partial CES following surgical decompression of spinal stenosis in a patient with adjacent segment disease (ASD) in which no postoperative radiological evidence of residual compression or iatrogenic damage at the associated levels could be found. Given the lack of evidence for further decompression, the patient was successfully managed conservatively and returned to baseline on postoperative day 7.

CES following surgical decompression for lumbar stenosis is a rare but critical complication that results from either primary mechanical compression of the nerve roots or ischemia of the nerve roots secondary to venous congestion. Management of CES depends heavily on the presence of visible compression on imaging studies. The presence of ASD in this case may have resulted in a pro-inflammatory cascade that could have contributed to the development of CES.

Keywords

- cauda equina syndrome
- adjacent segment disease
- spinal stenosis
- decompressive
- spine surgery

Resumo

A síndrome da cauda equina (SCE) é uma complicação rara e crítica da hérnia de disco lombar com uma incidência relatada entre 0,08 e 0,5%. Quer a SCE ocorra devido à compressão da hérnia de disco ou como uma complicação da cirurgia, a descompressão

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cirúrgica continua sendo o esteio do tratamento da SCE. Em casos de SCE parcial, sem sintomas motores, o tratamento conservador também pode ser considerado.
Descrevemos um caso raro de SCE parcial após descompressão cirúrgica de estenose espinhal em um paciente com doença do segmento adjacente (CIA) no qual nenhuma evidência radiológica pós-operatória de compressão residual ou dano iatrogênico nos níveis associados pôde ser encontrada. Dada a falta de evidências para descompressão adicional, o paciente foi tratado com sucesso de forma conservadora e retornou à linha de base no 7° dia pós-operatório.
A SCE após descompressão cirúrgica para estenose lombar é uma complicação rara, mas crítica, que resulta da compressão mecânica primária das raízes nervosas ou isquemia das raízes nervosas secundária à congestão venosa. O tratamento da SCE depende muito da presença de compressão visível em estudos de imagem. A presença de ASD neste caso pode ter resultado em uma cascata pró-inflamatória que pode ter contribuído para o desenvolvimento de SCE.

Palavras-chave
- síndrome da cauda equina
- doença do segmento adjacente
- estenose espinhal
- descompressiva
- cirurgia da coluna

Introduction

Cauda equina syndrome (CES) is a rare and critical complication of lumbar disc herniation that typically presents with saddle anesthesia, acute onset bladder incontinence or retention, perineal numbness, bilateral leg pain, and/or lower limb weakness.[1,2] Rarely, CES can also occur as a complication following spine surgery, with a reported incidence varying between 0.08% to 0.5%.[1–9] Whether this complication occurs as a result of compression from disc herniation or as a complication of spine surgery, surgical decompression remains the mainstay of management of true CES. In cases of partial CES, without motor symptoms, conservative management may also be considered as an option.[1,2,10]

We describe a rare case of partial CES following surgical decompression of spinal stenosis, in a patient with adjacent segment disease (ASD), that was successfully managed conservatively, without surgical decompression. Additionally, we review and discuss the relevant literature on conservative management of partial CES and discuss possible causes as well as the role of ASD in such cases.

Illustrative Case

A 47-year-old man presented to our department with lower back pain and bilateral radicular leg pain 2 years following an L4-L5 posterior lumbar fixation performed at another hospital. Imaging revealed ASD at L3-L4 (►**Fig. 1A** and **B**), and the patient underwent an L3-L4 decompression with posterior screw fixation to fuse this segment with the previously fused L4-L5. Decompression was achieved with the use of a surgical microscope and the procedure was uneventful with blood loss of more than 100 mL. Post-anesthesia recovery from anesthesia was also uneventful.

On postoperative day 1, the patient developed acute bladder retention associated with pinpoint anesthesia in the perineal area encompassing the entire scrotum and the penile surface. A physical exam revealed no sensory or motor deficits in the lower limbs. Emergent magnetic resonance imaging and computed tomography showed no neural compression or abnormality (►**Fig. 2A–D**). The patient was then immediately started on dexamethasone, gabapentin, and tamsulosin, and underwent urinary catheterization. Urinalysis and laboratories, including erythrocyte sedimentation rate and c-reactive protein, were unremarkable. Electrophysiology showed normal peroneal motor and sural sensory nerve velocities and latencies; however, mildly reduced tibial compound muscle action potentials were noted bilaterally. Needle electromyography demonstrated mildly enlarged motor unit potentials in the L5 and S1 innervated muscles without fibrillation potentials, consistent with chronic bilateral lower lumbosacral radiculopathies (►**Fig. 3**). On postoperative day 5, the patient began to regain sensation and bladder control, and by day 7 returned to baseline.

Discussion

Observations

Despite CES being a well-known clinical finding in patients with lumbar disc herniation, postoperative CES, especially partial CES, remains rare. The literature on postoperative CES is sparse and mainly consists of case reports or series with few patients.[1,2,4,7,11–13] To our knowledge, this is the first report of partial CES as a complication of corrective surgery for ASD.

In cases of postoperative CES, several potential perioperative factors have been proposed or identified, including choice of anesthetic agent, the occurrence of compressive lesions including epidural hematomas or abscesses, mispositioning of fat pad grafts, or retained surgical Gelfoam or sponges.[1,2,5,7,13–15,18]

Cases with no postoperative radiologic evidence of compression have also been described,[1,2,4,10] and several studies have attempted to explain the pathophysiology of these cases. In 1977, Murphy proposed that, even in the presence of extrusion of disc material, it is not compression but rather tension on the nerve roots that cause CES.[19] The tenuous microvascular supply to the conus medullaris is also likely a

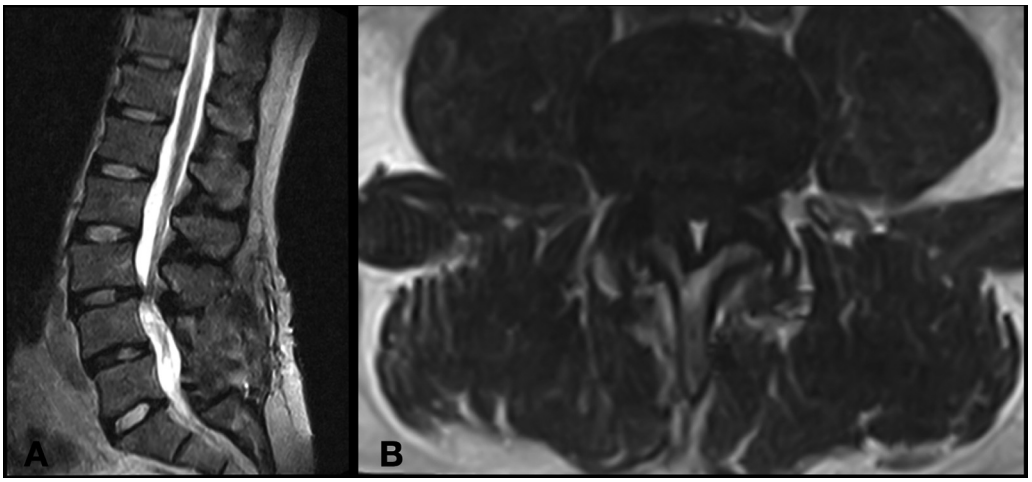

Fig. 1 (A) Sagittal and (B) axial views of the preoperative T2-weighted magnetic resonance imaging showing spinal stenosis due to adjacent level segment disease at L3-L4 in a 47-year-old male who previously underwent L4-L5 posterior lumbar fixation.

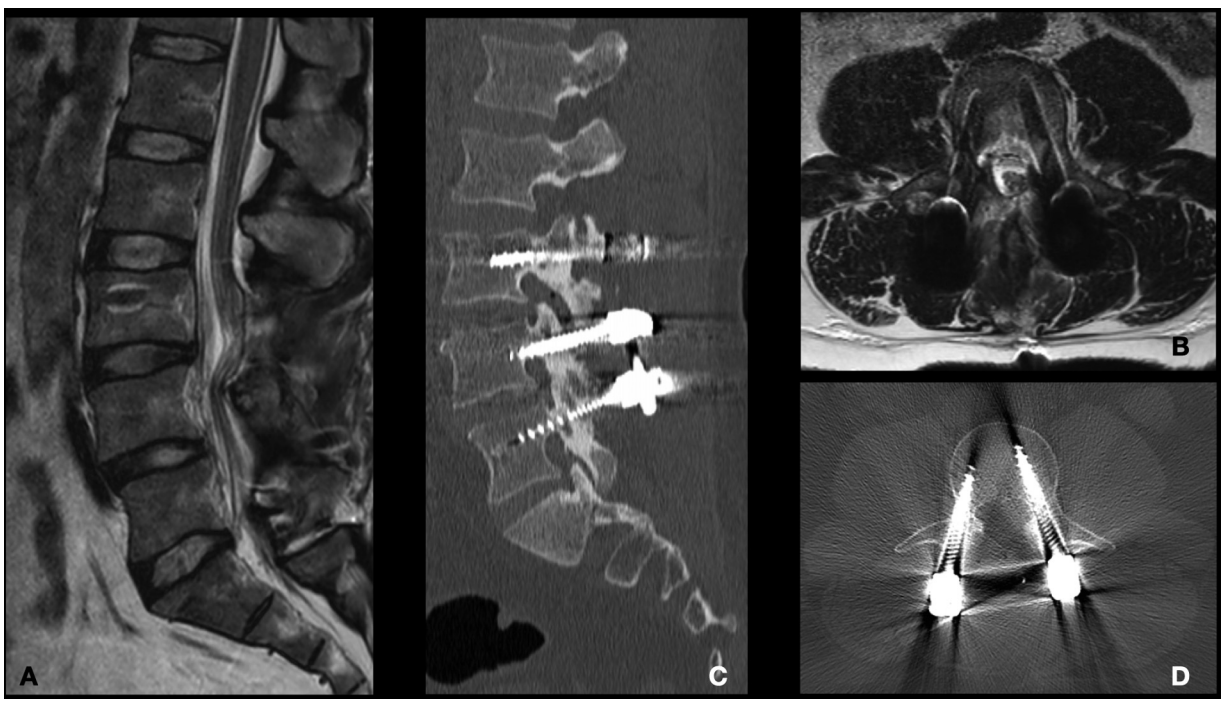

Fig. 2 (A) Sagittal and (B) axial views of the postoperative T2-weighted magnetic resonance imaging showing decompression of L3-L4. (C) Sagittal and (D) axial postoperative computed tomography showing correct screw placement.

contributing factor,[7,20] as an area of hypovascularity right below the conus medullaris has been identified. Dural tension in this hypovascular area could thus induce root ischemia resulting in CES.[5,18] Henriques et al. and Evins et al. have also proposed that postoperative edema may cause venous congestion, which can also lead to nerve root ischemia.[2,21] The role of venous congestion in CES is further supported by porcine models, wherein multi-level compression traps blood between the compression sites, inducing significant venous stasis.[22–24] Additionally, Hoyland et al. further found, in a large cadaveric series, that 72% of observed disc herniations compressed or distorted the venous plexus or small veins within the intervertebral foramen.[3] As such, initial compression by any mechanism can be compounded by ensuing venous congestion, which can then result in ischemia and intraneural edema, further decreasing perfusion.

Furthermore, Duncan and Bailey found that patients who developed postoperative CES in the absence of compression shared several comorbidities known to disrupt microvascular supply, including hypertension and diabetes mellitus.[1] Furthermore, spinal decompression for CES in patients with no imaging evidence of compression has also been shown to be ineffective, further supporting the role of vascular etiology.[1,4,5]

Lessons

CES following surgical decompression for lumbar stenosis is a rare but critical complication that likely results from either primary mechanical compression of the nerve roots or

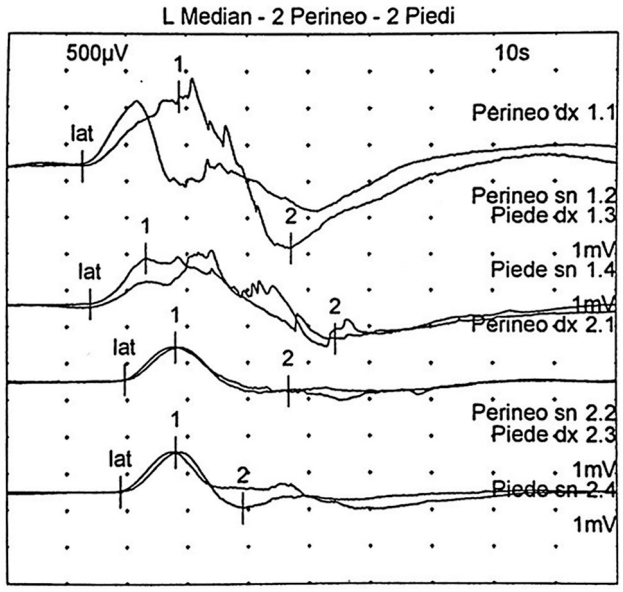

Fig. 3 Needle electromyography showing mildly enlarged motor unit potentials in the L5 and S1 innervated muscles without fibrillation potentials, consistent with bilateral diffuse lumbar radiculopathies.

ischemia of the nerve roots secondary to venous congestion. Management of CES often depends on the presence of visible compression in imaging studies. In patients with ASD, increased force on the intervertebral disc—from the mechanical stress caused by the arthrodesis of the adjacent segment—initiates a biochemical cascade with activation of pro-inflammatory cytokines that can result in hypoxic injury to the disc itself.[20]

Thus, it is possible that this pro-inflammatory and hypoxic environment contributed to nerve root ischemia in the case presented herein. As such, the association of pro-inflammatory cytokines with ASD and their role in the development of CES warrants further study as a potential risk factor for CES.

Conflict of Interest

None.

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Cervicothoracic Arthrodesis: The Best Management for Dropped Head Syndrome, A Case Series

Artrodese Cervicotorácica: O melhor manejo para síndrome da cabeça caída, uma série de casos

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Abstract

The authors present two cases of Dropped Head Syndrome (DHS), a condition distinguished by the chin-on-chest deformity due to weakness of the posterior muscle group of the neck. This is a unimodal syndrome and is most common among individuals in their seventh and eighth decade of life, with an average age of around 75 years. DHS is more prevalent in women, with a 3:2 ratio compared with men. Our reports document the disease's natural progression, increasing kyphosis, and resistance to initial conservative treatments. Both patients reported functional limitations, as their ability to walk and eat without assistance was hindered by loss of the horizontal gaze and dysphagia. After these treatment failures, we utilized an arthrodesis approach to target the C2-T6 segments of the cervical-thoracic spine. All previous complaints were resolved, the deformity was reduced, and the patients regained their functional independence. The surgical approach is indeed more efficient, although the combination of both methods yielded even better clinical outcomes. Arthrodesis from C2 to the upper thoracic spine segments is considered the most appropriate surgical technique for maintaining subaxial spine movement. This is due to its excellent rate of correcting deformities, preserving horizontal gaze, and improving or maintaining a neurological state.

Keywords
- dropped head syndrome
- kyphosis and surgery

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Resumo

Os autores apresentam 2 casos de síndrome da cabeça caída (SCC), um quadro destacado devido à presença da deformidade-queixo-no-peito, decorrido da fraqueza do grupo muscular do pescoço. A síndrome se apresenta de forma unimodal, sendo predominante entre a sétima e a oitava década de vida, com uma idade média de cerca de 75 anos. É mais predominante em mulheres, apresentando uma razão de 3:2 em relação aos homens. Em nossos relatos, evidenciamos a evolução natural da doença, por meio de uma cifose crescente ao longo dos anos resistente às terapias conservadoras iniciais. Ambos os pacientes apresentavam queixa de limitação funcional, devido à incapacidade de deambular e se alimentar sem auxílio, resultante da perda do olhar horizontal e da disfagia. Após essa falha, a conduta adotada foi a artrodese dos seguimentos cervico-torácicos da coluna, buscando os seguimentos C2-T6. Obteve-se resolução das queixas prévias, reduzindo a deformidade e reavendo a independência funcional dos pacientes. A abordagem cirúrgica é de fato mais eficiente, embora a combinação de ambos os métodos tenha produzido resultados clínicos ainda melhores. A artrodese de C2 até os segmentos superiores da coluna torácica é considerada a técnica cirúrgica mais adequada para manter o movimento subaxial da coluna. Isso se deve ao seu excelente índice de correção de deformidades, preservação do olhar horizontal e melhora ou manutenção do estado neurológico.

Palavras-chave

- síndrome da cabeça caída
- cifose e cirurgia

Introduction

Dropped head syndrome (DHS) is a rare condition characterized by pathological kyphosis resulting from extreme weakness of the extensor muscles of the neck, leading to chin-to-chest deformity.[1,2]

DHS can also be defined as scaphocephaly or anterocolis, the latest example being the result of dystonia of the cervical muscles. Currently, there is no global data available on the prevalence of dropped head syndrome. However, when associated with cervical dystonia, the incidence falls within the range of 0.06–0.08 per 100,000 individuals per year.[1,3]

The objective of this study is to present two cases of dropped head syndrome to enhance comprehension of diagnostic aspects and treatment options.

Case Report

Case One

An 87-year-old woman has had cervical kyphosis for four years. This condition has progressed over time, aggravating her previous symptoms of pain, loss of horizontal sight, and dysphagia. During the physical examination, a weakened extensor neck muscle and the uncommon chin-on-chest deformity were visible, establishing the diagnosis of drooping head syndrome. Imaging revealed a "chin-brow radiographic angle" measuring 113° and a "chin-brow vertical angle" measuring 57°, (►**Figs. 1** and **2**). The presence of shortening in the tendons of the sternocleidomastoid muscle is a significant factor in determining the extent of corrective measures needed.

Initially, a conservative approach involving physiotherapy and analgesics was employed. However, no improvements were observed during this intervention. Consequently, a surgical procedure was performed later.

The surgical procedure performed was C2-T6 instrumentation with osteotomy at C5-C7. Transpedicular screws were implemented at C2 and throughout the thoracic spine, while lateral mass screws were utilized at C3-C7. Two rods were utilized due to the unavailability of the transition rod, alongside 2 reinforcing crosslinks. (►**Fig. 3**) We chose to perform fixation at C2 due to the favorable alignment of the condyle/C1/C2 while preserving the anatomy and allowing recovery of the horizontal movements of the neck and the "yes-yes" movements intrinsic to the muscles attached to the condyle-C1. Before the procedure, the patient had difficulty performing daily activities independently, such as eating and walking. Following the surgery, the deformity was corrected, and the spine resumed its natural curvature. One year post-procedure, the patient revisited the clinic and reported an absence of pain and neurological issues, along with an improved level of functional independence.

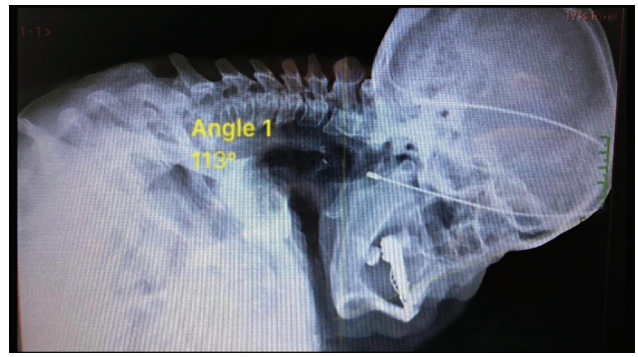

Fig. 1 "Chin-brow radiographic angle" of 113° on a lateral cervical radiograph.

Fig. 2 "Chin-brow vertical angle" of 57° noted on physical examination.

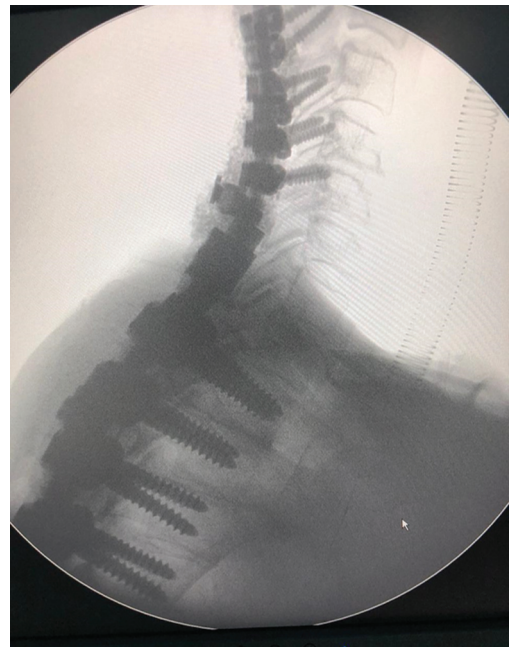

Fig. 4 Post-operative radiograph presenting C2-T6 cervicothoracic arthrodesis.

Case Two

An 87-year-old woman presented with progressive cervicothoracic kyphosis over three years. She had complaints of pain, loss of horizontal gaze, dysphagia, and walking difficulty. A physical examination revealed weakened neck extensor muscles, shortened M. sternocleidomastoid tendons, and a chin-on chest deformity. Imaging indicated a "chin-brow radiographic angle" of 147°, characteristic of drooping head syndrome.

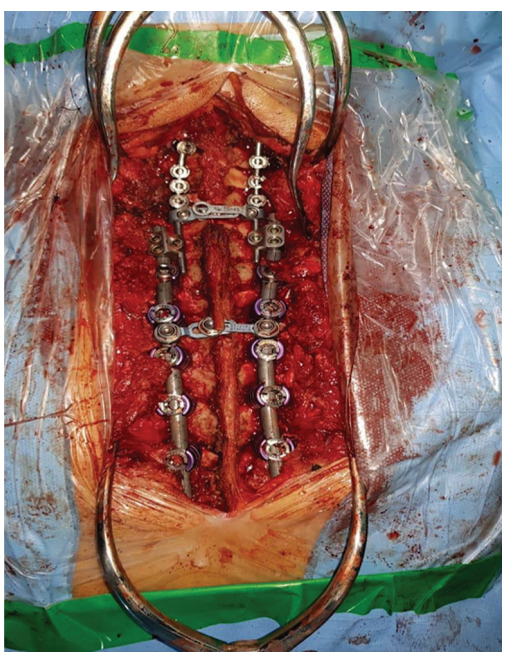

Fig. 3 C2-T6 cervicothoracic arthrodesis with Schwab 1 osteotomy in C5–7 vertebrae recorded in the perioperative period.

Initially, a conservative treatment approach was attempted, which included physical rehabilitation via physiotherapy and analgesia to alleviate pain. However, this approach proved unsuccessful, and the deformity remained unresolved over time.

The second approach utilized instrumentation of the C2-C6 and T1-T6 vertebrae. Transpedicular screws were utilized at the C2 level and in the thoracic spine, while lateral mass screws were used at the levels of C3-C7 (►**Fig. 4**)

In both instances, we opted for fixation from C2 to preserve the horizontal movements of the neck that are intrinsic to the muscles attached to the condyle/C1. Before surgical intervention for the deformity, her main complaint was a lack of functional independence due to an inability to eat or walk unaided. One year following the procedure, the patient revisited the clinic and disclosed experiencing neither pain nor neurological complaints, while showing an increase in functional independence. (►**Fig. 5**)

Discussion

Dropped head syndrome (DHS) typically occurs between the ages of 70–80, with an average age of 75 years, and is more common in women (a 3:2 female-to-male ratio). DHS is characterized by a sudden loss of neck muscle tone and subsequent head drop. Conversely, instances of pediatric DHS are rare and often attributed to genetic mutations.[1,4]

Drooping head syndrome can be categorized as either primary/idiopathic or secondary to neurological dysfunction, supported by clinical evidence and natural history.[3]

The clinical presentation can be classified as isolated/pure or non-isolated/complex. The most common form is complex anterocollis (AC), which occurs in 7% of all cervical dystonia cases, with an incidence of 0.06–0.08/100,000 per year. Additionally, AC is often associated with dystonia in other areas of

Fig. 5 Post-op evaluation of surgical deformity correction.

the body or with other manifestations of neurological disorders. AC can also be categorized as progressive or non-progressive, congenital, or acquired, and paroxysmal or non-paroxysmal. Pure anterocollis is less common, with an annual incidence of ~0.008–0.275 per 100,000 individuals.[3,5,6]

AC is usually observed secondarily and is more prevalent among patients diagnosed with Parkinson's disease and multiple system atrophy (MSA), with a prevalence of 6% and 42% respectively. Furthermore, there may exist a genetic relationship attributable to the occurrence of movement disorders within the patient's family medical history.[7,8]

Patients with Dropped Head Syndrome exhibit a chin-on-chest deformity, neck pain, dysphagia, loss of horizontal gaze, and some nervous system disorders. Consequently, functional independence and quality of life are significantly affected, leading to a direct impact on social relationships, as well as daily activities.[1,8–10]

The loss of horizontal sight is a result of the imbalance and global malalignment of the spine in the sagittal and coronal planes. This is due to the compensatory mechanism of the deformity, resulting in a loss of thoracic and lumbar curvature.[10]

Another important manifestation is extreme stiffness of the neck flexor muscle group, which can be felt on palpation. There may also be weakness of the proximal appendicular muscles and, in rare cases of cervicobrachial polymyositis, of the trapezius muscle and the extensor muscles of the hand and fingers.[1,4,10–12]

In our reports, the patients lost the horizontal gaze, due to the deformity and rigidity of the anterior musculature, which resulted in the shortening of the M. sternocleidomastoid. These points were considered by the team to be crucial, as the degree of rigidity of these muscles can inhibit passive extension of the head, compromising surgical correction of the deformity.

Radiography (X-ray), computed tomography (CT), and magnetic resonance imaging (MRI) have a crucial role in visualizing parameters to assess the spine and soft tissues. This assessment provides valuable insight into determining the severity of the deformity and deciding on a possible therapeutic approach. Moreover, Positron Emission Tomography (PET) can be important in assessing muscle metabolism, studying the complementary effect in identifying dystonic muscles, and differentiating the forms of anterocollis: CACOL and ACAP.[3,5,12,13]

Electroneuromyography (EMG) is a valuable electrodiagnostic test for identifying the involvement of muscle groups, particularly in cases of involuntary contraction and muscle weakness, and can effectively distinguish between simple and diffuse anterocollis.[3]

Muscle biopsy can reveal inflammatory muscle diseases and, when examined histopathologically, can also indicate mitochondrial myopathies caused by genetic conditions, including isolated myopathy of the extensor muscles of the neck (INEM).[12–14]

There are two approaches to treating DHS, either through surgery or conservative methods.[4] However, due to insufficient evidence, it remains uncertain which approach is the most effective for initial treatment. Therefore, conservative therapy is usually tried first, and if the results are unsatisfactory, more invasive therapies may be necessary. Therapies may be necessary.[15]

Conservative treatments comprise medication, etiological, and physical therapies, with the first focusing on the use of immunosuppressants as a form of symptom relief. Etiologic therapy aims to resolve the pathologies that could cause this syndrome. Additionally, physical therapy includes physical support, physiotherapy, and necklaces.[1]

Despite combining drug and physical therapies, results are still inconsistent. Using collars and pharmacological drugs is thus not effective in most cases.[4]

In our study, we initially opted for more conservative therapies in an attempt to optimize drug therapy and physical rehabilitation. Unfortunately, both patients exhibited worsening deformities, reduced functional independence, and worsening pain complaints. Consistent with existing literature, our findings suggest lower efficacy rates associated with conservative therapy.

Drain found that surgical therapies are significantly more effective than physical therapies, with success rates of 92.2% and 18.2%, respectively. Moreover, combining physical and surgical therapies can result in 100% effectiveness. Patients who received treatment targeted to their etiology experienced a resolution rate of 73.5%. Immunosuppressants produced a positive outcome in 78.9% of cases.[1]

The surgical procedure aims to restore the horizontal gaze, correct sagittal alignment, and decompress neural elements. There are two primary methods to perform the procedure: arthrodesis of a single segment and cervicothoracic arthrodesis.

According to Cavagnaro et al., when comparing the two approaches statistically, patients who received cervicothoracic arthrodesis had a better prognosis. Arthrodesis from C2 to

the upper thoracic spine segments is the most appropriate procedure, as it preserves subaxial spine mobility and enhances the overall surgical success rate.[1,2]

When evaluating only the restoration of horizontal gaze and the permanence or improvement of neurological status, cervical arthrodesis procedures proved successful in 91.3% of cases. In comparison, patients who underwent cervicothoracic arthrodesis had a 100% success rate, as reported by Cavagnaro et al.[2]

Our approach involved performing posterior arthrodesis of the C2-T6 levels, allowing for the fixation of two spine segments, including the cervico-thoracic junction. After the surgery, the chin-on-chest deformity was successfully reduced, leading to the restoration of horizontal gaze and relief of symptoms such as dysphagia and pain. Based on the literature, this technique is expected to achieve the highest rate of resolution while preserving the motility of the muscles attached to the C1 vertebra.

Cervicothoracic arthrodesis is a recommended approach for the treatment of this condition, which has an excellent prognosis. In our experience, most patients who undergo this therapeutic option exhibit improved functional independence, as evidenced by their ability to walk and feed themselves without assistance.[2]

Conclusion

Two approaches are available for treating Dropped Head Syndrome: surgical and conservative. The surgical approach is indeed more efficient, although the combination of both methods yielded even better clinical outcomes. Arthrodesis from C2 to the upper thoracic spine segments is considered the most appropriate surgical technique for maintaining subaxial spine movement. This is due to its excellent rate of correcting deformities, preserving horizontal gaze, and improving or maintaining a neurological state. Furthermore, it is essential to emphasize the necessity for additional studies to demonstrate more clearly the circumstances that lead to the choice of the surgical approach.

Conflict of Interest

None.

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Orbital Pseudotumor: Neurosurgical Perspective

Pseudotumor orbitário: Perspectiva neurocirúrgica

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Abstract

Idiopathic orbital inflammation is the third most common orbital affection, characterized by a benign inflammatory process, which is neither infectious nor neoplastic and can affect any orbital tissue. A 31-year-old female patient was referred to neurosurgical evaluation due to left orbital pseudotumor, which was nonresponsive to high doses of corticosteroid therapy. During the neurological examination, we identified reduced visual acuity, complete external ophthalmoplegia, ocular pain, and severe proptosis. A neurosurgical intervention with lateral orbitotomy was performed, with great pain relief. In the present case report, we discuss the disease and its natural course and call the attention of neurosurgeons to prompt intervention in selected cases.

Keywords
- orbit
- pseudotumor
- proptosis
- orbitotomy

Resumo

A inflamação orbital idiopática é a terceira causa mais comum de afecção orbital, caracterizada por processo inflamatório benigno, não infeccioso nem neoplásico, o qual pode acometer qualquer tecido orbital. Uma paciente de 31 anos, foi encaminhada para neurocirurgia em decorrência de um pseudotumor orbital à esquerda, o qual não respondeu ao tratamento com altas doses de corticosteroides. No exame neurológico, foram identificadas redução da acuidade visual, oftalmoplegia externa, dor ocular e ptose severa. Neste relato de caso, discutimos o curso natural da doença e chamamos a atenção dos neurocirurgiões para a intervenção de urgência em casos selecionados.

Palavras-chave
- órbita
- pseudotumor
- proptose
- orbitotomia

Introduction

The idiopathic orbital inflammation, also known as orbital pseudotumor, was first described by Gleason in 1903.[1] A benign inflammatory process of the orbital tissues characterizes the condition. The pathophysiology is not completely known, but some conditions, such as rheumatologic and autoimmune diseases, as well as infections, can be related as triggers and predispose the illness. The disease does not present a predilection for gender or race and usually is unilateral.[2,3]

We herein present a case of a 31-year-old female patient who was refractory to the medication therapy and was referred to neurosurgery for decompression and pain relief.

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Case Report

A 31-year-old female patient was diagnosed with left orbital pseudotumor. The patient was evaluated by an ophthalmologist that prescribed high doses of corticosteroids. Regarding increased doses, the symptoms became worse, and she was referred to neurosurgery for evaluation. An orbital magnetic resonance imaging (MRI) scan demonstrated ocular muscle infiltration and proptosis (►**Fig. 1**). Due to reduced visual acuity, complete external ophthalmoplegia, ocular pain, and severe proptosis, a lateral decompressive orbitotomy was proposed. With a small skin incision, the decompression was made without difficulties (►**Fig. 2**). A postoperative computed tomography demonstrated the lateral orbitotomy (►**Fig. 3**). Visual acuity improved on the first postoperative day. The patient is under rheumatologist follow-up using azathioprine.

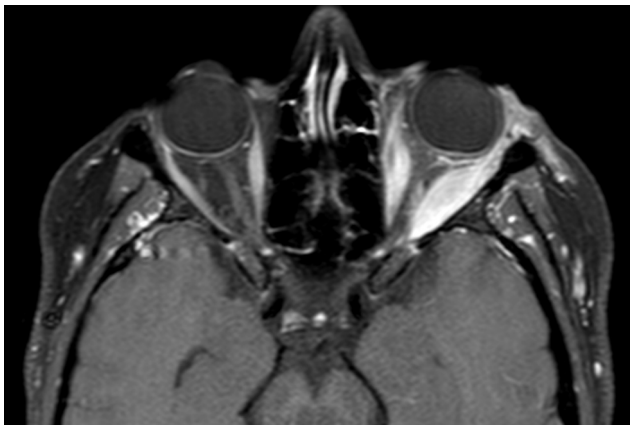

Fig. 1

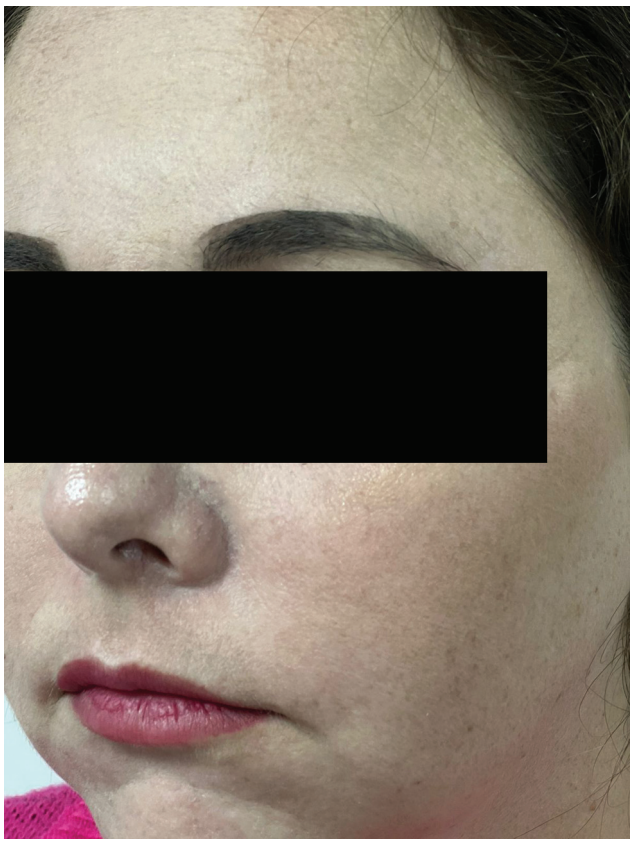

Fig. 2

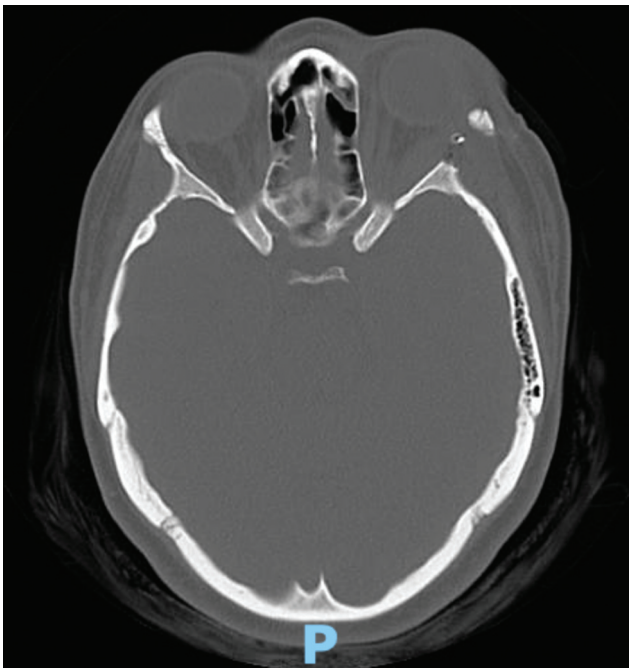

Fig. 3

Discussion

The clinical presentations are distinct, varying according to the chronicity, affected tissue, and mainly the anatomic location. Following the acute inflammation, the histopathologic presents with infiltrate and demonstrates the cardinal signs of the inflammation. As it becomes chronic, the fibrosis process takes place.[4]

This disease is self-limited in 28% of cases,[5] but the first-line therapy is corticosteroid use when needed. In this management, 78% presented positive results of the inflammation cardinal signs and other symptoms in 24 to 48 hours. However, only 37% were cured, and 52% presented with remission.[6,7] Furthermore, the second-line therapy is radiotherapy, indicated for patients with corticosteroid intolerance or resistance, being effective in 75% of the cases.[8,9]

Additionally, immunosuppressant therapy can be a possible treatment in patients with recurrence or persistent symptoms, but there is no actual consensus on the effectiveness, doses, and therapy time.[8] The surgical intervention takes the same place, and there are no studies on the correct indication and the best surgical approach. Several discussions suggest that worsening pain, visual disturbance, and cranial nerve palsy are the best indications for this condition.[10]

Conclusion

Surgical intervention for decompression can be necessary for some cases of idiopathic orbital inflammation. The lateral

orbitotomy can be a “visual saving” surgery and should always be in the neurosurgeon armamentarium.

Conflict of Interests

The authors have no conflict of interests to declare.

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Atypical Choroid Plexus Papilloma of the Foramen Luschka in an Adult: A Case Report and Literature Review

Papiloma atípico do plexo coróide do forame de Luschka em um adulto: Relato de caso e revisão da literatura

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Abstract

Choroid plexus papillomas are rare tumors of the central nervous system. They are mostly observed during childhood and are commonly located in the lateral ventricles. In adults, they are very rare and usually located in the fourth ventricle. We herein present a case of atypical choroid plexus papilloma of the foramen of Luschka in an adult. A 26-year-old male patient was presented with headache, dizziness, visual loss, and gait disturbance. Cranial imaging revealed a giant mass located in the foramen of Luschka with non-intense homogeneous contrast enhancement. Gross total removal of the tumor was achieved via the left telovelar approach. Transient swallowing difficulty and worsening of the nystagmus were observed in the early postoperative period. The patient was free of symptoms for 3 months postoperatively. The pathological examination yielded a diagnosis of atypical choroid plexus papilloma. We aimed to discuss the clinical findings and surgical treatment of the case.

Keywords
- atypical choroid plexus papilloma
- foramen of Luschka
- telovelar approach

Resumo

Os papilomas do plexo coroide são tumores raros do sistema nervoso central. Eles são observados principalmente durante a infância e são comumente localizados nos ventrículos laterais. Em adultos, eles são muito raros e geralmente localizados no quarto ventrículo. Apresentamos aqui um caso de papiloma atípico do plexo coroide do forame de Luschka em um adulto. Um paciente do sexo masculino de 26 anos apresentou dor de cabeça, tontura, perda visual e distúrbio da marcha. A imagem craniana revelou uma massa gigante localizada no forame de Luschka com realce homogêneo não intenso pelo contraste. A remoção total bruta do tumor foi obtida pela

Palavras-chave
- papiloma atípico do plexo coroide
- forame de Luschka
- abordagem telovelar

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abordagem telovelar esquerda. Dificuldade transitória de deglutição e piora do nistagmo foram observadas no período pós-operatório inicial. O paciente ficou livre de sintomas por 3 meses no pós-operatório. O exame patológico produziu um diagnóstico de papiloma atípico do plexo coroide. Nosso objetivo foi discutir os achados clínicos e o tratamento cirúrgico do caso.

Introduction

Choroid plexus papillomas are rare tumors of the central nervous system. They are mostly observed during childhood and commonly located in the lateral ventricles. In adults, they are much rarer and often located in the fourth ventricle. Although these tumors are usually located in the ventricles, in very rare cases they can be located in the parenchyma, foramina of Luschka, and cerebellopontine angle.[1,2] The 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System classifies choroid plexus tumors as papillomas (grade 1), atypical tumors (grade 2), and carcinomas (grade 3), according to number of mitotic figures.[3,4]

The microscopic appearance of atypical choroid plexus papilloma is like that of typical choroid plexus papilloma, but the number of mitoses is 2 to 5 per 10 high-power fields.[5] Atypical choroid plexus papilloma is very rare in adults. We herein report a giant, atypical, and very rare condition. In addition, the surgical treatment of these tumors involves difficulties due to tumor size and location. In the current report, we aim to discuss the clinical findings and surgical treatment of the case.

Case

A 26-year-old male patient was evaluated for headache, dizziness, visual loss, and gait disturbance. He presented decreased visual acuity, horizontal nystagmus in the left eye, ataxia, and dysarthria, along with an impaired cerebellar examination. Papilledema was present in the fundus examination. A cranial magnetic resonance imaging (MRI) scan revealed a giant mass located in the left foramen of Luschka, extending from the cerebellopontine angle to the foramen magnum, involving the walls of the fourth ventricle and causing direct compression on the brainstem. The mass was hypointense on T1-weighted MRI scans, hyperintense on T2-weighted images, and it presented non-intense homogeneous contrast enhancement. The fourth ventricle was compressed, resulting in non-communicating hydrocephalus (►**Fig. 1**).

The patient was operated in the prone position. Following the midline incision, a predominantly left-sided suboccipital craniectomy was performed. The left cerebellar tonsil extending to the foramen magnum was retracted upwards, and the tumor was revealed. Then, the borders of the tumor were visualized through a left telovelar approach. The tumor had partially invaded the fourth ventricle wall, middle cerebellar peduncle, and pons. The lower cranial nerves were also partially surrounded by the tumor and pushed out of their anatomical courses. The tumor tissue was dissected very carefully with the help of an ultrasonic aspirator, since the borders could not be clearly distinguished. The part of the tumor extending to the anterosuperior border of the foramen of Luschka was removed with preservation of the basilar artery and its branches, as well as the seventh and eighth cranial nerves. Then, through a left telovalar approach, gross total removal of the tumor was performed.

No additional neurological deficit was observed in the early postoperative period, except for worsening of nystagmus of the left eye. On the third postoperative day, the patient developed difficulty in swallowing. No postoperative bleeding or significant ischemia was observed in the imaging scans. The patient's oral intake was stopped for a few days, and he was put on steroids and antiedema agents, which gradually improved the swallowing difficulty. The result of the pathological examination was atypical choroid plexus papilloma, WHO grade 2 (►**Fig. 2**). At the follow-up after 3 months, the patient's vision had completely improved, and he had no nystagmus. The headache and vertigo complaints had improved, there was no gait disturbance, and the cerebellar examination was normal. The swallowing difficulty was completely resolved, and the patient was able to ingest liquid and solid foods without difficulty. A follow-up MRI scan showed no signs of any residual or recurrent tumor.

Discussion

Atypical choroid plexus papillomas are very rare in adults and usually located in the ventricles. Moreover, choroid plexus tumors can be observed very rarely in the foramen of Luschka. These factors make the differential diagnosis difficult. The foramen of Luschka is more commonly known as a passage through which ventricular tumors enlarge and extend into the extraventricular space. This is quite typical, especially for ependymomas.[6] In the case herein reported, although the tumor invaded the wall of the fourth ventricle, there was no significant mass in the ventricle. The tumor had extended anteriorly to the subarachnoidal space and based on the radiological findings, the differential diagnoses of expenditures of ependymoma and medulloblastoma were difficult. Vestibular schwannoma was also considered in the differential diagnosis due to its proximity to the internal acoustic canal and the seventh and eighth cranial nerves. However, vestibular schwannomas are extra-axial lesions that enlarge by pushing the cerebellar tissue instead of infiltrating it, and their borders are usually clearly defined.

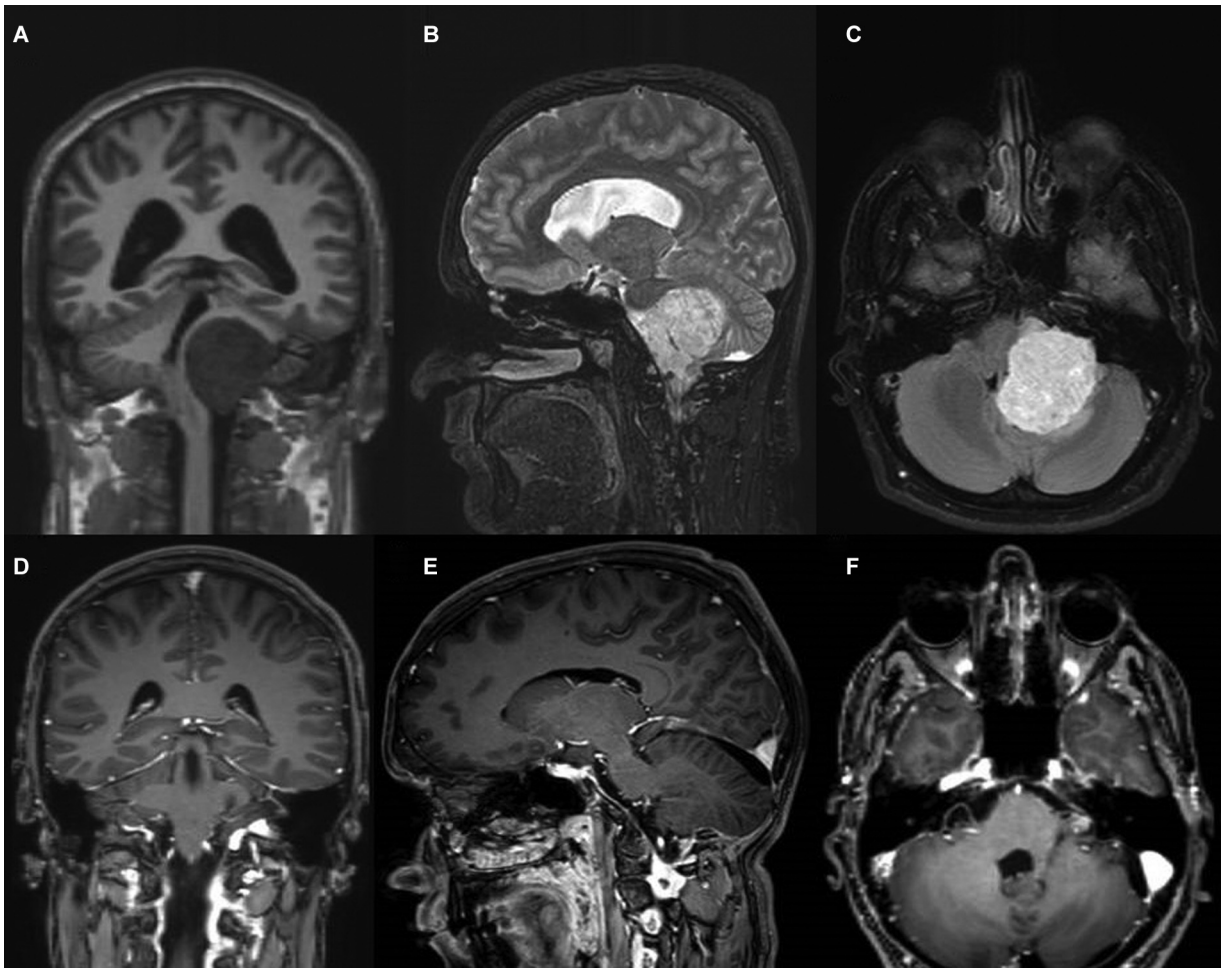

Fig. 1 (A) T1-weighted coronal magnietic resosnance imaging (MRI) scan showing the tumor invading down the foramen magnum. (B) T1-weighted contrast-enhanced sagittal image showing a giant tumor seated on a large dural base. (C) Fluid-attenuated inversion recovery-weighted contrast-enhanced axial section image showing fourth ventricular compression. (D–F) Control-enhanced MRI scan performed 6 months postoperatively, surgical trace from which the tumor was removed in the coronal section, no residual tumor or recurrence is observed.

In addition, the tumor extended anteriorly into the subarachnoid space and showed proximity to the petroclival dura mater with a broad base. Therefore, it was like meningiomas in this location. Unlike meningiomas, contrast-enhanced MRI scans did not show dural thickening and dural tail in the case herein reported. Rarely, glial tumors, metastases, epidermoid cyst, and paraganglioma can also be observed in the foramen of Luschka and should be considered in the differential diagnosis.[7]

Due to the anatomical extension of the foramen of Luschka, tumors in this location may lead to findings related to the pons, medulla, cranial nerves, and cerebellum, and they may also cause hydrocephalus. In the case herein reported, there were complaints of vertigo, tinnitus,

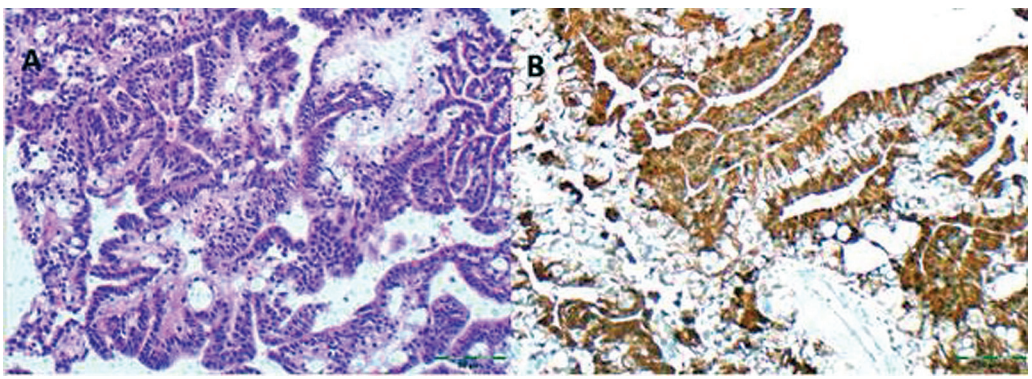

Fig. 2 (A) Photographs showing a papillary structure with a layer of columnar epithelial cells and fibrovascular stroma (hematoxylin and eosin stain, 100x magnification). (B) S100 immunoreactivity (200x magnification).

headache, and nausea/vomiting symptoms, along with difficulty in walking and speaking, as well as decreased visual acuity. There were dysmetria and dysdiadochokinesia on the left side. Moreover, the presence of horizontal nystagmus in the left eye was remarkable in the present case. The patient's nystagmus was not position-related, non-rotatory, and there was no ophthalmoplegia on the eye examination. The eye movements were normal. The severity of nystagmus in the left eye increased postoperatively. Unilateral horizontal nystagmus that is not accompanied by ophthalmoplegia and not positional is a very extreme condition. Middle cerebellar peduncle or medial longitudinal fasciculus damage has been reported as a possible cause of nystagmus in a case with atypical choroid plexus papilloma located in the cerebellar peduncle.[8] In the case herein reported, the fact that horizontal nystagmus was not related to position, and the absence of a rotatory component or of any ophthalmoplegia accompanied by nystagmus suggest a unilateral partial lesion of the paramedian pontine reticular formation (PPRF) in the pons. It should be kept in mind that horizontal nystagmus may occur due to giant tumors located in the foramen of Luschka and/or after surgeries performed in this area, and the patient should be evaluated in this respect before and after the operation. The horizontal nystagmus of the patient, which worsened after surgery, was completely resolved at the follow-up after 3 months.

For tumors located in the foramen Luschka, different surgical approaches can be applied according to the size and growth direction of the tumor. The retrosigmoid suboccipital approach can be used for tumors with an anterosuperior location and enlarged in the cerebellopontine angle; subtonsillar approaches, for tumors located more posteroinferiorly; the transvermian approach, for tumors growing toward the fourth ventricle; and the transcerebellar approach, for large tumors.[2,7,9] Adib et al.[9] divided the choroid plexus papillomas located laterally to the brainstem into three types based on the line between the medulla oblongata and the pons. The tumor is defined as type 1 if it is located superiorly to the line; type 2, if it is located inferiorly to the line; and type 3, if it extends to both parts. Type-3 tumors are large and may extend from the cerebellopontine angle to the foramen magnum.[9] In the case herein reported, the tumor was compatible with type 3 according to this classification, and it extended from the cerebellopontine angle to the foramen magnum. Considering the location and size of the tumor, the telovelar approach was preferred to reach the medial, lateral, anterosuperior and foramen magnum of the foramen of Luschka, and the tumor was grossly removed.

For the treatment of the tumors which are closely adjacent to the foramen of Luschka, the anteroinferior cerebellar artery (AICA), the posteroinferior cerebellar artery (PICA), the seventh, eighth, and lower cranial nerves may be damaged during surgery, especially in cases of large tumors. In addition, atypical choroid plexus tumors may also invade the surrounding tissues, as in the case herein reported. Therefore, dissection of the tumor from the surrounding tissues, especially from the brainstem, involves difficulties and may lead to undesirable situations. In the present case, the horizontal nystagmus in the left eye intensified after the operation, and dysphagia developed 3 days postoperatively.

The treatment of atypical choroid plexus tumors is surgical total resection. The role of adjuvant chemotherapy and radiotherapy in the treatment of these tumors is controversial. However, due to the localization and size of the tumor, adjuvant chemotherapy and radiotherapy are recommended in cases in which the tumor cannot be completely removed, or it has recurred.[4,10] In the case herein reported, the tumor was grossly removed. Therefore, adjuvant chemotherapy and radiotherapy were not administered considering possible side effects and discussions on treatment efficacy. Frequent follow-up was recommended for possible recurrence and metastasis.

Conclusion

Although rare, atypical choroid plexus papilloma should be considered in the differential diagnosis of tumors located in the foramen of Luschka. Atypical choroid plexus papillomas present difficulties in surgery because they can invade the surrounding tissues. In cases of giant tumors extending from the pontocerebellar angle to the foramen magnum, the suboccipital telovelar approach provides the appropriate corridor for gross total removal.

Informed consent

Informed consent was obtained from all the individuals included in the study.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published, and that due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Craniosynostosis in 2-Month-Old Infant Managed with Minimally Invasive Endoscopically Assisted Remodelation (MEAR)

Craniossinostose em lactente de 2 meses tratado com remodelação minimamente invasiva assistida por endoscopia (MEAR)

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Abstract

Craniosynostosis is an atypical closure of one or multiple sutures that cause abnormal skull shape. Main complications include intracranial hypertension, alteration of cognitive development, seizures, and blindness, among others. The incidence is 1 in 2000 live births, and it is higher in males. This case report presented a 2-month-old infant with scaphocephaly identified on the physical examination. The early approach was a CT scan and cephalometric assessment to confirm the diagnosis and Schedule the surgery treatment. The minimally invasive endoscopic remodeling was successfully performed with positive outcomes. Literature review was performed on digital bases like PubMed, Web of Science and Scopus. Minimally invasive endoscopically assisted remodelation (MEAR) benefits to correct craniosynostosis are a shorter stay at hospital, less perioperative complications and lower medical cost. Using technologies and innovative techniques the surgical approach could be improved to reduce complications and maximize outcomes. Thus, neurosurgery departments must know and implement this technique.

Keywords
- craniosynostosis
- minimally invasive
- endoscopic
- case report

Resumo

A craniossinostose é um fechamento atípico de uma ou múltiplas suturas que causa formato anormal do crânio. As principais complicações incluem hipertensão intracraniana, alteração do desenvolvimento cognitivo, convulsões e cegueira, entre outras. A incidência é de 1 em 2000 nascidos vivos, sendo maior em homens. Este relato de caso apresentou um bebê de 2 meses com escafocefalia identificada no exame físico. A abordagem inicial foi uma tomografia computadorizada e avaliação cefalométrica para confirmar o diagnóstico e programar o tratamento cirúrgico. A remodelação

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endoscópica minimamente invasiva foi realizada com sucesso, com resultados positivos. A revisão da literatura foi realizada em bases digitais como PubMed, Web of Science e Scopus. Os benefícios da remodelação assistida endoscópica minimamente invasiva (MEAR) para corrigir a craniossinostose são menos tempo no hospital, menos complicações perioperatórias e menor custo médico. Usando tecnologias e técnicas inovadoras, a abordagem cirúrgica pode ser melhorada para reduzir complicações e maximizar os resultados. Portanto, os departamentos de neurocirurgia devem conhecer e implementar esta técnica.

Palavras-chave
- craniossinostose
- minimamente invasivo
- endoscópico
- relato de caso

Introduction

Craniosynostosis is an abnormally shaped skull caused by a premature fusion of sutures. Scaphocephaly is the most common form of craniosynostosis, the early closure of the sagittal suture produces a longitudinal skull elongation to compensate for the growth. In severe cases, intracranial pressure could occur with other complications and face malformations.[1] Otherwise, syndromic craniosynostosis includes a fusion of multiple cranial sutures and other abnormalities of the face and limbs.[2]

The prevalence of craniosynostosis ranges from 3.1 to 5.06 per 10,000 births.[3] Scaphocephaly accounts for ∼50% of craniosynostosis cases, with an incidence of 1 in 2000 live births.[4] Nonsyndromic craniosynostosis has an incidence of 0.4 to 1.0 in 1000 births.[5] There is a gender variation in presentation, with boys having a 4:1 prevalence of sagittal craniosynostosis, while girls have a 3:2 prevalence of unicoronal craniosynostosis compared with boys.[5]

According to the mechanisms underlying premature closure of cranial sutures, the abnormal dural attachments drive an excessive tension that arrests bone growth and leads to early suture closure.[6] Fibroblast growth factor (FGF) and transforming growth factor β lead the mechano-transducion signals to stimulate the osteogenic cell proliferation at the suture line.[7] Also, gene mutations and chromosomal alterations such as abnormality in FGF receptors,[2] implicating FGFR2, FGFR3, TWIST1, and EFNB1.[7] Environmental factors that may predispose the disease are oligohydramnios, uterine fetal head constriction, exposures to teratogens, use of epileptic drugs (phenytoin, valproic acid) and maternal smoking.[2]

The diagnosis is primarily based on the physical examination confirmed by the CT scan. Also, three-dimensional surface reconstructions using CT can assist in the classification of craniofacial disorders and planning surgical treatment.[8] The CT scan findings concordance with clinical diagnosis in 98% of the cases, 3D imaging allows planning the surgical osteotomies approach to reduce the operative time, and overall risks associated and simulate the surgical results.[9] Furthermore, cephalometry measurement is a standardized technique to confirm longitudinal head growth with the index cranial (ratio of the maximum width to length of the skull) considered normal 74–80 UI in males, and 73–79 UI in females. Craniosynostosis is contemplated under 70 UI, having scaphocephaly CI between 60–67 UI.[10]

In this case, non-syndromic craniosynostosis involves the closure of just one of the sutures, which could be sagittal, coronal, metopic, or lambdoid. The case report presents a 2-month-old patient who was diagnosed with scaphocephaly, a CT scan confirmed it and assisted in planning the approach using a MEAR technique, which is gradually implemented through this decade in the neurosurgery departments.

Case Study

The case is a 2-month-old infant with a height of 51 cm and a weight of 5.2 kg. Mother healthy, father healthy, pregnancy progress normal, delivery on time, cephalad, birth weight 3770 g, PD 50 cm, normal postpartum adaptation. Conscious, afebrile, no signs of acute infection, hydration good, skin clear.

Head: scaphocephaly, sclera white, conjunctiva pink, pupils isochoric, ears and nose without discharge, throat normal
Neck: Filling of jugular veins normal, nodes not enlarged.
Chest: symmetrical, breathing auscultatory, no side effects, eupnoea, AS regular, the sounds are limited, non-pathological murmur.
Abdomen: calm, painless, peristalsis audible, palpation without palpable resistance
Genitalia: male genitalia
Extremities: no deformities, no swelling
Indicative neurological findings: Picomotor development corresponds to age, finding - isochoric pupils, no nystagmus, and facial expressions that seem symmetrical. No signs of meningeal irritation.

Diagnosis Assessment

To confirm the scaphocephaly clinical diagnosis, a CT scan and cephalometry were required. Diagnosis process: FOO 431 mm/over metopion = +3.4 SD of norm (nonhereditary value) Dynamics of postnatal brain/cerebral growth - see chart FOO **IC 62.0** IU.

Disproportional cephalogram: biparietal = −1.4SD, neurocranium length = + 3.6SD, forehead width= −0.1SD of normal, cranial base width −1.7 SD.

A 2-month-old boy with a craniosynostosis diagnosis confirmed by a CT scan and cephalometric markers of a premature obliteration of the sagittal suture. ►**Figs. 1** and **2**

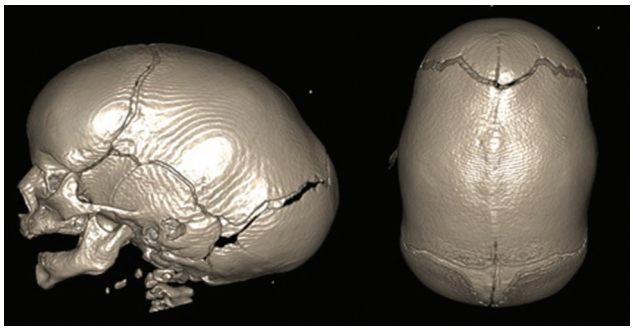

Fig. 1 CT scan, 3D reconstruction previous surgery.

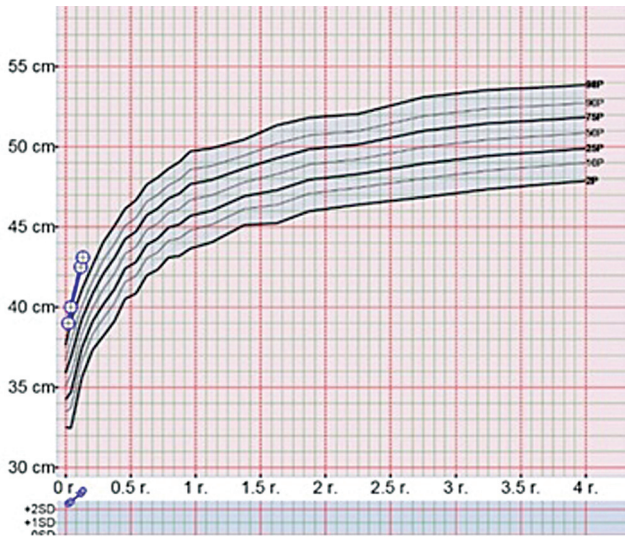

Fig. 2 Cephalometry with +3.4 SD.

Surgical Intervention

In early diagnosis cases, the indication is a minimally invasive surgical technique with an endoscopic strip craniectomy along the prematurely closed sagittal suture with lateral barrel-stave osteotomies. The endoscope helps to control the extent of craniectomy lateral basal and illuminates the operative field to disclose bony spikes, unevenness, and bumpiness.[11]

The surgery starts with two incisions of 3- to 5-cm length ~5 cm behind the bregmatic fontanelle and above lambda. Next, the surgeon makes two burr holes in the parietal bones, separates the adjacent dura, connects it across the midline, and dissects the dura with a Penfield dissector. Then, the anterior and posterior burr holes relate to bone-cutting scissors, a 2–5-cm-wide sagittal strip craniectomy, and 5–15-mm-wide lateral craniotomies behind the coronal suture and in front of the lambdoid sutures on both sides. Also, the skull remodelation is performed by unsticking the adhesions of the periosteum and dura mater to widen the posterior parietal regions reshaping the parietooccipital skull. Finally, the periosteum is approximated, and the skin is stitched in layers with intradermal atraumatic suture. ►**Fig. 3**

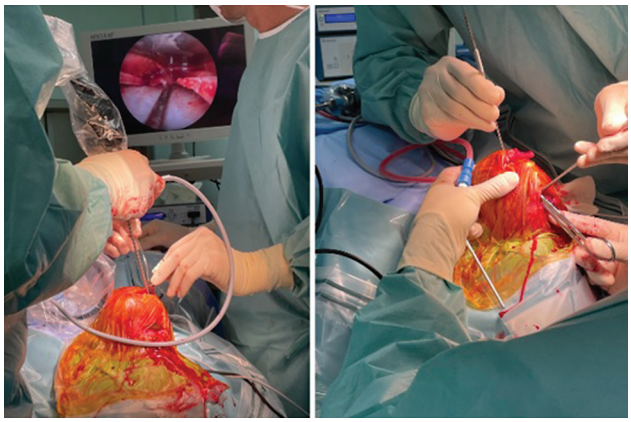

Fig. 3 The MEAR technique performed in this craniosynostosis case.

Follow-up and Outcomes

The patient was observed at the ICU overnight with moderate head edema that was resolved quickly, and a 3D head CT scan was performed. The child was followed by the neurosurgery department and an orthodontist with a regular register of cephalometry and a 3D head scan.

Surgical intervention was favorable to prevent complications like intracranial hypertension and its consequences, for instance: blindness, brain damage, seizures, and neurodevelopment affections.[2,3] ►**Figs. 4** and **5**

Discussion

This surgical technique was developed and implemented in 2017 in Motol University Hospital; Neurosurgery Department.[11] The craniosynostosis cases are managed with modern surgical techniques. The emphasis, in this case, is the importance of an early diagnosis using a CT scan and cephalometric parameters to achieve an adequate surgery approach. Furthermore, the endoscope is an excellent tool to control the operative field, especially in laterobasal depths

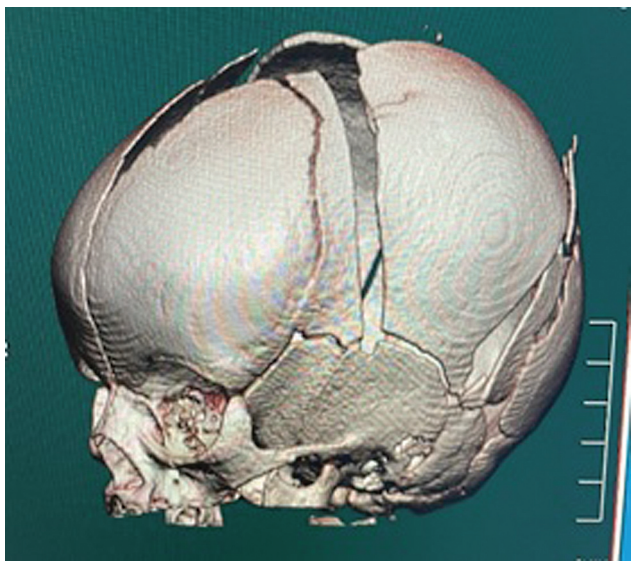

Fig. 4 5 CT scan 3 days after remodalation surgery.

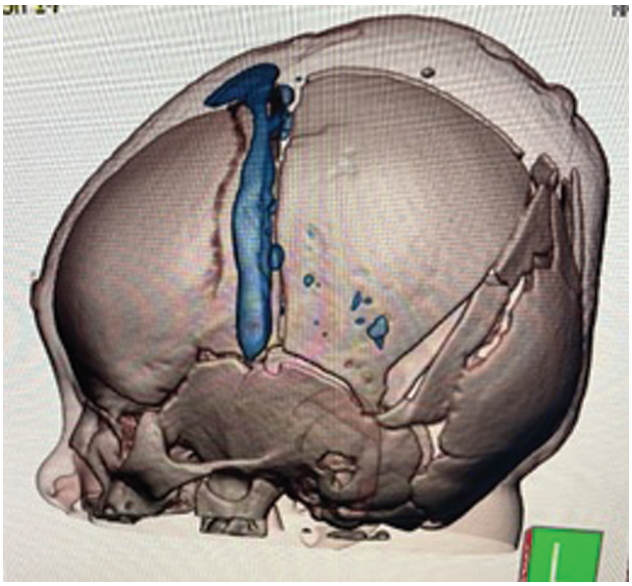

Fig. 5 CT scan 3 days after remodalation surgery.

where it is valuable to improve the outcomes and reduce the complication risk.

Fassl V. et. identified the age range indication for endoscopically assisted craniosynostosis surgery in children < 3 months old, even a frame 4–9 months old depending on the deformity case. Mentioning the difficulty of performing the technique in patients older than 6 months.[12] The early imaging diagnosis through a CT scan allows attain the surgical age indications, additionally detecting incidental pathologies.[9] The alternative imaging diagnostic, MRI aids in detecting cerebral pathologies, vascular malformations, cranial neuropathies, and soft-tissue abnormalities. Moreover, ultrasonography could identify the loss of hypoechoic signal from the sutural space, irregularly thickened border, and asymmetry of the fontanels (sensitivity = 96.9%, specificity = 100%).[8,9]

The minimally invasive surgeries significantly decrease blood loss and reduce rates of transfusion in contrast with the open craniotomies.[13] Indeed, the operative time and length of hospital stay are shorter as well, Yan H. et. describe a medical cost reduction in endoscopic procedures cheaper than open procedures.[13] Other benefits are less morbidity, low postoperative pain, and faster recovery.[14]

Considering the intraoperative complications, the endoscopic assisted surgery appears to lower cardiovascular, pulmonary, and dural adverse situations. Despite this, the difference in postoperative complications, such as surgical wound infection, is not significant compared with open craniotomy.[15] The follow-up could extend even for 13 months, initiating helmet therapy as soon as possible within 24 hours postoperative until 5.0 months to 1 year. Criteria to discontinue the helmet therapy comprised either achieving normal cranial parameters.[12]

Endoscopic-assisted remodeling attributes the successful short and long-term outcomes to the younger age of suturectomy; certainly, the differences in outcomes with this technique remain an important element of this vanguard paradigm.[16] New technologies and innovative techniques improve surgical strategies to offer the best treatment for patients.[17] The neurosurgery departments must know about all these techniques. For sure the surgeons will continue improving techniques, such as virtual surgical planning or 3D printed models, to maximize outcomes and minimize surgical trauma in patients.[17]

Conclusion

The proper early diagnosis of craniosynostosis will permit an adequate surgery intervention by the neurosurgery departments. Hence, the medical system and hospitals should promote innovation in the technological field to enhance medical training with updated techniques to give the best treatment for the patient. Limitations like medical assistance accessibility, limited resources, or surgical skills could be strengthened in many countries, impelling research and institutional cooperation. Finally, highlighting the importance of early contact with patients and clinical cases by medical students might be beneficial to achieve high-level education and the best quality medical attention.

Conflict of Interest

The authors report no conflict of interest.

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Surgical Treatment of Racemose Cysticercosis in the Quadrigeminal Cistern: A Case Series

Tratamento cirúrgico de cisticercose racemosa na cisterna quadrigêmea: Uma série de casos

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Abstract

Introduction Racemose neurocysticercosis is rare and distinctive among the variety of neurocysticercosis pathologies, and it is characterized by the development of cysts in the basal subarachnoid region. This uncommon presentation involves the formation of multiple, non-encapsulated cystic membranes resembling a bunch of grapes due to the exogenous budding of aberrant proliferating *Taenia solium* larvae. Typically observed in expansive areas of the brain, such as the suprasellar, sylvian, and quadrigeminal cisterns, or around the rostral brainstem, these cysts lack scolex, do not always involve edema, and can escape detection with contrast enhancement depending on their life cycle.

Case Description In both cases presented here, the patients' multilobulated cysts had components in the posterior incisural space that extended below the mesial temporal region. Consequently, there was no need for a more complex approach to the pineal region, and cyst removal was achieved solely with the subtemporal approach. This is possible due to the cysts' lack of adherence to neurovascular structures. Following cyst drainage, their capsules were easily removed with a forceps.

Conclusion To achieve a successful outcome, these cases require a comprehensive understanding of neurocysticercosis variations as well as individualized surgical planning based on lesion characteristics and solid postoperative pharmacological management. The effective treatment of neurocysticercosis is clearly complex and still evolving, and continued vigilance and research will enhance our ability to manage the challenges this parasitic neurological condition presents.

Keywords
- racemose neurocysticercosis
- basal subarachnoid cysts
- subtemporal approach
- neurosurgery

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Resumo

Introdução A neurocisticercose racemosa é rara e distinta entre a variedade de patologias de neurocisticercose, e é caracterizada pelo desenvolvimento de cistos na região subaracnóidea basal. Essa apresentação incomum envolve a formação de múltiplas membranas císticas não encapsuladas, assemelhando-se a um cacho de uvas, devido à brotação exógena de larvas de *Taenia solium* proliferantes aberrantes. Normalmente observados em áreas expansivas do cérebro, como as cisternas supraselar, silviana e quadrigeminal, ou ao redor do tronco cerebral rostral, esses cistos não têm escólex, nem sempre envolvem edema e podem escapar da detecção com realce de contraste, dependendo do seu ciclo de vida.

Descrição do caso Em ambos os casos apresentados aqui, os cistos multilobulados dos pacientes tinham componentes no espaço incisural posterior que se estendiam abaixo da região temporal mesial. Consequentemente, não houve necessidade de uma abordagem mais complexa para a região pineal, e a remoção do cisto foi obtida apenas com a abordagem subtemporal. Isso é possível devido à falta de aderência dos cistos às estruturas neurovasculares. Após a drenagem do cisto, suas cápsulas foram facilmente removidas com uma pinça.

Conclusão Para atingir um resultado bem-sucedido, esses casos exigem uma compreensão abrangente das variações da neurocisticercose, bem como um planejamento cirúrgico individualizado com base nas características da lesão e no manejo farmacológico pós-operatório sólido. O tratamento eficaz da neurocisticercose é claramente complexo e ainda está em evolução, e a vigilância e a pesquisa contínuas aumentarão nossa capacidade de gerenciar os desafios que essa condição neurológica parasitária apresenta.

Palavras-Chave

- racemose neurocisticercose
- cistos subaracnóideos basais
- subtemporal abordagem
- neurocirurgia

Introduction

Neurocysticercosis (NCC) is the most common parasitic disease affecting the human nervous system and is a substantial public health concern throughout the developing world. The clinical presentation of NCC has many variables such as lesion quantity and location, and the host's immune response to the parasitic agent. Diagnosis primarily depends on neuroimaging and is complemented by serological detection of antibodies/antigens in the serum or occasionally in the cerebrospinal fluid.[1] Patients with exclusively intraparenchymal brain parasites typically manifest seizures, which tend to lessen over time. Conversely, parasites situated within the ventricles and the basal subarachnoid space undergo progressive growth and infiltration, potentially giving rise to hydrocephalus and/or intracranial hypertension. Such manifestations often lead to morbidity and mortality. Calcified NCC still contributes to a persistent and heavy burden of disease.[1,2]

The present case series underscores the multifaceted nature of NCC and emphasizes the importance of personalizing therapeutic strategies for each patient. This disease also poses challenges to management which must be considered. The integration of advanced diagnostic modalities and evolving therapeutic strategies reveals significant progress in addressing this rare and complex variant of NCC.

Case Presentation

Case 1

A 34-year-old female patient presented with severe headache without other reported signs or symptoms. The magnetic resonance imaging (MRI) revealed a voluminous cystic lesion in the quadrigeminal cistern with subtemporal extension and involvement of the ambient cistern and pontocerebellar angle (►**Fig. 1**). A posterior petrous approach was undertaken, and, with superior traction of the temporal lobe, the voluminous cystic lesion was expelled and completely excised via the subtemporal route. Notably, there was no need to open the presigmoid dura mater or the dura mater of the posterior fossa, and the patient had an uneventful postoperative recovery. Histopathological analysis confirmed the diagnosis of NCC. Postoperative treatment included a 5-day course of albendazole.

Case 2

A 54-year-old male patient presented with bilateral papillary edema, without focal neurological signs, and a history of prior ventriculoperitoneal shunting. The gadolinium-enhanced MRI revealed multilobulated cystic lesions in the basal cisterns, left Sylvian fissure, and quadrigeminal cistern (►**Fig. 2**). A left extended frontotemporal approach was chosen, the Sylvian fissure was widely dissected, and the cysts were easily resected. Additional cysts were removed

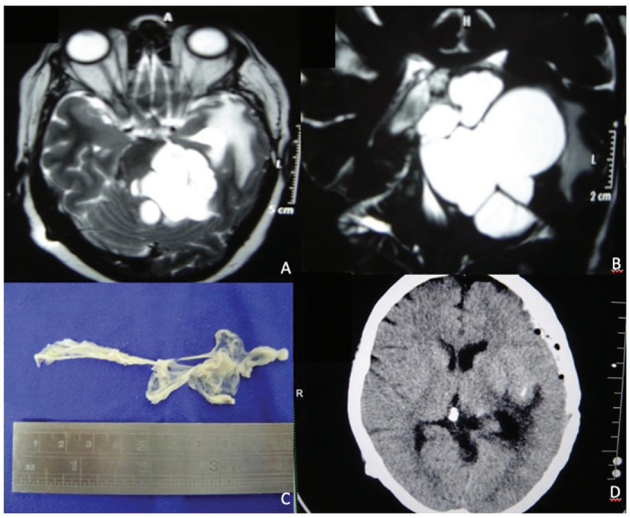

Fig. 1 Axial and coronal T2-weighted magnetic resonance imaging revealing a voluminous multiloculated cystic lesion occupying the quadrigeminal cistern (**A, B**). Resected walls of the cyst (**C**). Postoperative skull computed tomography showing cyst resection.

from the left opticocarotid and interpeduncular cisterns. After this, the posterior incisural space was approached through the subtemporal route. The exposed cyst was drained, and its capsule was excised with a forceps. The patient developed mild aseptic meningitis and experienced one episode of generalized tonic-clonic seizure. Nevertheless, he was discharged from the hospital after 7 days, asymptomatic, and put on a 5-day course of albendazole.

Discussion

In both cases presented, a multilobulated cyst exhibited a component in the posterior incisural space that extended below the mesial temporal region. As a result, a more intricate approach to the pineal region was deemed unnecessary, and cyst removal was accomplished exclusively through the subtemporal approach. This was feasible due to the cysts' lack of adherence to neurovascular structures, facilitating their straightforward removal with forceps following drainage.

The therapeutic spectrum encompasses symptomatic management, antiparasitic regimens, and surgical modalities, and a combined approach is often necessary. Notably, albendazole administered over a five-day period has emerged as a viable therapeutic option for intramedullary spinal cord cysts.[3] In cases warranting surgical intervention, options range from lesion resection to shunt placement.

Racemose NCC presents a distinctive and rare manifestation within the NCC pathology spectrum. It is characterized by cyst development in the basal subarachnoid region. This uncommon presentation involves the formation of multiple non-encapsulated cystic membranes that resemble a bunch of grapes. These are the exogenous budding of aberrantly proliferating *Taenia solium* larvae. Typically observed in expansive brain regions, such as the suprasellar, Sylvian, and quadrigeminal cisterns, or around the rostral brainstem, these cysts lack scolex, do not always involve edema, and can escape detection with contrast enhancement depending on their life cycle.[4]

Clinical consequences of racemose NCC include mass effect, cranial nerve entrapment, arachnoiditis leading to meningeal inflammation and/or hydrocephalus. Less frequently, small-vessel infarcts may occur secondary to occlusive endarteritis. These manifestations are often challenging to detect on computed tomography (CT) scans and so require MRIs for accurate diagnosis. Treatment challenges are not uncommon, and multiple courses of antiparasitic therapy may be required for parasitic clearance. In instances of intraventricular NCC, neuro-endoscopic procedures may be essential for optimizing outcomes.[5]

Advancements in NCC management over the past few decades include the use of anti-parasitic drugs, improved antiinflammatory treatments, and minimally invasive neurosurgical interventions. However, prognosis remains contingent upon the specific location and burden of parasites, with subarachnoid and intraventricular NCC exhibiting heightened rates of morbidity and mortality.[6]

These cases illustrate the intricacies of NCC and emphasize the significance of carefully chosen surgical approaches, along with the crucial role of postoperative pharmacological treatment, for effective treatment and recovery. Ongoing

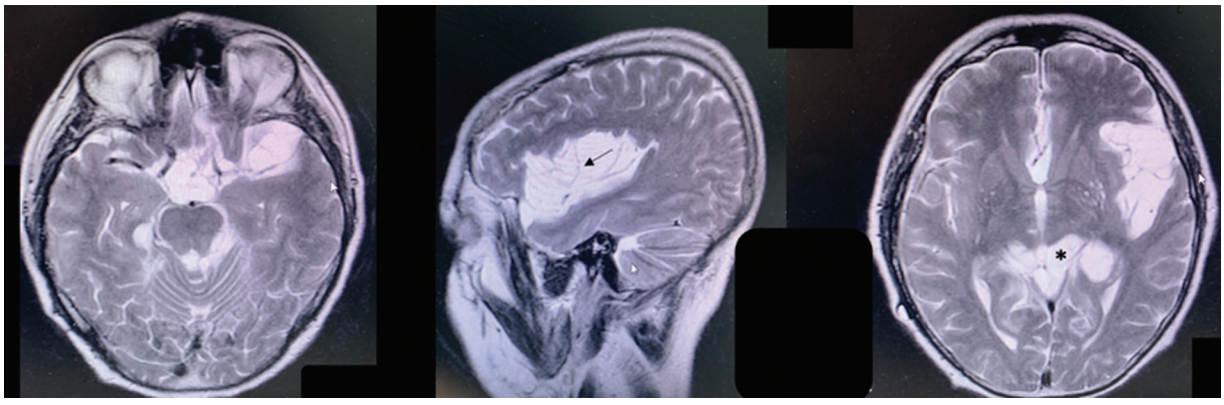

Fig. 2 Axial T2-weighted magnetic resonance imaging (left and right), sagittal (middle), revealing multiple loculated cystic lesions in the territory of the Sylvian fissure (arrow) and in the quadrigeminal cistern (asterisk).

clinical monitoring is imperative to identify and manage potential complications.

Conclusion

The cases of NCC herein presented exemplify the nuanced nature of this parasitic affliction and underscore the importance of personalized surgical approaches guided by the specific characteristics of the lesions. Notably, the multilobulated cysts in both cases exhibited extensions into the posterior incisural space, requiring a meticulous surgical strategy.

The decision to employ a subtemporal approach proved effective in both instances, obviating the need for more intricate procedures involving the pineal region. Success was attributed to the unique property of these cysts, which did not adhere to neurovascular structures. Furthermore, the ease of cyst capsule removal with forceps postdrainage contributed to the overall surgical success.

These cases highlight the significance of a comprehensive understanding of NCC variations and reinforce that the effective treatment of NCC is still evolving. Continued vigilance and research in this domain will further enhance our capabilities in managing the complexities associated with this parasitic neurological condition.

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

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Transcranial Approach for Venous Embolization of Dural Arteriovenous Fistula

Abordagem transcraniana para embolização venosa de fístula arteriovenosa dural

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Abstract

Transvenous embolization emerges as a viable intervention for addressing intracranial dural arteriovenous fistulas (DAVF). Accessibility to the fistulous site via the internal jugular vein (IJV) may be impeded by associated dural sinus apoplexy or thrombosis, prompting the development of a transcranial approach for venous embolization in such scenarios. The presented case details the utilization of a transcranial approach for venous embolization of DAVF. This method allows unobstructed entry to DAVFs situated on superficial dural sinuses that lie beyond the reach of the IJVs. The efficacy of this approach parallels that of the conventional retrograde venous methodology. The precise location and appropriate extent of the craniectomy play pivotal roles in ensuring the success of this technique.

Keywords

- Transcranial approach
- venous embolization
- dural arteriovenous fistula

Resumo

A embolização transvenosa surge como uma intervenção viável para tratar fístulas arteriovenosas durais intracranianas (FAVD). A acessibilidade ao local fistuloso pela veia jugular interna (VJI) pode ser impedida por apoplexia ou trombose do seio dural associada, levando ao desenvolvimento de uma abordagem transcraniana para embolização venosa em tais cenários. O caso apresentado detalha a utilização de uma abordagem transcraniana para embolização venosa de FAVD. Este método permite a entrada desobstruída em FAVDs situadas em seios durais superficiais que ficam além do alcance das VJIs. A eficácia desta abordagem é paralela à da metodologia venosa retrógrada convencional. A localização precisa e a extensão apropriada da craniectomia desempenham papéis essenciais para garantir o sucesso desta técnica.

Palavras-chave

- Abordagem transcraniana
- embolização venosa
- fístula arteriovenosa dural

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Introduction

Dural arteriovenous fistulas (DAVFs) denote aberrant communications within the dural layers, linking meningeal arteries with dural and/or venous sinuses and subarachnoid veins. They constitute 10 to 15% of all cerebral arteriovenous malformations. While numerous DAVFs remain asymptomatic and may not necessitate intervention, the presence of cortical venous reflux, intracranial hemorrhage, elevated intracranial pressure, and intolerable symptoms serve as primary indications for treatment.[1–3]

A comprehensive understanding of the natural history of DAVFs is of paramount importance in guiding decision-making and managing these lesions, including consideration of associated stenoses in the endovascular treatment access routes. With continuous advancements in endovascular technologies, the majority of DAVFs can be effectively addressed through transarterial or transvenous embolization. Cases resistant to complete endovascular resolution may require adjunctive surgery or radiotherapy.[3–7]

Moreover, challenges may arise when dealing with compromised venous routes due to thrombosed sinus venosus, and arterial access may pose a certain level of difficulty. In such instances, alternative access routes present themselves as formidable challenges for minimally invasive procedures.

Objective

Report an unusual fistula embolization technique dural arteriovenous by venous transcranial approach.

Case Report

A patient in their 40s presented with a history of worsening headache and dizziness. DSA disclosed DAVF involving the left transverse-sigmoid sinus transition, supplied by multiple feeders from the left external carotid branches (occipital, superficial temporal, middle meningeal, and posterior auricular arteries). The transverse-sigmoid junction was cloistered by distal transverse and proximal sigmoid sinus occlusion, leading to a prominent retrograde drainage into infratentorial engorged veins (►**Fig. 1A**). With DSA pinpointing, a small guided craniectomy was performed (►**Fig. 1B**). After that, transcranial direct puncture of the transverse-sigmoid junction under high-quality road-mapping guidance

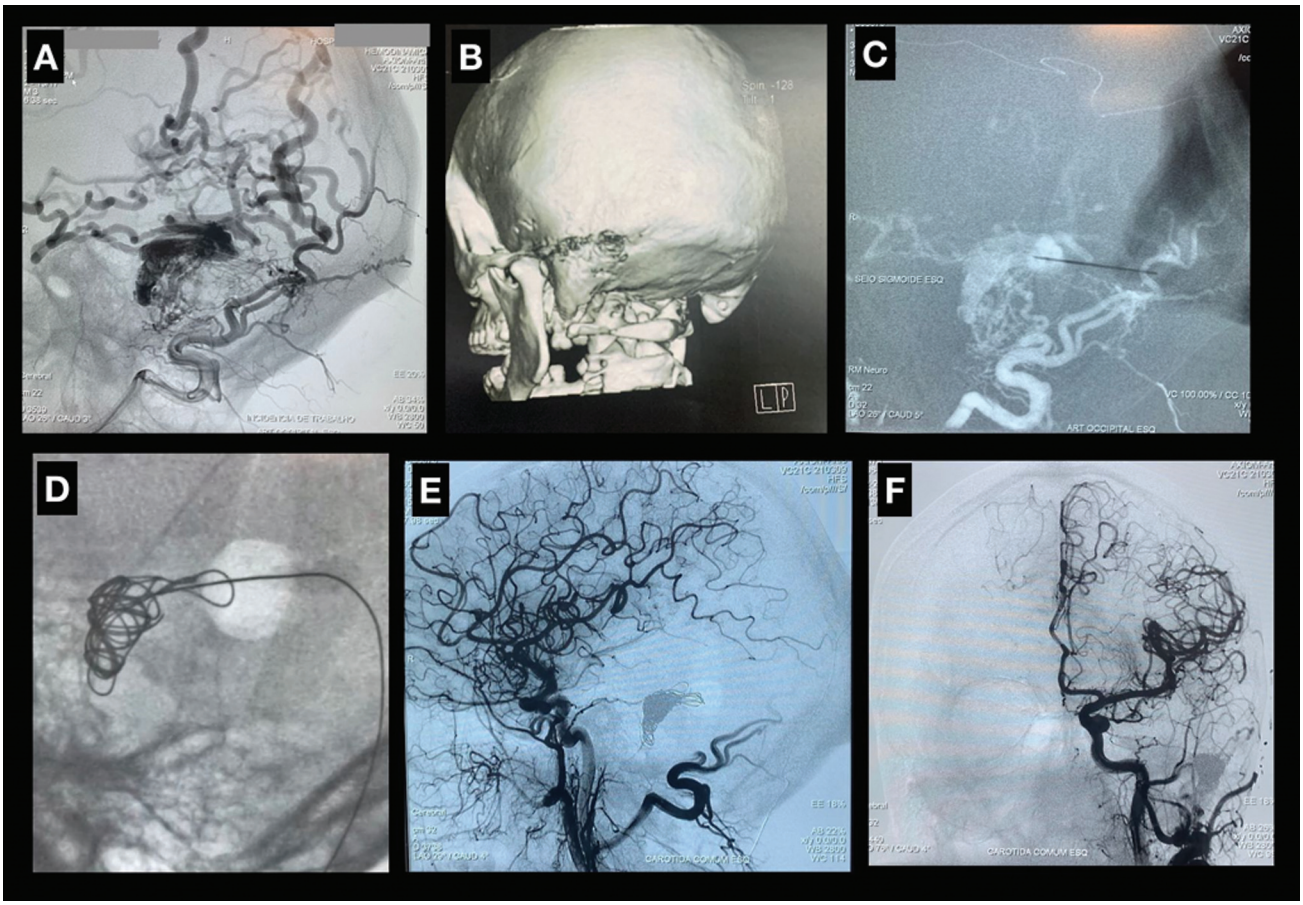

Fig. 1 Angiogram in lateral view (A) showing the transverse-sigmoid junction was cloistered by distal transverse and proximal sigmoid sinus occlusion, leading to a prominent retrograde drainage into infratentorial engorged veins. With DSA pinpointing, a small guided craniectomy was performed on transverse-sigmoid junction, showed in 3D brain CT scan reconstruction (B). Transcranial direct puncture of the transverse-sigmoid junction under high-quality road-mapping guidance was performed (C) and was packed the the transverse-sigmoid junction with coils (D). The final angiography showed complete obliteration of the lesion (E and F).

was performed (►**Fig. 1C**). A 18 G Jelco was used as a sheath for a 2.6F microcatheter insertion, packing the sinus with seven detachable coils (►**Fig. 1D**). The final angiography showed complete obliteration of the lesion (►**Fig. 1E** and **1F**). The patient woke up in the postoperative and was completely asymptomatic after one week.

In this scenario, when a dural arteriovenous fistula (DAVF) involves a sinus proximal to the skin, a viable and efficacious solution entails accessing the sinus through a direct puncture facilitated by a carefully planned craniectomy. Houdart et al. have documented their experience employing a curative transcranial approach for venous embolization of DAVFs in ten patients, nine of whom had previously undergone unsuccessful interventions, with coils being the predominantly utilized embolic agent. Our preference is to conduct the embolization procedure in the neuroangiographic suite, leveraging superior angiographic equipment and a more extensive array of endovascular tools, thereby instilling greater confidence in the intervention.[1–7]

Conclusion

The endovascular approach stands as the gold standard for treating dural arteriovenous fistulas (DAVFs). It is crucial to underscore that transcranial venous access represents an unconventional method for embolizing dural fistulas. Nevertheless, it should be regarded as a noteworthy alternative, particularly in cases involving dural fistulas with entrapped sinuses. The precise localization and optimal extent of the craniectomy are indispensable factors for the successful execution of this technique.

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None.

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Capítulo de livro

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

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