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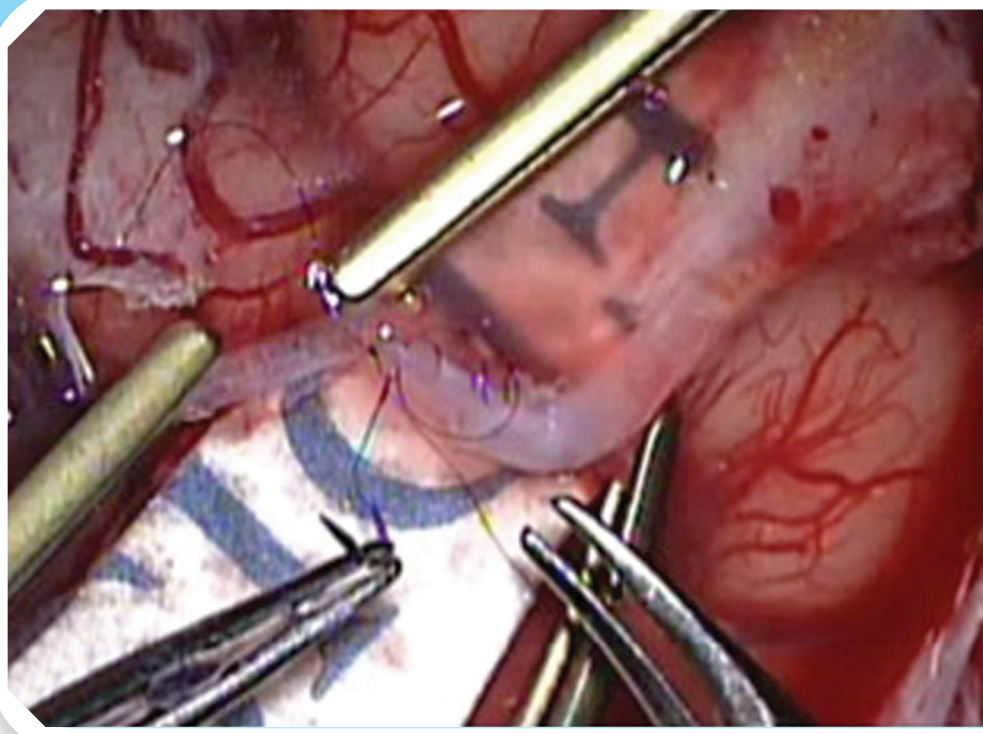

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Case Reports

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Basal Ganglia Traumatic Hematoma: Case Series and Literature Review

Hematoma traumático em gânglios da base: Série de casos e revisão da literatura

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Abstract

Introduction Basal ganglia traumatic hematoma (BGTH) is rare, occurring in 3% of closed traumatic brain injuries, and it is associated with a poor prognosis. In the present paper, the authors present a series of 16 BGTH cases, describing their causes, treatment, and results.

Patients and Methods Thisis a retrospective study of 16 patients diagnosed with BGTH, associated with a literature review in the PubMed, ScienceDirect, and Google Scholar databases, using the terms *craniocerebral trauma* AND *basal ganglia* and *basal ganglia* AND *hematoma* AND *trauma*. Articles published in the period from 1986 to 2019 were selected, resulting in a total of 19 articles that met the inclusion criteria taking into account their citations and their respective impacts.

Results Sixteen patients were studied. They were all male, with an average age of 21 years and 5 months. The main cause of BGTH was traffic accident (12). The mean score in the Glasgow coma scale at admission was 8. All patients underwent a computed tomography (CT) scan of the skull. The putamen was the most affected structure (5). Thirteen patients underwent conservative treatment, and three drained the associated intracranial hematoma. Nine patients died, and seven, and four had neurological sequel.

Conclusions The neurosurgeon's knowledge of GBTH, including diagnosis and clinical surgical management, is extremely important, as this type of lesion is associated with a poor prognosis.

Keywords
- basal ganglia
- craniocerebral trauma
- neuroimaging
- traumatic cerebral hemorrhage

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Resumo

Introdução O hematoma traumático dos gânglios da base (HTGB) é raro, ocorrendo em 3% dos traumatismos cranioencefálicos fechados, estando associado a mau prognóstico. Neste artigo, os autores apresentam uma série de 16 casos de HTGB, descrevendo suas causas, tratamento e resultados.

Pacientes e métodos Estudo retrospectivo de 16 pacientes com diagnóstico de HTGB, associado a uma revisão de literatura nas bases de dados PubMed, ScienceDirect e Google Scholar, utilizando os termos: "Craniocerebral Trauma" AND "Basal Ganglia" and "Basal Ganglia" AND "Hematoma" AND "Trauma." Foram selecionados artigos com período de 1986 a 2019, resultando em um total de 19 artigos que atenderam aos critérios de inclusão levando em consideração suas citações e seus respectivos impactos.

Resultados Dos 16 pacientes foram estudados, todos do sexo masculino e com idade média de 21 anos e 5 meses. A principal causa de HTGB foi acidente de trânsito (12). A pontuação média na escala de coma de Glasgow na admissão foi de 8. Todos foram submetidos a uma tomografia computadorizada do crânio. Putamen foi o mais afetado (5). Treze pacientes foram submetidos a tratamento conservador e três apresentaram o hematoma intracraniano associado. Nove pacientes morreram e sete, e quatro tiveram sequelas neurológicas.

Conclusões O conhecimento dos neurocirurgiões sobre HTGB, diagnóstico e manejo clínico cirúrgico é de extrema importância, pois está associado a um mau prognóstico.

Palavras-chave

- gânglios da base
- hemorragia traumática cerebral
- neuroimagem
- trauma craniocerebral

Introduction

Basal ganglia traumatic hematoma (BGTH) is characterized by being in the basal ganglia (caudate nucleus, putamen and globus pallidus) or in adjacent structures, such as the thalamus and the internal capsule.[1,2] The basal ganglia hematoma often occurs spontaneously in hypertensive patients, and it is rarely caused by trauma; it is associated with a poor prognosis[3] and severe injuries.[4] Basal ganglia traumatic hematomas represent 3.2% in closed traumatic brain injuries (TBIs).[5] It often occurs in high-speed trauma, and falls from heights are one of the causes of pediatric BGTH.[6] Basal ganglia (BG) hematomas > 2 cm are considered large,[7,8] and those with diameter < 2 cm can be considered a hemorrhage due to cerebral contusion,[9] associated as part of the spectrum present in diffuse axonal injury (DAI).[5] Basal ganglia deep cerebral contusion and brain gray matter deep region are classified as intermediary contusion, characteristic of DAI.[10] Basal ganglia traumatic hematoma patients have a high incidence of coagulating disorders, DAI, contusion, intraventricular hemorrhage, and extra axial hematomas.[1]

The authors present a series of 16 BGTH cases, describing its causes, treatment, and results.

Patients and Methods

This is a retrospective study of 16 patients diagnosed with basal BGTH, aged 16 to 44 years, admitted to Hospital de Urgência de Sergipe (Aracaju, SE, Brazil), in the period from 2009 to 2013. The following aspects were analyzed: age, gender, injury laterality, injured basal ganglia, imaging tests, treatment, and prognosis.

The literature review was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. The inclusion criteria were studies and case reports with a time frame between 1986 and 2019, with individuals of any determined age group, diagnosed with BGTH. Studies not developed in humans, published in databases with no abstract, systematic reviews, and letters to the editor, were excluded.

The literature review was performed in July 12, 2020 using the following databases: PubMed, ScienceDirect, and Google Scholar, using the terms *craniocerebral trauma* AND *basal ganglia* and *basal ganglia* AND *hematoma* AND *trauma*. Duplicate studies were removed, resulting in a total of 19 articles that met the inclusion criteria taking into account their citations and their respective impacts.

Results

In the present case series, all patients were male, with a mean age of 21 years and 5 months. The main causes of BGTH were traffic accident (12) and accidental fall (3) (►**Table 1**). The mean Glasgow coma scale (GCS) score on admission was 8. All patients underwent a computed tomography (CT) test, showing that the main affected nuclei were the putamen (5), the caudate nucleus (4), and the internal capsule (4) (►**Figures 1–9**). In the analysis of the laterality of the lesion, in five patients the lesion was located on the right side, in five it was on the left side, and in six, there were lesions on both sides (►**Table 2**).

Table 1 Clinical-epidemiological characteristics of 16 BGTH patients

Clinical-epidemiological characteristics (n = 16)		
Characteristics	**No.**	**Percentage**
Sex		
Male	16	100%
Female	0	0.00%
Causes		
Traffic accident	12	75.00%
Accident fall	3	18.75%
Physical aggression	1	6.25%
Treatment		
Surgical	3	18.75%
Conservative	13	81.25%
Results		
Good general condition	3	18.75%
Neurological sequelae	4	25.00%
Death	9	56.25%

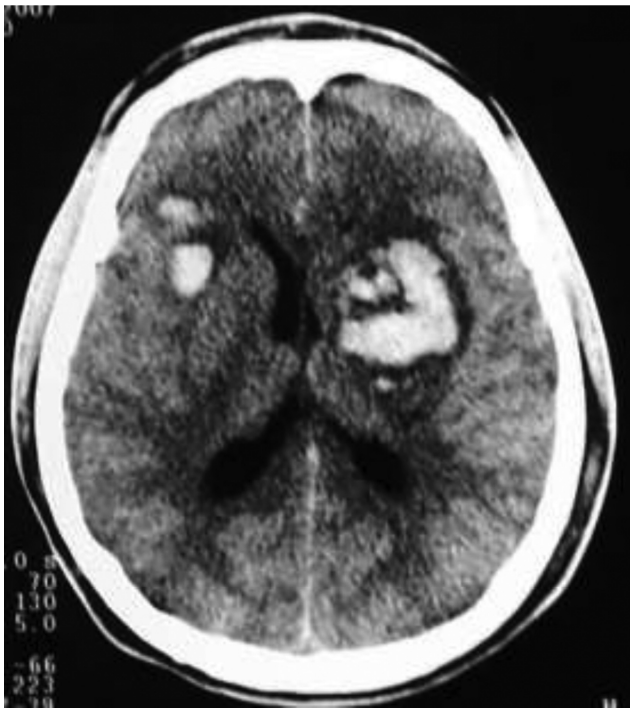

Fig. 2 Non-contrast skull computed tomography showing bilateral basal ganglia hematoma.

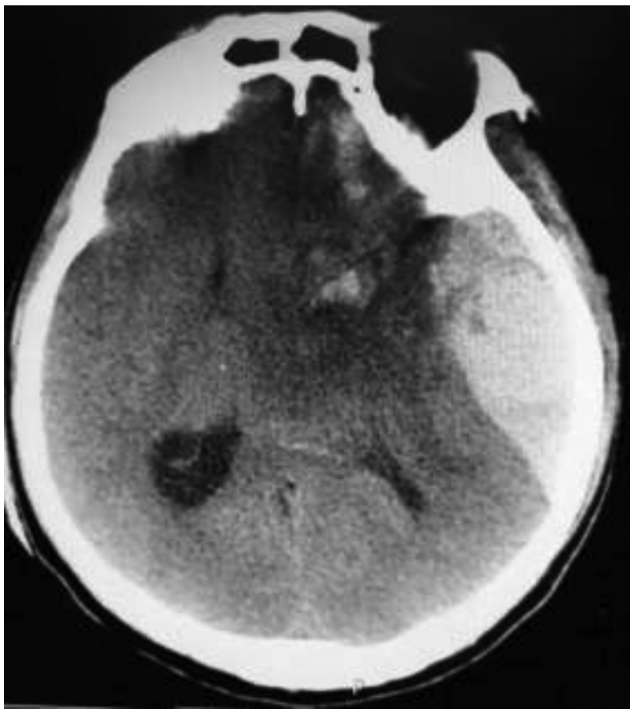

Fig. 1 Skull computed tomography without contrast showing acute epidural hematoma in the left temporoparietal region and frontal contusion hematoma in left basal ganglia.

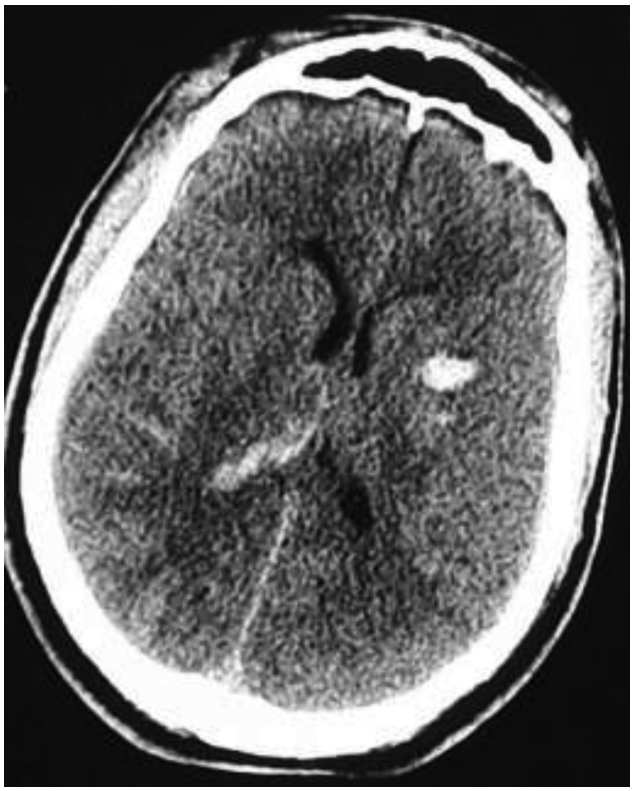

Fig. 3 Non-contrast skull computed tomography showing hemorrhage in the right lateral ventricle associated with left basal ganglia hematoma.

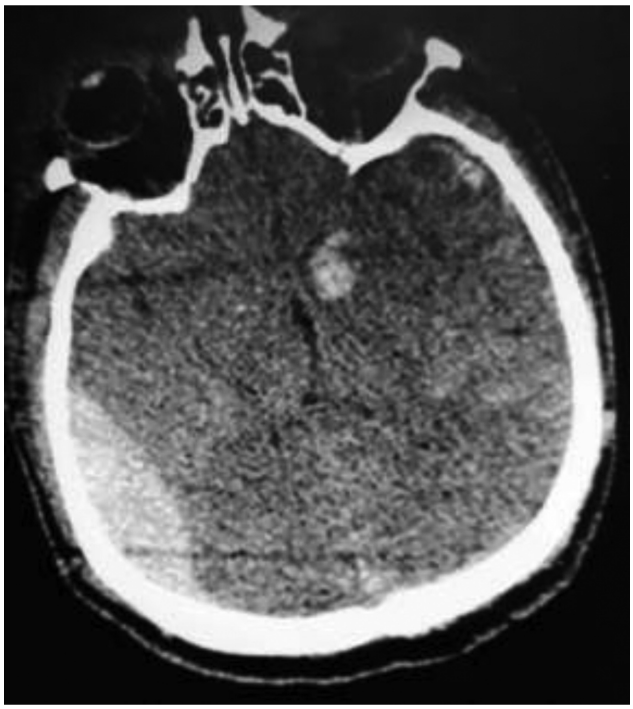

Fig. 4 Non-contrast skull computed tomography showing right parietal hematoma, left temporal contusion and left basal ganglia hematoma.

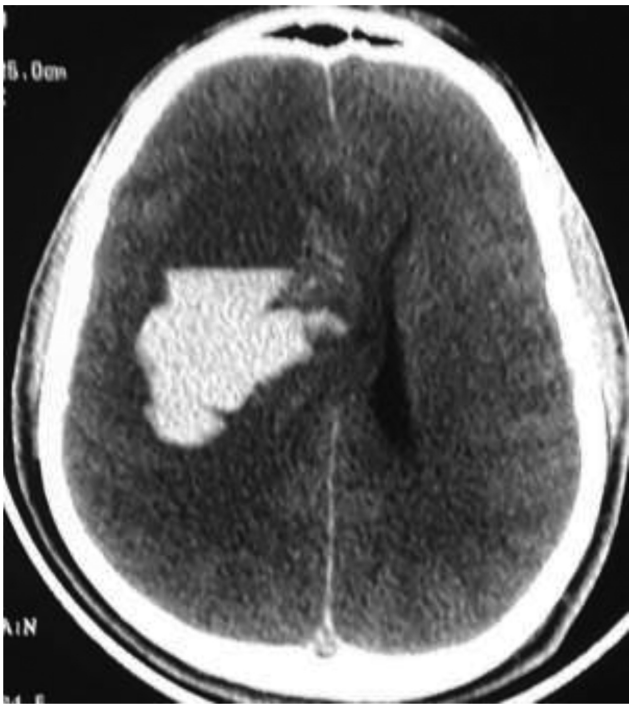

Fig. 6 Computed tomography of the skull without contrast with large right basal ganglia hematoma and compression of the right lateral ventricle, with deviation of the midline structures.

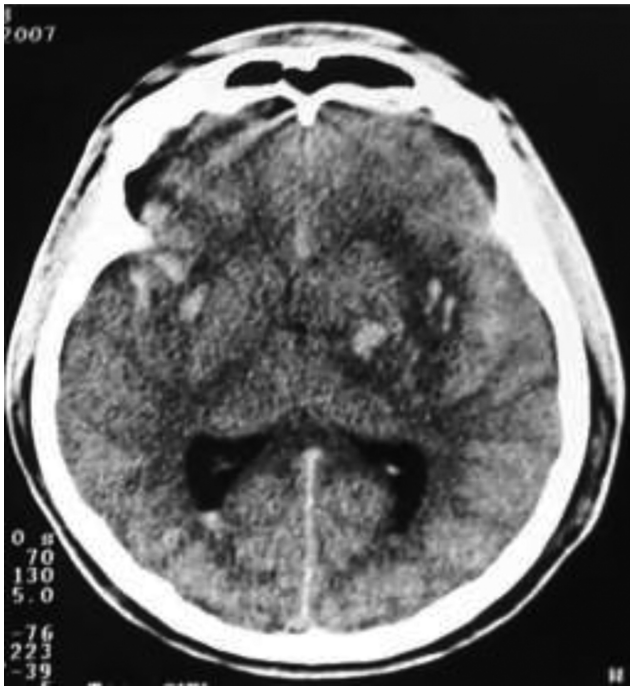

Fig. 5 Non-contrast skull computed tomography showing bilateral lesion in basal ganglia.

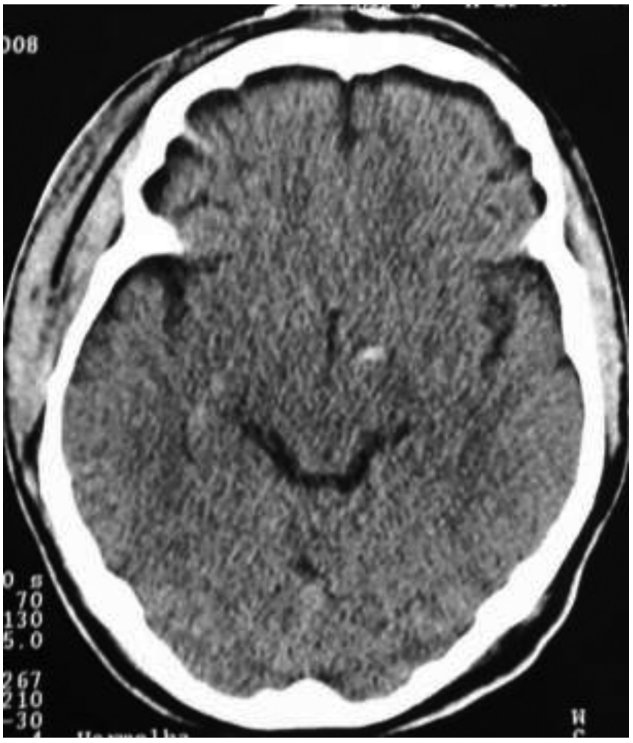

Fig. 7 Computed tomography of the skull without contrast with hematoma in left basal ganglia.

Thirteen patients underwent conservative treatment and three underwent intracranial hematomas drainage—two epidural hematomas (EDH), and one subdural hematoma (SDH). Seven patients survived, four had neurological sequelae, and nine patients died.

Discussion

Epidemiology

Basal ganglia TBIs in closed cranial lesions represent 3%,[1,6,8] and, when found in autopsies, they represent 10%.[3] In a study

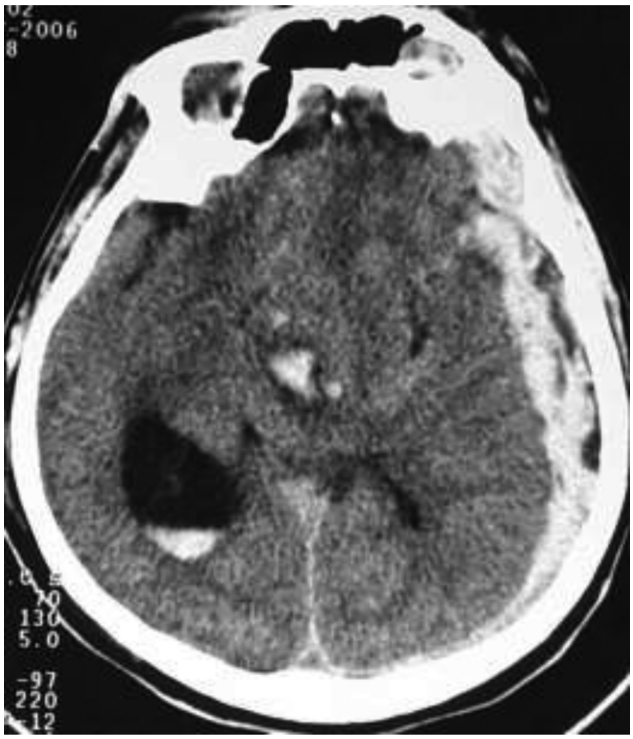

Fig. 8 Non-contrast skull computed tomography showing left acute frontoparietal subdural hematoma, intraventricular hemorrhage, deviation of the midline structures and right basal ganglia hematoma.

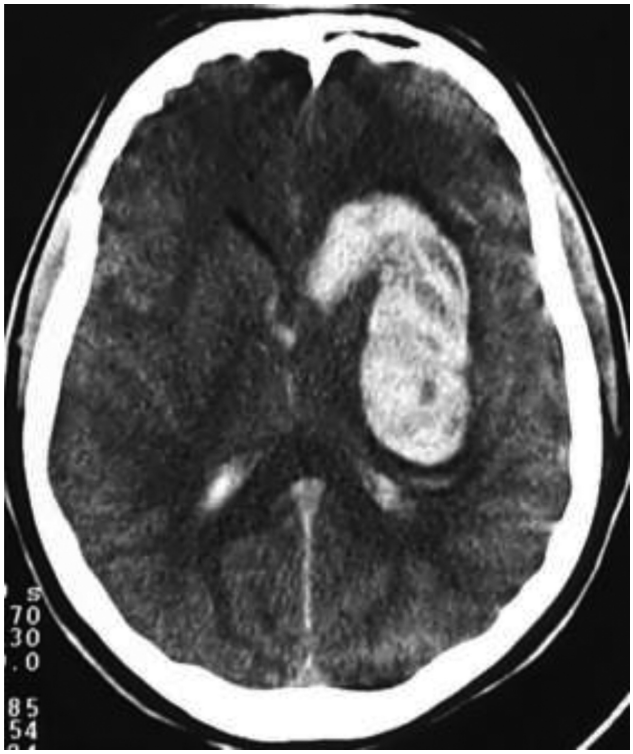

Fig. 9 Non-contrast skull computed tomography showing intraventricular hemorrhage, subarachnoid hemorrhage, massive left basal ganglia hematoma.

Moe et al., it was demonstrated that when associated with DAI affecting unilateral and bilateral BG, they represent 18% and 2%, respectively,[11] being extremely rare in the pediatric population.[9] Chung et al.,[4] in a study with 309 pediatric TBI patients, showed that all BG lesions were unilateral and represented only 2.5%.

Table 2 Skull computed tomography of 16 BGTH patients

Characteristics of skull computed tomography (n = 16)		
Characteristics	**No.**	**Percetage**
Lateralization		
Right	5	31.25%
Left	5	31.25%
Bilateral	6	37.5%
Associated injuries		
Subdural hematoma	3	18.75%
Epidural hematoma	2	12.25%
Cerebral contusion	5	31.25%
Diffuse axonal injury	4	25.00%
Basal ganglia hematoma location		
Putamen	5	31.25%
Caudado nucleus	4	25.00%
Internal capsule	4	25.00%
Globus pallidus	2	12.25%
Thalamus	1	6.25%

Basal ganglia traumatic hematoma is often small, uni or bilateral, located in the internal capsule and lenticular nucleus (putamen and globus pallidus),[2] which may occur in the thalamus and caudate nucleus,[12] and it may be accompanied by cranial fracture, brain stem lesions, subarachnoid hematoma,[3] EDH, and SDH.[8] When the hematoma occurs due to spontaneous hemorrhage, it is unilateral and commonly located in the internal capsule and thalamus.[2] Jayakumar et al.,[13] in a study with 22 patients, showed the following location distribution of BGTH: 41% in the putamen, 23% in the caudate nucleus, 23% in the internal capsule, and 13% in the thalamus, with the highest mortality associated with the first structure.

In the present study, 10 lesions were located unilaterally and 6 bilaterally. The affected nuclei were the putamen (5), caudate nucleus (4), internal capsule (4), globus pallidus (2), and thalamus (1). The associated injuries were SDH (3), EDH (2), brain contusion (5), and DAI (4).

Physiopathology

It is believed that BGTH occurs due to shear forces.[5] When there is a high-energy impact on the vertex, in the frontal or in the occipital lobe and directed to the tentory,[3,14] with extension and consequent rupture of the vessels due to shear forces[2,11,15] resulting in hemorrhages in the BG,[3] both the striking and counter-striking movements can develop this mechanical action.[16] The vessels associated with this phenomenon are the anterior choroidal artery and the striated lenticular perforating arteries,[5,7,8] with the latter being associated with pediatric BGTH. The middle cerebral artery

(MCA) is associated with bleeding and infarction of the basal ganglia and the thalamus.[17] As the skull of children is elastic, the shear forces occur mildly in them compared with adults.[6]

Bilateral lesions in the BG are associated with a low value on the GCS score due to the connection of these structures to the ascending reticular activating system (ARDS).[11] The measure of remaining awake after TBI is related to bilateral atrophy of the globus pallidus and putamen.[10]

Symptomatology

As the BG are the union of several parts of the brain's gray matter, the symptoms manifest depending on the BG involved. When the internal capsule has a hematoma, the associated symptom is motor deficit. Extrapyramidal symptoms appear when the substantia nigra is damaged. Visual deficits and language and sensory disorders are associated with the lateral geniculate bodies and the thalamus. When the ARDS has a hematoma, the patient is unconscious.[7]

In their study, Moe et al.[11] demonstrated that patients with bilateral BG lesions and absence of other intracranial lesions present low level of awareness at the accident site or at hospital admission. Colquhoun et al.,[5] in a study conducted with 26 patients, showed the presence of a lucid interval in nine patients, and the presence of focal neurological deficit was associated with unilateral hematoma in the BG.

Diagnosis

The diagnosis is made through imaging exams. Computed tomography and magnetic resonance imaging (MRI) show a hematoma with localization in the BG, associated with a skull fracture,[13] and intraventricular and subarachnoid hematomas.[5] Diffuse axonal injury can be found in the imaging exams, being frequently associated with a low GCS score.[2] Computed tomography can present a diffuse lesion of the cerebral white matter, present in one third of patients with BGTH, often associated with increased intracranial pressure and a poor prognosis.[18]

Treatment

The treatment of BGTH follows the protocol of intracranial hematomas, considering the neurological status, mass effect, and high intracranial pressure.[5] Management can be achieved through conservative treatment, surgical drainage of the hematoma, aspiration of the hematoma guided by ultrasound or stereotactic CT.[1,2] Surgical drainage is recommended for hematomas with a volume greater than 25 ml, especially when associated with increased intracranial pressure.[7,14] In the present study, 13 patients were treated conservatively and 3 surgically, aiming at draining bruises associated with BGTH lesions, two EDH and one SDH.

Complications

The poor prognosis of patients with BGTH[4] is related to the global characteristic of this brain lesion,[13] associated with the presence of intracranial hypertension,[5] presenting a poorer prognosis rate higher than other traumatic intracranial hemorrhage types.[9] The factors associated with poor prognosis are age $>$ 60 years, DAI, large volume hematoma, extra-axial hematomas, abnormal pupillary and motor responses, severe TBI[14,16] and late hematoma increase.[2]

Zakharova et al.,[19] in a study with 278 patients, demonstrated that lesions located in the BG have a prognosis of adverse outcomes such as vegetative state, severe neurological deficit, and death. The high incidence of BG hematomas during autopsies demonstrates the clinical course of death.[7,8] Mortality in pediatric patients varies between 14 and 33%.[6]

In the present case series, seven patients survived, three were in a good general condition, and four had neurological sequelae such as dysphasia, motor deficit, convulsive crises, and involuntary movements, and nine patients died.

Conclusion

Neurosurgeons' knowledge of BGTH is extremely important, including the symptoms related to the affected areas, the diagnosis, and clinical or surgical management, since this type of lesion is associated with a poor prognosis.

Conflict of Interests

The authors have no conflict of interests to disclose.

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Artifacts in MRI: Villain or Hero? Using Artifacts for Diagnosing Central Nervous System Diseases

Artefatos em RM: vilões ou heróis? Usando os artefatos para diagnóstico de doenças do sistema nervoso central

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Abstract

An artifact is a feature present in an image which is not part of the original structure. It can occur as a consequence of several factors. It may be mistaken for pathologic conditions, leading to adverse consequences for the patients. The aim of the present study is to present a selection of the main artifacts described in brain and spinal magnetic resonance images to improve the ability of the physicians to recognize them and to reduce their interference on the final interpretation of a scan. The authors searched the scientific community for artifacts in magnetic resonance imaging (MRI), which were selected to focus on central nervous system (CNS) findings. With the Picture Archiving and Communication System (PACS) database from the center where this study was conducted, the authors designated brain and spine MRI scans with conspicuous artifacts to compose the present study. The artifacts were then classified as those that contribute to the diagnosis and those that must be distinguished from pathologic lesions. Considering the novel classification proposed by the present study, physicians might be stimulated to reevaluate their opinions regarding artifacts, perhaps considering them helpful to evaluate certain conditions even if they cannot be fully corrected, as shown by this distinct approach to artifacts with specific findings concerning differential diagnosis of CNS conditions.

Keywords
- artifacts
- MRI
- central nervous system

Resumo

Um artefato está em uma imagem, mas não faz parte da estrutura original. Ele pode ocorrer como consequência de uma miríade de fatores e pode ser confundido com condições patológicas, levando a consequências adversas para os pacientes. O objetivo do presente estudo é apresentar uma seleção dos principais artefatos descritos em imagens de ressonância magnética (RM) cerebral e da coluna vertebral, a fim de melhorar a capacidade dos médicos de reconhecê-los e reduzir sua interferência na interpretação final. Os autores pesquisaram na literatura por artefatos em imagens de

Palavras-chave
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- ressonância magnética
- sistema nervoso central

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RM, os quais foram selecionados para se concentrar nos achados do sistema nervoso central (SNC). Com o banco de dados Picture Archiving and Communication System (PACS) do centro onde o presente estudo foi realizado, os autores separaram exames de RM do cérebro e da coluna com artefatos conspícuos para compor o presente estudo. Os artefatos foram então classificados como aqueles que contribuem para o diagnóstico e os que devem ser diferenciados de lesões patológicas. Considerando esta classificação proposta, os médicos podem ser estimulados a reavaliar suas opiniões a partir de artefatos, e estes podem ser úteis para avaliar certas condições, mesmo que não possam ser totalmente corrigidas, como mostrado por esta abordagem distinta para artefatos com achados específicos relativos ao diagnóstico diferencial de condições do SNC.

Introduction

Magnetic resonance imaging (MRI) is the modality of choice to evaluate central nervous system (CNS) parenchyma. Due to the complex technology involved in generating the scans, artifacts are prone to occur.[1–3]

An artifact is a feature present in an image that is not part of the original structure. It is a consequence of hardware/software failures; physiologic motion, as cerebrospinal fluid (CSF) flow; or ferromagnetic objects within the patient, like neurosurgical clips.[2,4]

Comprehending artifacts is challenging: multiple authors[3,5–7] have demonstrated that the physical principles related to their occurrence should be minimally understood to minimize the emergence of artifacts, as misunderstanding an artifact as a disease may have adverse consequences for the patient.[4]

Therefore, beyond discerning basic physics interactions that merge into an artifact, the present study illustrates that recognition of an artifact itself is useful to recall true pathologies and often aids in differential diagnosis of CNS diseases. Thus, although artifacts usually impair the information contained in the image, we demonstrate that, in some cases, it can be used as a tool to help in differential diagnosis.

Materials and Methods

This is a retrospective study that summarizes the artifacts found in brain and spine MRI. After approval by the institutional review board and by the local ethics committee, artifacts were listed and narrowed down to focus on CNS findings. According to the findings, we analyzed them as artifacts that contribute to diagnosis and artifacts similar to pathologic lesions.

The images were evaluated and selected by an experienced neuroradiologist (10 years of experience).

The authors selected 10 artifacts among their research, considering 5 that contribute to diagnosis and 5 similar to pathologic findings.

The classification proposed by the present study aims to instigate physicians to consider artifacts as findings that, apart from disturbing the original object, are helpful to evaluate certain conditions even if they cannot be fully corrected.

Results and Discussion

Artifacts Contributing to Diagnosis

This section includes findings that, due to the nature of their occurrence, might aid physicians diagnosing certain conditions.

Chemical Shift Artifact: The different frequency of resonance between fat and water generates an artifact presented as bright and dark lines along the interface of water and lipids[1–5] (►**Fig. 1**). Commonly, it shows up in organs filled with fluids,[2,3] but it can also appear in brain MRI and it is simple to detect. The presence of fat within lesions can generate this artifact, which may point, for instance, extravisceral extension of peripheral tumors.[2] When exhibited as a dark line, it is called black boundary artifact, or chemical shift type 2[1,3] (►**Fig. 1A**).

Its correction relies on adjustments of imaging acquisition parameters, like switching phase- and frequency-encoding directions; increasing receiver bandwidth; and applying fat suppression.[3–6]

Flow Artifact: Both CSF and blood flow artifacts are physiologic phenomena that may interfere with image acquisition during an MRI scan.

Cerebrospinal fluid flow artifacts relates to pulsation of CSF during sequence acquisition,[1,4] which usually presents as ghosting[3,4] (►**Fig. 2A**). Its presence indicates adequate or increased CSF flow; its absence, however, may indicate

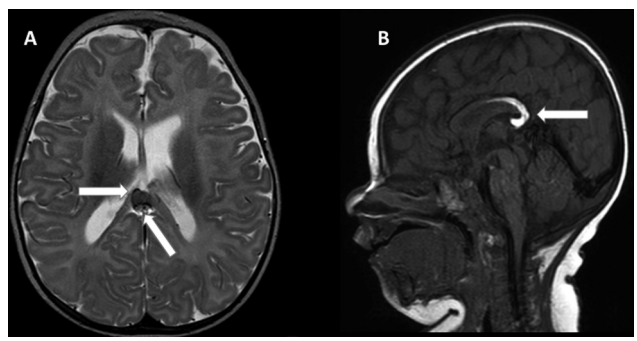

Fig. 1 Chemical shift artifact emphasizes a pericallosal lipoma. The chemical shift artifact suggests the diagnosis of a fat-containing lesion: Black boundary (A – axial T2WI) and chemical shift (B – sagittal T1WI), variations of the same artifact, highlight and delimit the contours of the lesion, thus reinforcing the hypothesis of a lipoma.

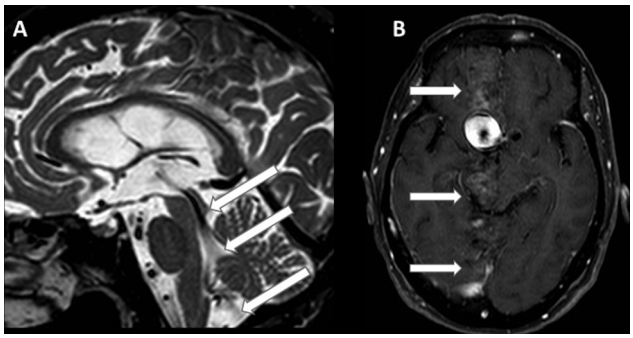

Fig. 2 Flow artifact identifying normal pressure hydrocephalus and an anterior circulation aneurysm. A – Sagittal T2W scan with increased CSF flow due to NPH, generating an artifact (arrows). The increased velocity and turbulent flow within the distended aqueduct of Sylvius generates a signal void that is represented by the flow artifact, generating the trumpet sign. Such finding may corroborate the presence of hydrocephalus. B – Axial T1W scan illustrating a giant aneurysm with an artifact due to turbulent blood flow (arrows). This artifact reinforces distinction between aneurysms and neoplastic/infectious lesions, as it is augmented by the vessel itself. A solid or solid-cystic lesion would not cause such interference.

decreased flow due to a structural abnormality of the spinal cord (►**Fig. 3**).

Likewise, the use of intravenous gadolinium may improve blood flow artifacts due to brighter blood signals.[7] However, such artifacts may be useful to distinguish solid lesions from cysts or aneurysms (►**Fig. 2B**).

Gradient moment nulling or application of saturation bands[3,4] are ways to reduce these artifacts. Besides, Li et al[7] have shown that a spiral spin-echo acquisition sequence was more efficient in reducing flow artifacts than the usually applied cartesian turbo spin-echo sequences. Therefore, it improves image quality, revealing even more subtle changes that were previously obscured.

Artifacts Similar to Central Nervous System Pathologies

This section includes artifacts that, if wrongly evaluated, may be confounded with organic diseases. However, some findings may help to distinguish artifacts from true pathologic lesions.

Entry slice artifact: this artifact correlates with the thickness of the slice and excitation of blood vessels.[1] If the slices are too thick, the spins of some vessels may be saturated by earlier excitation pulses that were directed to other slices. Then, the blood vessel acquires a bright, punctual signal in the first slice in which it appears.[8]

This artifact could be mistaken for venous thrombosis or ruptured dermoid cyst (►**Fig. 4**), which could lead to an important misdiagnosis that would have serious consequences for the patient.

To remove this artifact, the main tactics are placement of partial saturation bands before the first slice and after the last one; and gradient echo flow techniques.[8]

Cerebrospinal fluid flow artifact: cerebrospinal fluid flow may disturb the original signal and cause distortions that resemble diseases such as dural fistulae (►**Fig. 5**). A dural fistula is an arteriovenous shunt between the dural arterial supply of the nerve root and the underlying medullary vein[8] that appear as perimedullary dilations.

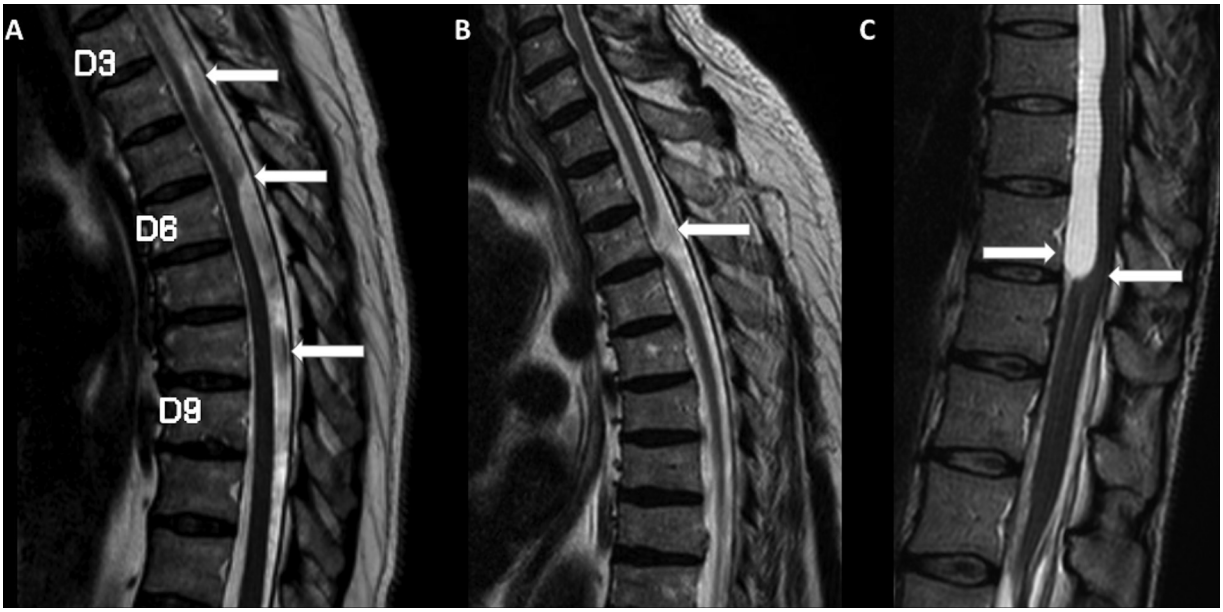

Fig. 3 Absence of CSF flow artifact and intradural cist. A – Sagittal T2WI illustrating a case of thoracic arachnoid web, which is a thick band of arachnoid tissue in the dorsal aspect of the spinal cord that distorts and pushes the cord anteriorly. Consequently, there is widening of the posterior liquoric column, resembling the shape of a surgical scalpel, hence the term "scalpel sign". B – Sagittal T2WI depicting a patient with ventral cord herniation. Note the focal distortion and rotation of the cord, which is protruding anteriorly through a dural defect, with consequent obliteration of the anterior liquoric space. In both scans, we can observe the habitual CSF flow artifact (arrows) in the posterior CSF spaces, since there is no obstruction to the flow in these compartments. The absence of the artifact, as seen on C, suggests, on the other hand, the presence of a condition that causes obstruction to the liquoric flow, represented in this case by a large T2-hyperintense cyst in the anterior aspect of the thoracic spine canal.

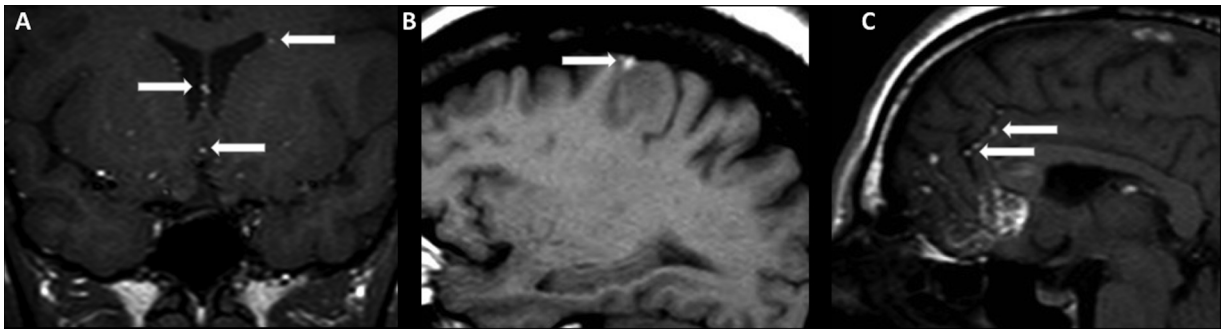

Fig. 4 Entry-slice artifact (**A**) should not be confused with venous thrombosis (**B**) or ruptured dermoid cyst (**C**). A careful look into the complete scan on the left shows this is the only slice in which the bright spot shows up, and, therefore, it is an artifact. It must be distinguished from a true cortical vein thrombosis: the scan must have multiple slices in which the bright spot appears, and, besides, it has to respect the CNS vascular anatomy. On C, it is possible to see the dermoid cyst inferiorly at the base of the frontal lobe and the fat in the subarachnoid space.

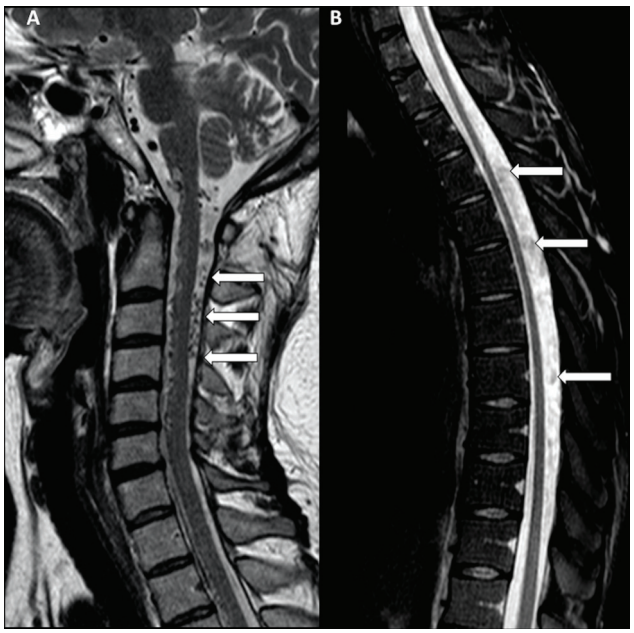

Fig. 5 CSF flow simulating a dural fistula. A – Sagittal T2WI illustrating a dural fistula, with prominent and dilated intradural vessels; B – Sagittal T2WI scan and CSF flow artifact around the spinal cord. For unsuspecting physicians, the alterations may resemble a dural fistula.

It may be distinguished from the artifact by a salt-and-pepper appearance in postcontrast images (►**Fig. 5A**). Even so, it can be challenging to differentiate such findings.

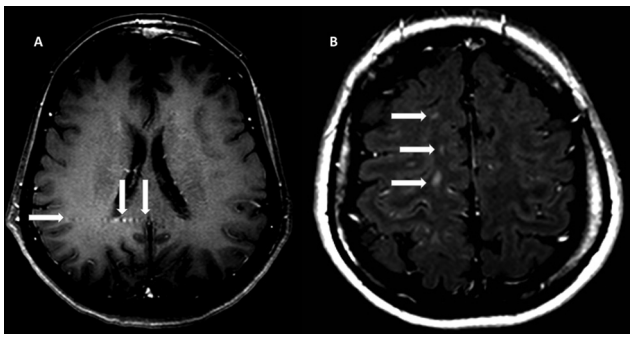

Fig. 7 Blood-flow artifact versus demyelinating focus in a patient with multiple sclerosis (MS). Axial T1WI scan with an enlarged subcutaneous vessel mimicking enhancement foci within the white matter (arrows; A) approaching the midline. Note that the artifact was generated respecting a linear horizontal pattern; Axial T1WI post-contrast of a patient with MS, where the demyelinating areas (arrows; B) present vertically, not as regular as the artifact, and respecting the right brain hemisphere.

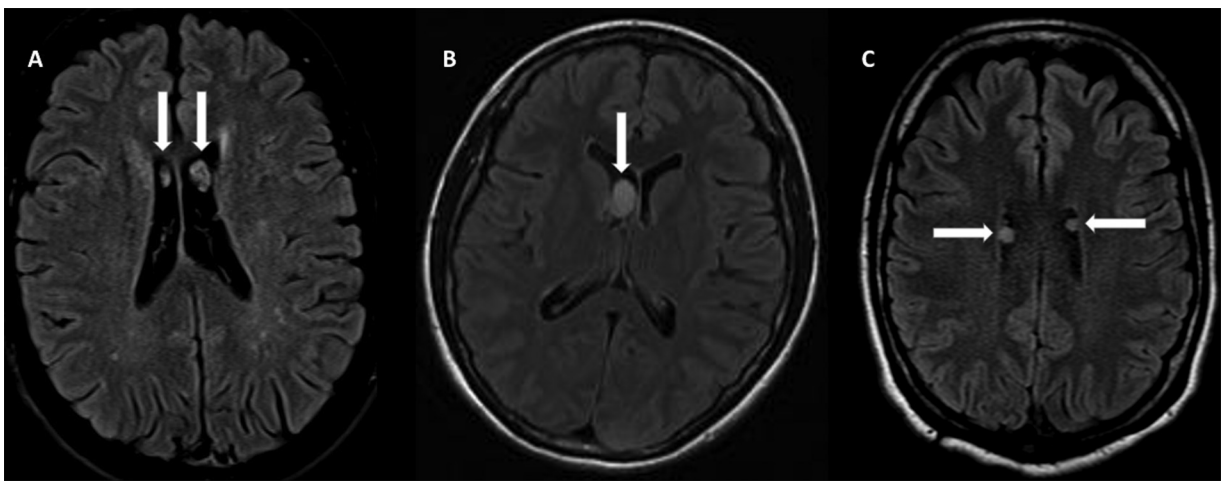

Fig. 6 Axial FLAIR scan with CSF pulsation artifact and its differential diagnosis. CSF flow artifact on the lateral ventricles (arrows; A), mimicking subependymal nodules (**B**) or ring-shaped lateral ventricular nodules (**C**). B – Patient with tuberous sclerosis and subependymal giant cell astrocytoma (SEGA; arrow). Size of the lesion, postcontrast enhancement and growth suggest that a subependymal nodule in a patient with tuberous sclerosis might have developed a subjacent SEGA.

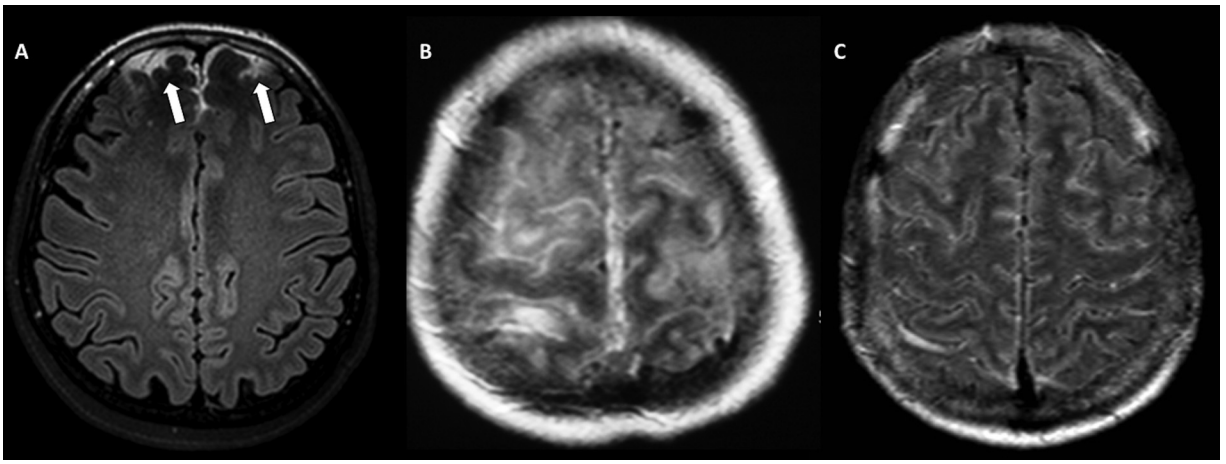

Fig. 8 Susceptibility artifact as hyperintense signal within the subarachnoid space. Susceptibility artifact in this case is a hyperintensity focused on the frontal lobes in an axial FLAIR scan (**A**), mimicking subarachnoid hemorrhage (**B**) or meningitis (**C**). Subarachnoid hemorrhage presents as a diffuse hyperintense signal filling the sulci and with blurrier limits. In both cases, the clinical features add a great deal to the differential diagnosis, as well as lumbar puncture findings.

Clinical correlation is essential, and spinal angiography may be considered in complex cases.

Cerebrospinal fluid flow may also present as nodullary figures within the ventricles, requiring differential diagnosis with tuberous sclerosis and ring-shaped lateral ventricular nodes[9,10] (►**Fig. 6**). To distinguish these entities from an artifact, clinical findings, past history and repetition of the scan are useful tools.

Blood-flow artifact: as described above, blood rushing through vessels might generate artifacts. Here, we illustrate an artifact mimicking multiple sclerosis active lesions (►**Fig. 7**).

Susceptibility artifact: the nonuniformity of the magnetic field is caused by the imaged object, either as a consequence of different magnetic susceptibilities of distinct tissues[1,3–5] or due to the presence of ferromagnetic objects within the body, such as dental braces.[2,3] Consequently, such artifacts correlate directly with the shape, size and amount of metal of the implant. It presents as signal loss and field distortion[1,3–5] (►**Fig. 8**).

Conclusions

As unwanted features that may show up in an MRI scan, artifacts may interfere negatively in the interpretation of an image. Nevertheless, some characteristics may contribute to the differential diagnosis of specific conditions. In this context, certain artifacts are expected to be routinely found in MRI studies, since some of them arise from physiologic phenomena within the body. Therefore, not only the presence of artifacts, but also their absence, may indicate an underlying pathology.

We have compiled, in a simple lexicon, a new perspective regarding the most common artifacts in CNS MRI scans, as some may help in the differential diagnosis of neurologic conditions and some resources present so far to improve image quality.

As MRI advances, new sequences arise and, alongside them, a variety of artifacts. Therefore, constant studying of these findings is necessary to improve the diagnostic ability to the most.

Ethical Approval

This study was approved by the local ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

For this type of study, formal consent is not required.

Author Contribution List

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Morais G. L. and Filho G. P. The first draft of the manuscript was written by Morais G. L., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Aquaporin-4 Expression in Meningioma Malignancy Progression

Expressão da aquaporina-4 na progressão da malignidade dos meningiomas[*]

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Abstract

Objectives The aim of the present study is to analyze if aquaporin-4 (*AQP4*) may also be a tumor progression marker for meningiomas.

Methods This is an immunohistochemistry study realized at the Universidade de São Paulo, São Paulo, state of São Paulo, Brazil: frozen meningioma samples from 81 patients (57 females and 24 males, age range from 22 to 81 years old, average 56.5 ± 14.1 years old), including 57 meningiomas World Health Organization (WHO) grade I (GI); 19 grade II (GII), and 5 grade III (GIII) were analyzed. The relative expression level of *AQP4* was analyzed by quantitative polymerase chain reaction (qPCR), using the SYBR Green approach and for staining detection. Tissue sections were routinely processed and subjected to antigen retrieval.

Results The expression of *AQP4* in meningioma samples ranged from 0 to 10.26, with a median of 0.001 in GI cases, of 0.008 in GII cases, and of 0.006 in GIII cases. Although not statistically significant ($p = 0.942$), GI meningiomas have a lower median *AQP4* expression level than higher malignant grade cases.

Conclusion The *AQP4* gene and protein expressions presented no association with meningioma malignant progression.

Keywords
- aquaporin-4
- malignancy
- meningioma

[*] *The present study was performed at the LIM 15 – Hospital de Clínicas da Universidade de São Paulo (USP).*

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Resumo

Objetivo O objetivo do presente estudo é analisar se a aquaporina-4 (*AQP4*) também pode ser um marcador de progressão tumoral para meningiomas.

Métodos Trata-se de um estudo imunohistoquímico realizado na Universidade de São Paulo, SP, Brasil. Amostras congeladas de meningioma de 81 pacientes (57 mulheres e 24 homens, faixa etária de 22 a 81 anos, média de 56,5 ± 14,1 anos), incluindo 57 meningiomas grau I (GI) da Organização Mundial da Saúde (OMS); 19 grau II (GII) e 5 grau III (GIII) foram analisados. O nível de expressão relativa de *AQP4* foi analisado por reação em cadeia de polimerase quantitativa (qPCR, sigla em inglês), usando a abordagem SYBR Green e para detecção de manchas. As seções de tecido foram rotineiramente processadas e sujeitas a recuperação de antígeno.

Resultados A expressão de *AQP4* em amostras de meningioma variou de 0 a 10,26, com mediana de 0,001 nos casos GI; 0,008 nos casos GII; e 0,006 nos casos GIII. Embora não sejam estatisticamente significantes ($p = 0,942$), os meningiomas GI apresentam mediana mais baixa do nível de expressão de *AQP4* do que os casos de grau maligno mais alto.

Conclusão Expressões de genes e proteínas AQP4 apresentadas na associação com progressão maligna do meningioma.

Palavras-chave

- aquaporina-4
- malignidade
- meningioma

Introduction

Meningiomas are brain tumors derived from arachnoidal cap cells in the meningeal coverings of the spinal cord and the brain.[1] They are the most common benign intracranial tumors,[2] and account for between 13 and 34% of all surgically removed primary brain tumors.[3]

Peritumoral brain edema in patients with meningiomas has been associated with aquaporin 4 (*AQP4*) expression levels.[4–7]

The aquaporins (AQPs) are members of a family of molecular water channels, and at least 13 isoforms have been identified in mammals.[8] They are small membrane panning proteins (monomer size 30 kDa), expressed in several cell types and involved with water transport.[9,10] Among them, AQP4 is the most abundant water channel in the central nervous system (CNS), particularly abundant on astrocytes, where AQP4 expression is mostly restricted to endfoot membranes contacting the basal lamina of capillaries.[11] The loss or reduction in this highly polarized AQP4 distribution on astrocytes forming the glia limitans of the blood-brain barrier has been implicated in the pathogenesis of normal pressure hydrocephalus, *pseudotumor cerebri* and brain edema.[12] The arrangements of AQP4 tetramers in a high-order complex, known as orthogonal array particles (OAP), are related to the water gating mechanism.[13] Also, the size of the resulting OAP structure is related to the ratio of the splice variants of AQP4, M1 isoform (323 amino acids long) and M3 isoform (22 amino acid shorter at the N-terminus than M1).[14]

Under pathological conditions, such as cancer, AQP4 presents upregulation, and its redistribution is not strictly located in the perivascular endfoot membrane; it is also inserted into nonendfoot membrane domains in high-grade astrocytomas. These findings were not observed in low-grade astrocytomas and, thus, it has been reported as a tumor progression marker in World Health Organization (WHO) grade II-IV astrocytomas.[15,16] However, the AQP4 expression pattern was not related with patient survival.[16]

The aim of the present study is to analyze if AQP4 may also be a tumor progression marker for meningiomas.

Methods

Frozen meningioma samples from 81 patients (57 females and 24 males, age range from 22 to 81 years old, average 56.5 ± 14.1 years old), including 57 meningiomas WHO grade I (GI); 19 grade II (GII), and 5 grade III (GIII)[17] were analyzed. The samples were collected during therapeutic surgery of patients treated by the Neurosurgery Group of the Department of Neurology at the Hospital das Clínicas at the School of Medicine of the University of São Paulo, São Paulo, State of São Paulo, Brazil, in the period of 2000 to 2007.[18] The samples were macrodissected and immediately snap-frozen in liquid nitrogen upon surgical removal. A 4µm-thick cryosection of each sample was analyzed under a light microscope after hematoxylin-eosin staining for assessment of necrotic, cellular debris and hemorrhagic areas, followed by removal from the frozen block by microdissection prior to RNA extractions.[19,20] Written informed consent was obtained from all patients according to the ethical guidelines approved by the Department of Neurology of the School of Medicine of the University of São Paulo (0599/10).

All donors signed an informed consent form, and the present study was approved by our Institutional Review Board under the registration number CAPPESq # 200/05. The present study had financial support by the São Paulo Research Foundation (FAPESP, in the Portuguese acronym), under the registration numbers: 2004/1233–6, 2013–02162–8, 2013/06315–3, 2013/07704–3.

Sample Preparation

Total RNA was extracted from frozen tissue using an AllPrep Mini Kit (Qiagen, Hilden, Germany). A conventional reverse transcription reaction was performed to yield single-stranded cDNA. The first strand of cDNA was synthesized from 1 µg of total RNA previously treated with 1 unit of DNase I (FPLC-pure, GE Healthcare, Uppsala, Sweden) using random and oligo (dT) primers, RNase inhibitor, and SuperScript III reverse transcriptase according to the recommendations of the manufacturer (Thermo Fisher Scientific, Carlsbad, USA). The resulting cDNA was subsequently treated with 1 unit of RNase H (GE Healthcare, Uppsala, Sweden), diluted with TE buffer, and stored at - 20°C until later use.

Quantitative Real Time PCR (qPCR)

The relative expression level of *AQP4* was analyzed by quantitative polymerase chain reaction (qPCR), using the SYBR Green approach. Quantitative data was normalized in relation to the geometric mean of two housekeeping genes, suitable for the analysis: hypoxanthine phosphoribosyltransferase (*HPRT*), and glucuronidase β (*GUSB*), as previously demonstrated by our group.[21] Primers were designed to amplify 80–130 bp amplicons, with a melting temperature of 60°C, and were synthesized by IDT (Integrated DNA Technologies, Coralville, USA) as follows (5′ to 3′): *AQP9* F: ATAGCAGCGAACAGGGAATGAC, *AQP9 R*: ATGGCTCACAGATTCCTGGAGA, *HPRT* F: TGAGGATTTGGAAAGGGTGT, *HPRT* R: GAGCACACAGAGGGCTACAA; *GUSB* F: GAAAATACGTGGTTGGAGAGCTCATT, *GUSB* R: CCGAGTGAAGATCCCCTTTTTA. All the reactions were performed in duplicate. The *AQP4* expression level was calculated according to $2^{-\Delta Ct}$,[22] where $\Delta Ct = Ct$ specific gene – geometric mean Ct of housekeeping genes for each grade of meningioma.

Immunohistochemistry

For staining detection, tissue sections were routinely processed and subjected to antigen retrieval. Briefly, slides were immersed in 10 mM citrate buffer, pH 6.0, and incubated at 122°C for 3 minutes using an electric pressure cooker (Bio-Care Medical, Walnut Creek, California, USA). Specimens were then blocked and further incubated with antibody raised against human AQP4 (mouse monoclonal, Clone 2456C1a, ab66495, Abcam, Cambridge, UK, 1:25) at between 16 and 20°C for 16 hours. Development of the reaction was performed with a commercial kit (Novolink; Novocastra, Newcastle-upon-Tyne, UK) at room temperature, using diaminobenzidine and Harris hematoxylin for nuclear staining. Optimization using positive control suggested by the manufacturer of the antibody was performed to obtain optimal dilution (normal lung tissue). The staining intensity of the tissue sections was evaluated independently by two observers. Digital photomicrographs of representative fields were captured and processed using PICASA 3 (Google, Mountain View, CA, USA).

Statistical Analysis

The statistical analysis of relative gene expression in different grades of meningioma were assessed using the Kolmogorov-Smirnov normality test and the nonparametric Kruskal-Wallis and Dunn tests. Differences were considered statistically significant when $p < 0.05$. Calculations were performed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA).

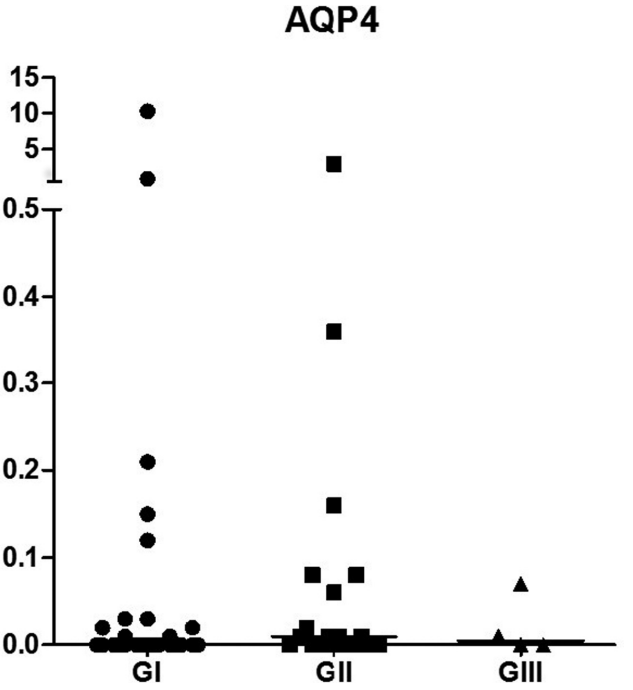

Fig. 1 AQP4's expression according to histological grade of the meningioma.

Results

The expression of *AQP4* in meningioma samples ranged from 0 to 10.26, with a median of 0.001 in GI cases, of 0.008 in GII cases, and of 0.006 in GIII cases. (►**Fig. 1**). Although not statistically significant (►**Table 1**), GI meningiomas have a lower median *AQP4* expression level than higher malignant grade cases.

The high level of heterogeneity found in gene expression data could also be observed in protein levels. Immunohistochemistry of AQP4 was first assessed in normal, non-CNS tissue (lungs), where there is a clear polarized distribution of the protein (►**Fig. 2A**). Next, we verified that in glioblastoma (GBM) tissue, AQP4 expression is high and homogeneous, and that the polarized state is lost (►**Fig. 2B**). In meningioma samples from grades I (►**Fig. 2C-F**), II (Figure G-I) and III

Table 1 Aquaporin-4 distribution according to meningioma grade

	Medium	*p-value*
AQP 4		
Grade I	0.21	*0.9410*
Grade II	0.22	
Grade III	0.02	

Abbreviation: AQP-4, aquaporin-4.

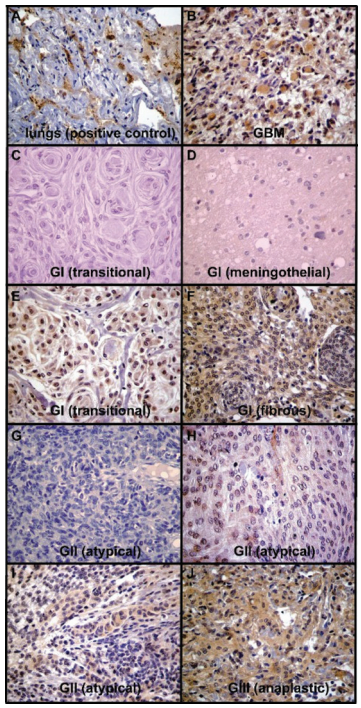

Fig. 2 Immunohistochemistry- **A**: AQP4 expression normal, non-CNS tissue (lungs); **B**: AQP4 expression in glioblastoma tissue is high and homogeneous, and the polarized state is lost; **C-F**: AQP4 expression in different meningioma grades I ; G-I: AQP4 expression in atypical meningiomas; J: AQP4 expression in anaplastic meningioma.

(►**Fig. 2J**), we observed that, although there are GI cases with none or low expression of AQP4, there are also cases expressing high levels of the protein. Grade II cases showed a similar pattern. There was only one available grade III sample, as those tumors are quite rare. Still, the same level of expression of AQP4 in this anaplastic case was found in grade I samples.

Discussion

Tumor surgical resection extent, histological grade, and angiogenesis are parameters addressed as indicators of tumor progression in meningiomas. However, a specific factor associated with meningioma malignancy has not been identified yet. Aquaporin-4 was described as a tumor progression marker among grade II to IV astrocytomas.[15,16] In meningiomas, AQP4 has been associated with peritumoral edema.[4–7] Although AQP4 expression was lower in meningiomas WHO grade I, no statistical difference was observed compared with meningiomas of higher grades, further corroborating previous immunohistochemistry results with this protein.[4] Interestingly, a diffuse AQP4 cytoplasmic staining was observed in positive meningiomas cases, as has been described previously in astrocytomas of high grade of malignancy. The characteristic polar distribution on glia limitans was also lost in meningiomas, similar to the observation on GBM[15]. The pathological impact of the redistribution of this protein in the tumor cell might be interesting to pursue to better understand its role in tumorigenesis.

Conclusion

Aquaporin-4 gene and protein expressions presented no association with the progression of malignant meningioma.

Disclosure

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

Ethical Approval

All procedures performed in the present study were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The present study was approved by our Institutional Review Board under the registration number CAPPESq # 200/05.

Informed Consent

All authors agree to the publication guidelines of the São Paulo medical Journal

The present article does not contain any studies with human participants performed by any of the authors.

Conflict of Interests

The authors have no conflict of interests to declare.

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Endovascular Therapy of 103 Aneurysms in the Internal Carotid Artery with Flow Re-Direction Endoluminal Device

Terapia endovascular de 103 aneurismas na artéria carótida interna com dispositivo endoluminal de redirecionamento de fluxo

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Abstract

Objective Intracranial aneurysms (AIs) are acquired vascular abnormalities that cause sacculations in the arterial wall and are present in ~2 to 5% of the population. Among the treatment options are endovascular interventions with the use of flow-redirecting stents. In the present study, we analyzed the flow re-direction endoluminal device (FRED).

Methods The present study aims to describe the results obtained from treatment with FRED in a series of patients affected by aneurysms in intracranial segments of the internal carotid artery. This is a cross-sectional, epidemiological, and observational study, whose data were obtained from the medical records of 81 patients from July 2018 to July 2019.

Results One hundred and three internal carotid artery aneurysms were observed in 81 patients, with a prevalence of women (91.35%), small (< 10 mm) (89.33%), and located at the C6 level (73.78%) of the internal carotid artery. Of the 81 patients, 16 had multiple aneurysms in the same artery. One hundred and three FRED stents were used in the treatment. These patients underwent angiography 6 months after the surgery, using the O'Kelly-Marotta classification (OKM) to assess the effectiveness of the device, and it was observed that: in 91 of the 103 procedures (88.34%), the FRED was fully open and well positioned, thus restoring the arterial flow and leading to a statistically significant result. In addition, a low complication rate (4.85%) was found, with ischemic stroke being the main complication (1.94%).

Keywords
- stent
- aneurysm
- endovascular
- treatment

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Conclusion This device can be an effective option in the treatment of internal carotid aneurysms since the aneurysm occlusion rate is excellent with a low rate of complications.

Resumo

Objetivo Aneurismas intracranianos (AIs) são anormalidades vasculares adquiridas, presentes em aproximadamente 2 a 5% da população, que causam saculações na parede arterial. Entre as opções de tratamento, estão as intervenções endovasculares com uso de stents de redirecionamento de fluxo. Neste estudo, analisamos o dispositivo de redirecionamento de fluxo endoluminal (FRED, na sigla em inglês).

Métodos Este estudo tem como objetivo descrever os resultados obtidos no tratamento com FRED em uma série de pacientes acometidos por aneurismas em segmentos intracranianos da artéria carótida interna. Trata-se de um estudo transversal, epidemiológico e observacional, cujos dados foram obtidos dos prontuários de 81 pacientes no período de julho de 2018 a julho de 2019.

Resultados Foram observados 103 aneurismas da artéria carótida interna em 81 pacientes, com a prevalência de mulheres (91,35%), aneurismas de pequeno porte (< 10 mm) (89,33%) e localizados no nível C6 (73,78%) da artéria carótida interna. Dos 81 pacientes, 16 apresentaram múltiplos aneurismas na mesma artéria. Cento e três stents FRED foram utilizados no tratamento. Esses pacientes foram submetidos à angiografia 6 meses após a cirurgia, e utilizando a classificação de O'Kelly-Marotta (OKM) para avaliar a eficácia do dispositivo, observou-se que em 91 dos 103 procedimentos (88,34%), o FRED estava totalmente aberto e bem-posicionado, levando assim à restauração do fluxo arterial e a um resultado estatisticamente significante. Além disso, foi encontrado baixo índice de complicações (4,85%), sendo o acidente vascular cerebral isquêmico a principal complicação (1,94%).

Conclusão Este dispositivo pode ser uma opção eficaz no tratamento dos aneurismas carotídeos internos, visto que a taxa de oclusão do aneurisma é excelente com baixa taxa de complicações

Palavras-chave
- stent
- aneurisma
- endovascular
- tratamento

Introduction

Intracranial aneurysms (IAs) are acquired vascular abnormalities that cause sacculations in the arterial wall. They are often located at the bifurcation of the arteries in the anterior circulation of the Willis polygon.[1] In addition, IAs are present in ~ 2 to 5% of the population and are the most common cause of non-traumatic, spontaneous subarachnoid hemorrhage.[2]

Flow redirectors (FRs) have clearly revolutionized the endovascular treatment of aneurysms. The two main principles on which the concept was founded are diversion of blood flow away from the aneurysm, inducing stasis and thrombosis within the aneurysm sac and endothelialization along the stent scaffold and restoration of the integrity of the arterial wall.[3]

There are several FRs available for clinical use, including, among others, the pipeline embolization device (PED; Covidien, Irvine, CA, USA); the SILK flow diverter (SILK; Balt Extrusion, Montmorency, France), and the Surpass (Surpass; Stryker Neurovascular, Fremont, CA, USA). The endoluminal flow redirection device (FRED; MicroVention, Tustin, CA, USA) is a relatively new FR. There are limited reports on the clinical results of its use.[4–7]

A large European study[8] observed a global rate of complete aneurysm obliteration of 69.2%, with a progressive increase in the proportion of aneurysms occluded within the duration of the follow-up, which reached a rate of 83.9% of complete occlusion in aneurysms followed-up by at least 1 year . In that same study,[8] transient and permanent morbidity occurred in 3.2% and 0.8% of procedures, respectively, with an overall mortality rate of 1.5%, and another study[9] pointed out the effectiveness of this device in 84.32% of cases, with 66% presenting aneurysm occlusion in the 1st year and 101 out of 109 (92.7%) posteriorly.

The FRED device is still new in the FRs market, with few studies on it; therefore, the present study aimed to evaluate the endovascular treatment of 103 intracranial aneurysms in 81 patients with FRED.

Methods

Ethical Aspects

All patients who participated in the present study were studied according to the precepts of the Declaration of Helsinki and the Nuremberg Code, respecting the Research Standards Involving Human Beings (Res. CNS 466/12) of the

National Health Council. The patients were included after ethical approval was obtained by the responsible institution

Casuistry

The inclusion criteria were patients with non-ruptured aneurysms, located in the C3 to C7 segments of the internal carotid artery, according to the anatomical division of Bouthillier et al. (1996),[10] regardless of the size of the aneurysm, age or gender of the patients, to simulate real-life visits. All patients were clinically stable at the time of surgery, which followed the protocols with antiplatelet agents and postoperative follow-up described later in the present article. All patients were treated with a FRED stent, and no patient was treated with another method before FRED. The surgeries were performed by professionals from the neurosurgery and endovascular surgery team in a specialized center from July 2018 to July 2019.

Antiplatelet Agents

The antiplatelet therapy established for all was performed as follows: prasugrel 10 mg started 7 days before the surgical procedure, and subsequently maintained for 6 months after the treatment. After this period, the use of prasugrel 10 mg should be discontinued, and the use of 100 mg of acetyl salicylic acid should be maintained for the rest of the patient's life.

Stent Choice

We chose to add the aneurysms eligible for FRED. For correct choice of the device used, all patients underwent digital subtraction angiography with three-dimensional volumetric reconstruction, using a biplane angiographic system to outline the length and anatomy of the aneurysm as well as to measure the proximal and distal diameters of the main artery in which the device was to be implanted. Because the ideal diameter of the FRED is the maximum diameter of the artery in which it is being implanted, it generally corresponds to the arterial diameter proximal to the aneurysm. The selection of the FR size is crucial to promote a safe and complete aneurysm occlusion.[11] In addition, the selection of the working length for flow deviation was based on the coverage of the neck of the aneurysm or the length of the fusiform or dissecting aneurysm with a margin of 2 to 4 mm at the proximal and distal ends, which represents only the length of the layer stent. Currently, FRED is available in 5 different diameters (3.5, 4.0, 4.5, 5.0, and 5.5 mm) recommended for vessel diameters ranging from 2.5 to 5.5 mm and working lengths (double layer cover) from 7 to 56 mm. A Chaperon catheter (MicroVention Inc., Aliso Viejo, CA USA), a Headway 27 microcatheter (MicroVention), and Traxcess 14 microwire guides (MicroVention) were used in all cases to choose the ideal model in the present study.

Description of the Technique

All procedures were performed with the patient under general anesthesia and through a unilateral femoral access. The implantation technique involves advancing the Headway microcatheter distal to the aneurysm and is partially partially implanting the initial part of the FRED. The device is then returned to the desired position and implanted slowly under constant fluoroscopy, ensuring that there is a good overlap of the stent against the vessel lumen. Two angiographic views are used to ensure this, and satisfactory positioning is confirmed with fluoroscopy. If the device is not positioned correctly on the neck of the aneurysm, the stent must be repositioned, provided that 80% of its length has been implanted. The aneurysm must be centered within the double layer of the FRED, and only the working length must cover the aneurysm to guarantee the flow deviation.[12]

Follow-Up

The 12-month treatment and posttreatment were evaluated for the degree of filling and flow stasis in the aneurysm with arteriography using the O'Kelly-Marotta (OKM),[13] according to which each aneurysm is classified with a letter, representing the degree of filling (A, total filling; B, subtotal filling; C, remaining input; D, no filling). This degree is followed by a number, which represents the degree of stasis (stasis in 1, arterial phase; 2, capillary phase; 3, venous phase). This monitoring was performed by the research team at the responsible institution and served as a basis for analyzing the effectiveness of the treatment.

Statistical Analysis

The data obtained were analyzed using the Biostat 5.3 software (Tefé, Amazonas, Brazil), using the chi-squared test, with a p-value < 0.05 and the 95% confidence interval in the hypothesis testing related to the device's effectiveness rates.

Results

Characteristics

A total of 81 patients were included in this research, as shown in (►**Table 1**), 7 of whom were male (8.65%) and 74 of whom were female (91.35%). A 10.57 female prevalence ratio was presented. In addition, the average age found was ~ 52 years, with 24 and 72 years as the extremes of age.

Although 81 patients were included in the study, a total of 103 aneurysms were found. This is justified by the occurrence of multiple aneurysms in the internal carotid segments of 16 of these participants (19.75%). Therefore, in relation to the total number of aneurysms found, the segments with the highest incidence were: C6 (73.78%); C7 (16.50%); C4 (6.71%), and C5 (2.91%); however, no aneurysm was recorded in segment C3.

Regarding the size of the aneurysms, an average length of 5.23 mm was found, with the smallest and largest being 1 mm and 26 mm, respectively. Therefore, of the total of 103 aneurysms, the following was found in relation to their length: there were 90 (87.37%) small (< 10 mm); 11 (10.67%) large (10–25 mm), and 2 (1.94%) giant aneurysms (> 25 mm).

Efficacy

The success rates in the procedure with aneurysm occlusion, fully open and well positioned stent with restoration of arterial flow, corresponded to 91 of the 103 procedures

Table 1 Epidemiological characteristics of patients with aneurysms located in the internal carotid artery, treated with flow re-direction endoluminal device, in a single center

Gender	
Male	7 (8.65%)
Female	74 (91.35%)
TOTAL	81 (100%)
Age (years)	24–73 (51.79 mean)
Aneurysm location	
C3	0 (0%)
C4	7 (6.71%)
C5	3 (2.91%)
C6	76 (73.78%)
C7	17 (16.50%)
TOTAL	103 (100%)
Aneurysm size	
Small (< 10 mm)	90 (87.37%)
Large (10–25 mm)	11 (10.67%)
Giant (> 25 mm)	2 (1.94%)
TOTAL	103 (100%)

Abbreviation: FRED, flow re-direction endoluminal device.
Source: Patient records.
Note: In the study, 16 patients presented with 2 or more aneurysms.

Table 2 Evaluation of the degree of filling and flow stasis in the aneurysm using the O'Kelly-Marotta classification scale in the treatment of internal carotid artery aneurysms

STENT-FRED	Nr. of aneurysms	%
OKM		
C–D	**91**	**88.34%***
B	4	3.88%
A	8	7.76%
Total	**103**	**100.00%**

Abbreviations: Nr.: number; OKM, O'Kelly-Marotta.
Source: Patient records.
Note: (A, total filling; B, subtotal filling; C, remaining entry; D, without filling).
*chi-squared test with $p < 0.05$ ($x^2 = 43.220$; p-value $= 0.0001$).

Table 3 Complications in patients with aneurysms treated with flow re-direction endoluminal device

Complications	Nr. of patients	Nr. of complications	%
Intrasurgical			
Stent's bad opening	11	1	0.97%
Femoral artery dissection	80	1	0.97%
Postoperative (until 7 days)			
Acute ischemic stroke	8–19	2	1.94%
Late (> 7 days)			
Carotid-cavernous fistula	39	1	0.97%
Total		**5**	**4.85%**

Abbreviations: FRED, flow re-direction endoluminal device; Nr., number.
Source: Patient records.

(88.34%). These results are compatible with OKM classifications C and D. There were 4 subocclusions (3.88%), corresponding to classification B, and 8 aneurysms did not obtain occlusion (7.76%), corresponding to classification A (p-value < 0.01). In these variables, these data were obtained with outpatient monitoring and angiography control 12 months after the procedure, as shown in ►**Table 2**.

Regarding major complications, there were a total of 5 patients (4.85%) affected. In the intraoperative period, there was poor opening of the stent and dissection of the femoral artery, through which endovascular materials entered, both with an incidence of 0.97% each. Consequently, there were 2 acute strokes in the postoperative period of up to 7 days, and a carotid-cavernous fistula, being responsible respectively for (40%) and (20%) of the total complications, as shown in ►**Table 3**.

Discussion

In the present study, it was observed that the female gender predominated in the total of consultations, with 74 patients (91.35%), compared with only 7 male patients (8.65%). In addition, the average age found was of ~ 52 years for the diagnosis of aneurysms, which is in accordance with previous studies. Regarding the epidemiology of this pathology, it was pointed out that female gender and age are also non-modifiable risk factors for carotid aneurysms, which was observed in a meta-analysis of 95,000 patients; similar results were also found by Wang, et al. in 2014.[2] In addition, the average age found in the literature was 50 years, ranging from 22 to 76 years.[14]

Even though there were 83 patients, the total number of aneurysms found was 103. This can be explained because 16 patients (19.27%) had multiple aneurysms, a result higher than that found by Binh et al. in 2020,[14] who pointed to a ratio of 11, 90% incidence of multiple aneurysms in their study. The interesting thing observed in our analysis was that all patients with multiple aneurysms were affected on the same side.

Regarding the size of the aneurysms, we found: 90 (87.37%) small (< 10 mm); 11 (10.67%) large (10–25 mm), and 2 (1.94%) giant aneurysms (> 25 mm). The largest number of small aneurysms is widely found in the literature.[14–16]

Our study evaluated the viability of the flow in the artery during surgery and after 6 months of positioning the device. The success rates in the procedure with total occlusion of the aneurysm with a completely open and well-positioned stent with arterial recovery flow corresponded to 91 out of 103 procedures (88.34%), corresponding to classifications C and D of the OKM. There were 4 subocclusions (3.88%), and 8 aneurysms did not obtain occlusion (7.76%), which is

superior to results found in the first 12 months of a multicenter study[17] with 113 patients undergoing FRED-STENT intervention demonstrated a high rate of complete aneurysm occlusion in 12 months (73.3%). In addition to this, the Guimaraens et al. study, in 2020,[9] pointed out the effectiveness of this device in 84.32% (66%) of cases, presenting aneurysm occlusion in the 1st year, and 101/109 (92.7%) afterwards. Similar results were found in a large multicenter European study,[8] which indicated 83.9% efficacy in the 1st year of follow-up. These results confirm that flow deviation is a highly effective technique associated with a remarkably high rate of complete aneurysm occlusion. They also demonstrate that, after the flow deviation, aneurysm occlusion is a relatively slow and progressive process that sometimes takes several months to achieve completion. In our research, following the device selection methodology, the antiplatelet agent and adequate follow-up of patients allowed us to find good results, sometimes better than those in the literature.

Finally, Guimaraens et al., in 2020,[9] pointed out that major complications were observed in 6.5% of cases: 3 strokes (1 transient ischemic attack, 2 mild strokes), 6 in-stent thrombosis, out of which 3 presented bleeding, but only 1 (0.5%) was clinically relevant. In our study, there were a total of 5 patients (4.85%) with complications in the intraoperative period. There was poor opening of the stent and dissection of the femoral artery, both with an incidence of 0.97% of complications. Consequently, there were 2 acute strokes in the postoperative period of up to 7 days, and a carotid-cavernous fistula, being responsible for 1.94% and 0.97% of the total complications, respectively. We observed that the complication rate was very close to that observed in the literature, a surgical risk inherent to the highly complex procedure.

Conclusion

Our study observed that flow redirection is a technique with favorable performance associated with a high rate of complete aneurysm occlusion. Among the options of devices, STENT-FRED presented effectiveness in 88.54% of the 103 procedures included in this study. In addition, a low rate of serious complications was observed (4.84%), which indicates this to be an effective option in the treatment of internal carotid aneurysms, reiterating that the aneurysm occlusion is a relatively slow and progressive process that, at times, takes several months to achieve completion. Currently, there is a need for more studies on this type of device, compared with other FR devices. We hope that the present research will help to foster the analysis of this treatment option.

Conflict of Interests

The authors have no conflict of interests to declare.

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EC-IC Bypass: "Learning Curve" Experiences of Initial 100 Bypasses in Bangladesh

Bypass EC-CI: Experiências de "curva de aprendizado" de desvios iniciais em Bangladesh

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Abstract

Objectives Extracranial to intracranial (EC-IC) bypass is an important part of the armamentarium of a neurosurgeon in managing different vascular and neoplastic pathologies. Here, we report our initial experiences of EC-IC bypasses as experiences in the 'learning curve', including preparation and training of the surgeon, getting cases, patient selection, imaging, operative skills and microtechniques, complications, follow-up, and outcome. Lessons learned from the 'learning curve experiences' can be very useful for young vascular neurosurgeons who are going to start EC-IC bypass or have already started to perform and find themselves in the learning curve.

Methods From July 2009 to September 2018, 100 EC-IC bypasses were performed. We looked back to these cases of EC-IC bypass as our initial or 'learning curve' experiences. The recorded data of patient management (EC-IC bypass patient) were reviewed retrogradely. Our preparation for EC-IC bypass was described briefly. Case selection, indications, preparation of the patient for operation, techniques and technical experiences, preoperative difficulties and challenges, postoperative follow-up, complications, patency status of the bypass, and ultimate results were reviewed and studied.

Result A total of 100 bypasses were performed in 83 patients, of which 43 were male and 40 were female. The age range was from 04 to 72 years old (average 32 years old). Eleven patients were lost to follow-up postoperatively after 3 months and they were not even available for telephone follow-up. The follow-up period ranged from 3 to 120 months (average of18.4 months). Eight bypasses were high flow bypasses, whereas the number of low flow STA-MCA bypasses was 92. Indication of bypass were (in 83 cases):**1.** Arterial stenosis/occlusion/dissection causing cerebral ischemia (middle cerebral artery [MCA] stenosis/occlusion-05, MCA dissection-04, internal carotid artery [ICA] occlusion-19); **2.** Intracranial aneurysm-30; **3.** Moya-Moya disease-21; and **4.** Direct carotid cavernous fistula

Keywords
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- high flow bypass

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[CCF]-04. Common clinical presentation was hemiparesis & dysphasia in ischemic group with history of transient ischemic attack (H/O TIA) (including Moya Moya disease). Features of subarachnoid hemorrhage (SAH) were the presenting symptoms in intracranial aneurysm group. The average ischemic time, due to clamping of recipient artery, was 28 minutes (range: 20–60 minutes). There was no clamp-related infarction. Two anastomoses were found thrombosed intraoperatively.

One preoperatively ambulant patient deteriorated neurologically in the postoperative period. She developed hemiplegia but improved later. Here, the cause seemed to be hyperperfusion. Headache resolved in all cases. TIA and seizures were also gone postoperatively. Ophthalmoplegia recovered in all cases in which it was present, except in one CCF, in which abducent nerve palsy persisted. Complete unilateral total blindness developed in one patient postoperatively (due to ophthalmic artery occlusion), where high flow bypass with ICA occlusion were performed. Red eye and proptosis were cured in CCF cases. Motor and sensory dysphasia improved in all cases in which it was present, except for one case in which preoperative global aphasia converted to sensory aphasia in the postoperative period. Three patients died in the postoperative period. The rest of the patients improved postoperatively. All patients were ambulant with static neurostatus and without new stroke/TIA until the last follow-up. All bypasses were patent until the last follow-up.

Conclusion The initial experiences of 100 cases of EC-IC bypass revealed even in inexperienced hand mortality and morbidity in properly indicated cases were low and result were impressive according to the pathological group and aim of bypass. Lessons learned from these experiences can be very helpful for new and beginner bypass neurosurgeons

Introduction

The first vascular anastomosis in history was described by Eck in 1877 with his operation on dogs to make a side-to-side anastomosis between the hepatic vein and the inferior vena cava.[1–3] French surgeon Alexis Carrel published the first arterial end-to-end anastomosis in 1902[1,4] and received the Nobel Prize in 1912. Kredel[5] attempted encephalomyosynangiosis in humans in 1942, but it was later abandoned due to an increased prevalence of postoperative seizures. Then, in 1949, Beck et al.[6] published their revascularization technique of a carotidjugular fistula. Jacobson et al. reported the first human microneurosurgical procedure in 1962: an middle cerebral artery [MCA] endarterectomy.[1,2,7–9]

Pool et al.,[1,10,11] in 1961, first adventured into cerebral revascularization with a synthetic material using a plastic tube to make a superficial temporal artery (STA) to anterior cerebral artery bypass, but an angiogram showed that the tube was thrombosed, although the patient recovered and survived. Woringer et al.[12] did the first extracranial to intracranial (EC-IC) bypass of the common carotid artery (CCA) – intracranial (IC) internal carotid artery (ICA) using a saphenous vein (SV) graft in 1963, but the patient died, although the graft was patent on autopsy.[1,2]

The first successful EC-IC bypass was performed by Prof. Yaşargil in 1967 in a patient with occluded ICA and, since then, it has become an essential way for managing patients with hemodynamic cerebral ischemia, complex intracranial aneurysms or skull base neoplasms.[13–15] The cases with cerebral hemodynamic ischemia have an annual stroke rate of 25%, which increases by 2% per year.[13] They can have a fatal ischemic stroke. Moyamoya disease is also included in this category.[13,16]

Yaşargil also did STA-middle cerebral artery (MCA) bypass for moyamoya disease in 1972. In 1971, Lougheed made the first EC-IC bypass using an SV graft. Ausman performed an EC-IC bypass using a radial artery (RA) graft in 1978. In the 1970s, Sundt et al.[17] and others performed posterior circulation revascularization for the management of steno-occlusive disease, vertebrobasilar insufficiency, and unclippable complex aneurysms.[1]

In ischemic stroke, after the failure of an EC-IC bypass trial in 1985,[1,2] neurovascular surgeons were looking for cases in which an EC- IC bypass would help the patients in neurological recovery and prevent future ischemic stroke. Moreover, EC-IC bypass is also used for the treatment of moyamoya disease, complex aneurysm, arterial dissection, and complex skullbase tumor. Here, we report our initial experiences of the first 100 bypasses as experiences in 'learning curve' covering the preparation and training of the surgeon, getting cases, patient selection, imaging, operative skills and microtechniques, complications, follow-up, and outcome. Lessons learned from the 'learning curve experiences' can be very useful for young vascular neurosurgeons who are going to start EC-IC bypass or have already started it and are in the learning curve.

Methods

We started EC-IC bypass in 2009. Patients who underwent EC-IC bypass from July 2009 to September 2018 were included in the present study. In this time frame, we performed 100 EC-IC bypasses. We looked back to these cases of EC-IC bypass as our initial or 'learning curve' experiences. The recorded data of patient management (EC-IC bypass patients) were reviewed retrogradely. Our preparation for EC-IC bypass was described briefly. Case selection, indications, preparation of the patient for operation, techniques and technical experiences, preoperative difficulties and challenges, postoperative follow-up, complications, patency status of the bypass, and ultimate results were reviewed and studied.

After undergoing the bypass, all patients were followed-up regularly (clinically and radiologically).

Representative Cases

Case 1 (►Figure 1a & 1b)

A 27-year-old male young doctor presented with right sided hemiplegia, aphasia, and visual field defect. His hemiplegia improved from initial Medical Research Council [MRC] grade 0/5 to 3 +/5 in the right lower limb and 2/5 in the right upper limb 1 day after admission. His perception and comprehension of speech were normal, but he had motor aphasia and right homonymous hemianopia. Computed tomography (CT) scan and magnetic resonance imaging (MRI) of the head showed left-sided patchy infarcts and ischemic zones in left parieto-temporo-occipital zones. Digital subtraction angiography (DSA) and CT angiography (CTA) of the brain showed left M1 stenosis with scarcity of left MCA vessel (►**Figure 1a** & **1b** [B, C and D). Perfusion weighted (PW) images showed perfusion mismatch.

On an urgent basis, the patient underwent left-sided STA-MCA bypass.

Operation

Under general anesthesia (GA), the patient was placed on the supine position with the head turned $> 60°$. At this point, we used digital palpation technique and a handheld Doppler probe to map out the course of both the frontal and parietal branches of the STA.

The incision was started at the level of the zygoma and extended up to the near midline behind the hairline. Both branches were procured up to the superior temporal line very carefully (to avoid thermal damage or avulsion injury). Papaverine solution and plain local anesthetic agent (2% lidocaine) was used to irrigate the STA for vasospasm prevention. A mini pterional craniotomy was performed very carefully (so as to not damage the procured STA). After durotomy, a small posterior Sylvian fissure split was done to find out a suitable M3 as a recipient vessel for the bypass. Among the frontal and parietal branches, the suitable and larger frontal branch was used to make a STA-MCA anastomosis. After the bypass (►**Figure 1B**[A]), patency was checked clinically and with microdoppler. The dura was loosely closed around the STA (not watertight). Along the temporal margin of the bone flap, a portion was removed so that the STA would not be kinked or compressed by the bone. Mini plates and screws were used to fix the bone flap. The rest of the wound was closed accordingly without drain.

Postoperative Course

The patient recovered well from anesthesia. In the postoperative days, the patient recovered quickly from hemiparesis and aphasia. By the end of the 7th postoperative day (POD), the patient became ambulant, but his visual field remained as preoperatively. By the end of 4 weeks after the operation, he returned to his professional work and muscle power on right side of the body was improved (MRC grade 4 +/5). A postoperative CT scan showed no hematoma or new infarct. The CTA showed a patent STA-MCA bypass on the left side.

Case 2 - High Flow Bypass (CCA-RA-MCA bypass) (►Figure 2a-2f)

A 55-year-old right-handed man presented with clinical features of recurrent subarachnoid hemorrhage (SAH), that is, sudden severe headache and vomiting. His Hunt and Hess grade was G-1. He was a smoker but nondiabetic and non-hypertensive. A CT scan showed SAH in the carotid, the basal and both Sylvian fissures. A computed tomography angiography of the brain showed a left-sided supraclinoidal large fusiform ICA aneurysm (►**Figure 2a**). He was counselled for urgent operation. We decided to do a left sided CCA-RA-MCA (M2) high flow bypass with occlusion of the left ICA at the neck. The Allen test was done bilaterally and it showed that the ulnar arterial flow was adequate for hand circulation in the absence of the radial artery.

Operation (►Figure 2c-2e)

Under general anesthesia with endotracheal intubation, the patient was placed in the supine position. His head was fixed with a 3-pin head holder with neck extension and head turning to the opposite (right) side (30°). The head end of the table was elevated (20°). Eyes, ears, pressure points, and nerve areas were protected. The left upper limb was placed on a side 'limb rest' with extended elbow, 30° abducted from the trunk in supine for radial artery procurement. After preparation, the front of the left forearm, the left side of the neck, and the left pterional areas were draped properly.

With a longitudinal incision, the radial artery was harvested from the brachial bifurcation at the elbow to the wrist (20 cm). The artery was distended with intraluminal injection of heparin and papaverine mixed with normal saline. Then, the artery was kept in heparin and papaverine mixed with normal saline. The forearm wound was closed with a drain.

A curved incision on the left side of the neck was made from the tip of the mastoid process and extended downwards and medially 2 cm posterior to the angle of the mandible to the midline. After cutting the platysma and investing deep fascia the sternocleidomastoid muscle was retracted laterally. With further dissection of the posterior belly of the digastric muscle, the hypoglossal nerve, the internal jugular

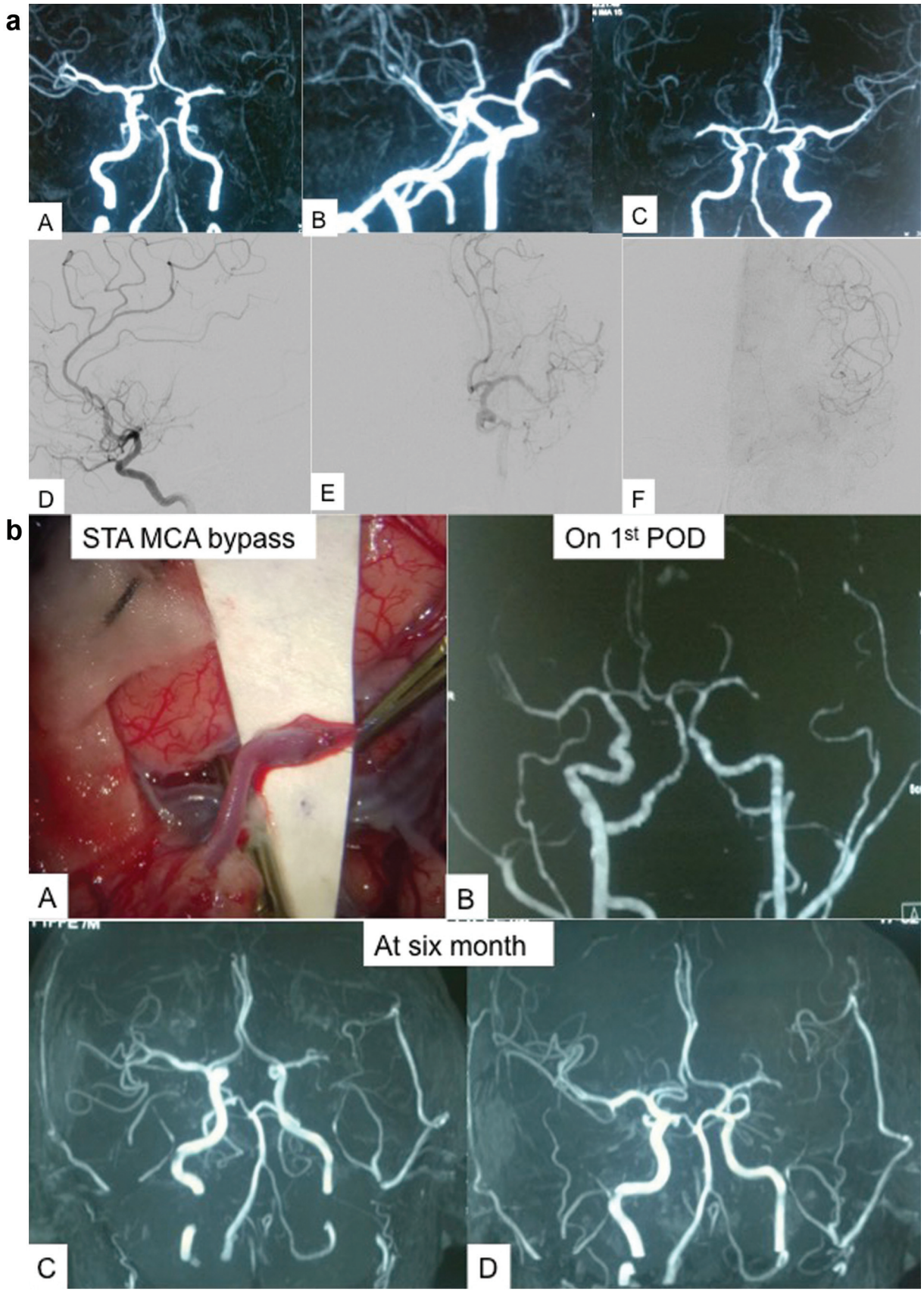

Fig. 1 (**a**): (**A, B & C**) CTA of the brain showing severe stenosis of the left MCA. (**E, F & G**) Cerebral DSA showing left MCA stenosis with delayed filling of the MCA territory. (**b**) (**A**) Preoperative picture of STA-MCA bypass. (**B**) CTA of the brain on the 1st POD showing left STA-MCA bypass. (**C & D**) CTA of the brain 6 months after the operation showing patent STA-MCA bypass.

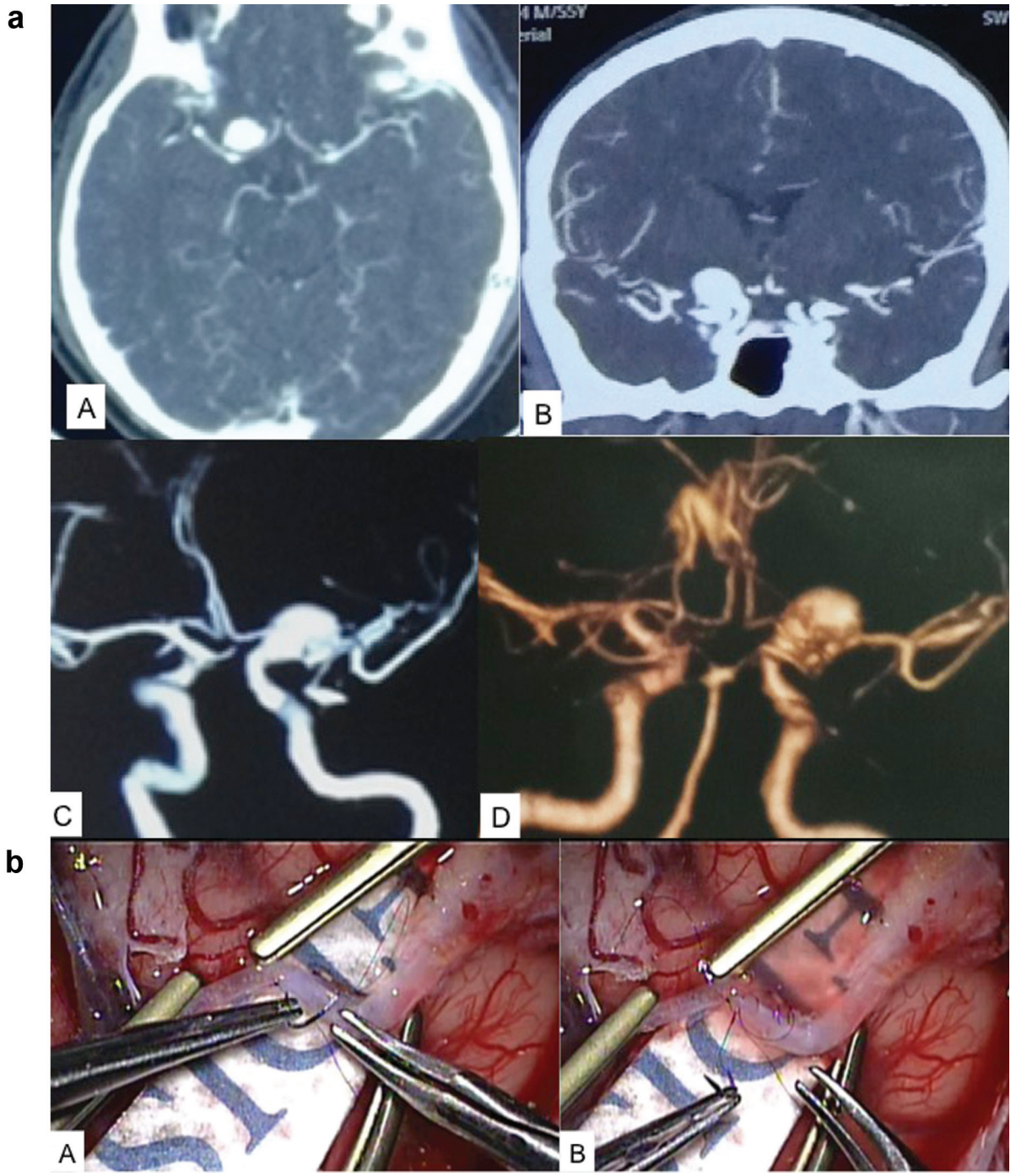

Fig. 2 (**a**)**:** (**A, B, C & D**) CTA of the brain showing a large fusiform aneurysm involving the left supraclinoidal ICA. (**b**)**:** (**A & B**) preoperative pictures of insurance STA-MCA bypass before performance of EC-IC high flow bypass. (**c**)**:** (**A & B**) preoperative pictures; sylvian dissection, identification and preparation of the temporal M2 as recipient artery for anastomosis with radial artery (RA) graft. RA, radial artery; M2 (MCA). (**d**): **A & B**-preoperative pictures of RA and M2 anastomosis. (**e**)**: A & B** preoperative pictures of RA and CCA anastomosis. (**f**)**:** Postoperative CTA of the brain and neck vessel on the 2nd POD showing CCA-RA-M2 high flow EC-IC bypass and nonvisualization of the left supraclinoidal ICA aneurysm.

vein, the common carotid, the internal carotid, and the external carotid artery with its branches were identified.

A left-sided precoronal posthairline curvilinear incision was made and the superficial temporal artery (STA) with its parietal branch was procured and prepared for STA-MCA protective bypass as donor artery. A temporally extended pterional craniotomy was performed. The temporal bone was removed down to the middle fossa floor. In the cervical wound, a blunt index finger dissection was made in between the digastric muscle and the hypoglossal nerve upward and superiorly to the styloid process, and then the finger dissection was continued upward, medially, and anteriorly to the lateral pterygoid plate. A curved medium-sized artery forceps was passed from the middle fossa floor to the fingertip, and, with finger guidance, the arterial tip was brought out into the cervical wound, and then a 26Fr thoracostomy tube

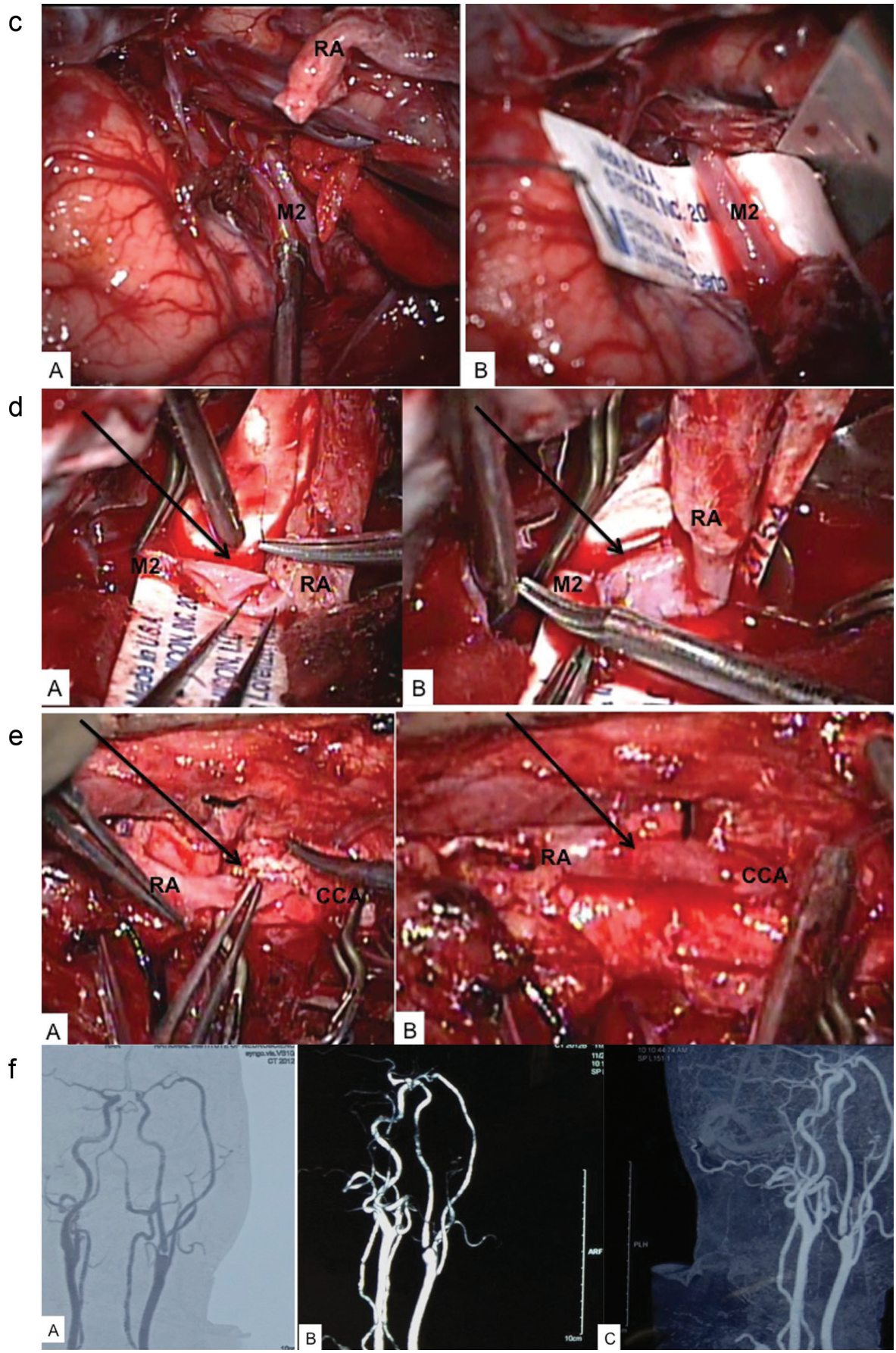

Fig. 2 (*Continued*)

was passed from the cervical wound to the middle fossa floor. The radial artery (RA) graft was passed from the middle fossa floor to the cervical wound through the tube. With stabilization of both ends of the RA graft, the thoracostomy tube was removed. The RA graft was made twist-free by injecting heparinized solution into the lumen.

After durotomy, a STA–MCA (Temporal M4) 'insurance bypass' was done with 10/0 nylon and checked for patency and function with micro Doppler (►**Figure 2b**). After Sylvian dissection, the temporal M2 was identified and prepared for bypass (►**Figure 2c**). The cranial end of the RA graft was also prepared for bypass, and the RA graft and temporal M2 bypass was made (►**Figure 2d**) after systemic heparinization with 3,000 units of heparin. The patency of anastomosis was checked by retrograde flow of blood through the caudal end of the RA graft in the cervical wound.

With the control of the common carotid artery (CCA), an anastomosis was made between the caudal end of the RA graft and the CCA (►**Figure 2e**). The patency and flow through the anastomoses and RA graft were checked with micro Doppler. The left ICA was identified as well as dissected to ligate it at its origin with 1-0 silk. The cervical wound and the craniotomy wound were closed with drains.

Postoperative Course

Postoperatively, the patient was on tab. Aspirin (75 mg daily). A CT scan on the 1st POD showed no infarct or any gross hematoma. A CT angiogram on the 2nd POD showed left external carotid artery (ECA)-radial artery graft (RAG)-M2 bypass with regression of the ICA fusiform aneurysm, but the ICA was visualized completely up to the ligation point at the neck. The patient made an uneventful recovery and was discharged on the 8th POD. Thirteen months after the operation, he returned with clinical features of SAH. A CTA showed a left ICA bifurcation aneurysm that had ruptured. But the bypass was patent and the ICA was again visualized up to its ligation at neck (►**Figure2f**). We decided to reoperate the patient, but he did not agree with any kind of further intervention. After the last SAH, he is under regular follow-up for the last 7 months, without further bleeding.

Results

Dreaming Through: Brain Thought to Hand Skill (►Figure3)

When the main author was a 3rd year MBBS student, he became interested in neurosurgery after watching a video of the removal of an intracranial meningioma in the college library (the operation was done by late professor Rashid Uddin Ahmed). At that time, he was firmly motivated to be a neurosurgeon. During his intern period, when he was placed in the neurosurgery department, he presented on surgical management of intracranial hemorrhages on a clinical meeting and, at that time, he first knew about the EC-IC bypass for

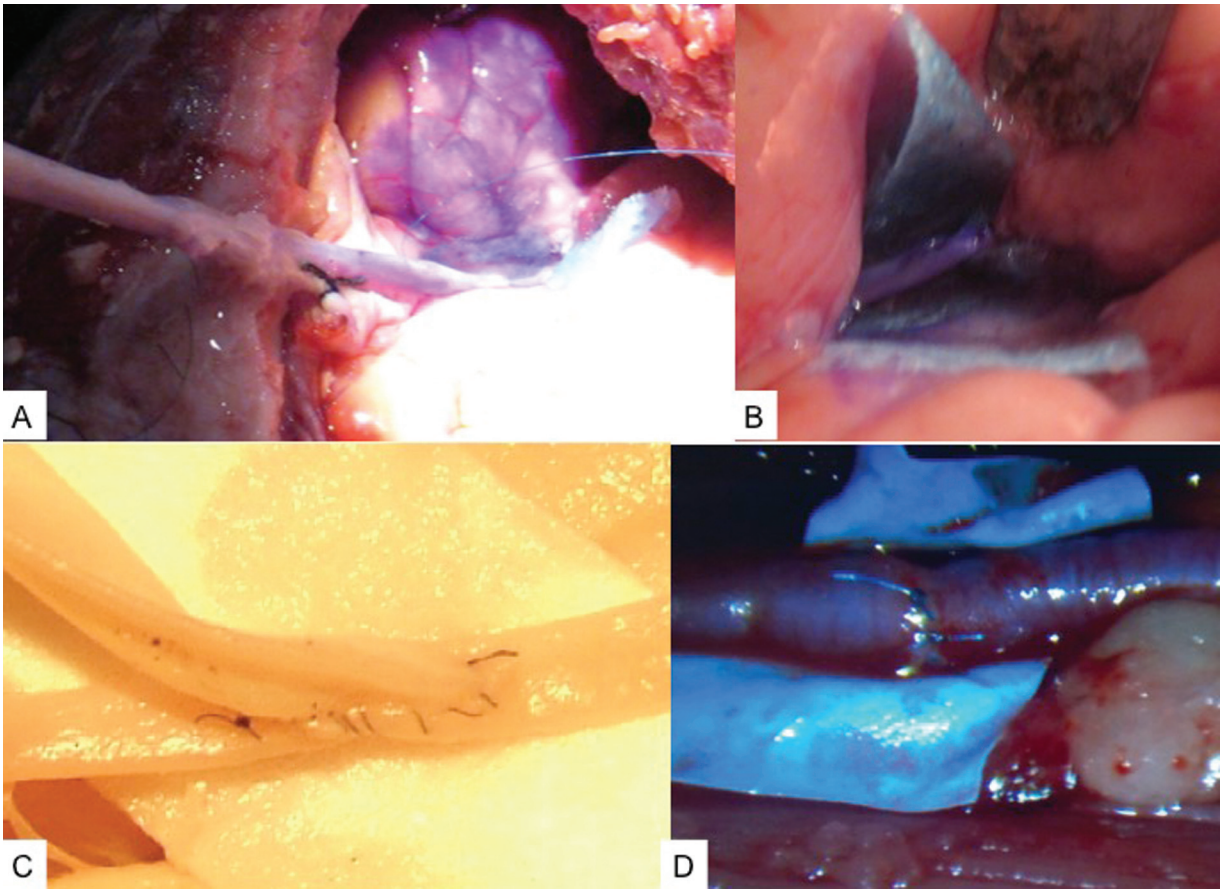

Fig. 3 Practices of microvascular anastomosis before clinical application. (A & B) Radial artery graft anastomosis with M2 in Sylvian fissure of fresh cadaveric brain. (C) Microvascular anastomosis practice on formalinized dry brain. (D) Microvascular anastomosis practice on live hen.

the management of various intracranial vascular lesions. Brain bypass!!! Is it really possible, who used to do it? Is there anyone in Bangladesh who practices brain bypass? The answer was no.

In 2001, in a neurosurgical meeting, a Japanese neurosurgeon showed a very brief video on petrous to supraclinoidal ICA bypass. In the World Federation of Neurosurgical Societies (WFNS) meeting in 2007 in Nagoya, Japan, a few lectures on vascular surgery really inspired us on focusing on EC-IC bypass. We started to practice anastomosis on fresh cadaveric brains [radial artery-MCA (M2)] in the forensic department, which was very poorly equipped.

During a fellowship (2009) in the department of neurosurgery, KEM Hospital, Mumbai, India, under professor Atul Goel, the main author took the opportunity to practice microvascular anastomosis on formalinized brain surfaces in his microneurosurgery lab under operating microscope. There, the main author practiced more than 50 times. Some Italian fellow (who was also visiting at the same time) told the main author to practice it on live rats or Guinea pigs. But that was not possible there. Then, we practiced on live hen and rats several times in the microvascular lab of the department of plastic surgery, Dhaka Medical College and Hospital, Dhaka (►**Figure 3**).

Getting the Clinical Cases

After achieving adequate motor skills and background knowledge, we were looking for cases that were appropriately indicated for EC-IC bypass, but we were not getting any cases. Finally, we got a case of M1 giant aneurysm. We decided to do an EC-IC bypass in this case, but when the relatives of the patient heard that it would be our first case and no one had performed this operation before in this country, they left the hospital to go outside the country. In this way, we failed to operate on our first case for another 4 or 5 cases for which bypass was indicated. Ultimately, we could convince our first case to undergo EC-IC bypass, a 14-year-old girl with M2-M3 dissection.

It took one and a half year more to get the second case. After starting bypass, we did only four cases in first 3 years and 7 cases in the next 2 years. Then, we got cases more frequently.

Preoperative Assessment of the Patients

In ischemia

Patients in this case series with transient ischemic attack (TIA)/stroke/recurrent stroke were evaluated clinically for history of TIA or recurrent/hemodynamic TIA (in rest or during work) or progressive hemiparesis/aphasia/visual disturbances or sudden hemiplegia/hemiparesis/aphasia with subsequent significant recovery (in days to in a week). Permanent hemiplegia cases were not considered for EC-IC bypass. Then the cases were evaluated radiologically for ischemia with or without infarcts and possible revascularization by EC-IC bypass. Computed tomography scan of the brain was done to exclude hemorrhage and other pathologies, such as tumors. Magnetic resonance imaging of the brain was done in ischemic protocol (all images including diffusion weighted [DW], afferent diffusion coefficient [ADC], PW, DTI and magnetic resonance angiography [MRA] and MRV, including neck vessels) to see cerebral ischemic zones (DWand PW mismatch), the corticospinal tract and other major tracts and intracranial or extracranial arterial stenosis. To see the arterial pathology, dynamic CTA was also done in all cases. DSA was done in 36 cases. When clinical features, cerebral ischemia on MRI and arterial stenosis/occlusion on angiogram were concordant with each other, only then cerebral revascularization by EC-IC bypass was done.

In other Indications

1. Moyamoya disease
2. As replacement: Intracranial giant fusiform ICA aneurysm or caroticocavernous fistula (CCF) where ICA ligation at neck and EC-IC bypass was planned.
3. Protective bypass in skullbase tumor where ICA was encased by tumor and the chance of injury or occlusion of ICA or ICA had to be removed with the tumor.
4. Protective bypass in giant MCA or ICA aneurysm where the trunk of the MCA or of the ICA occlusion/compromise was a possibility.
5. Protective bypass in aneurysm with proximal stenosis.
6. Insurance bypass during high flow EC-EC bypass.
7. Treatment of CCF.
8. Arterial dissection.

Preoperative Patient Preparation

Counselling and other preoperative preparations were as usual except in cerebral ischemic patients, in whom preoperative antiplatelet drugs were continued. In these cases, platelet concentrates were made available preoperatively, but were not required in any case.

Preoperative Assessment of Donor Artery

Preoperatively, the STA was assessed with digital palpation and Doppler in all cases for its presence and rough estimation of caliber and flow. Preoperatively, the STA was also assessed with angiogram (external carotid angiogram: DSA, CTA and MRA).

The Allen test was performed in cases where the RA was planned to procure as conduit for high flow EC-IC bypass.

Procurement of Donor Artery; STA/RA

In initial cases, we did Donor arterty procurement without microscope, but later we found that it is more comfortable with a microscope. Now, we routinely use a microscope in the procurement of the donor vessel. We procure the STA and its frontal and parietal branches up to the superior temporal line (length between 7 and 9 cm) (►**Figure 4**). Initially, we used 2% plain lignocaine instillation on the STA to avoid vasospasm, but in the later part of our experiences, we used papaverine solution along with lignocaine. After application of a temporary clip on the STA, we routinely irrigated its lumen with heparin solution several times.

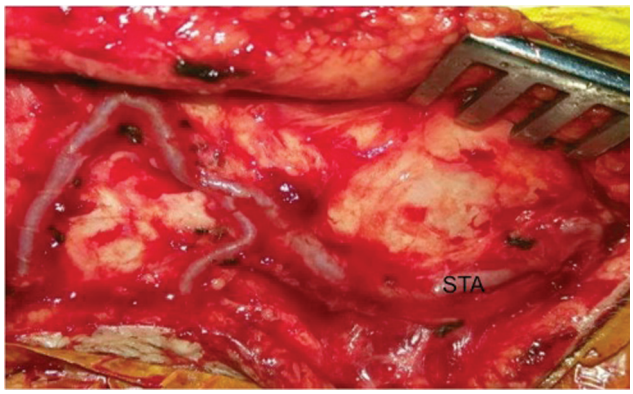

Fig. 4 Preoperative picture of procurement of the right STA and its branches.

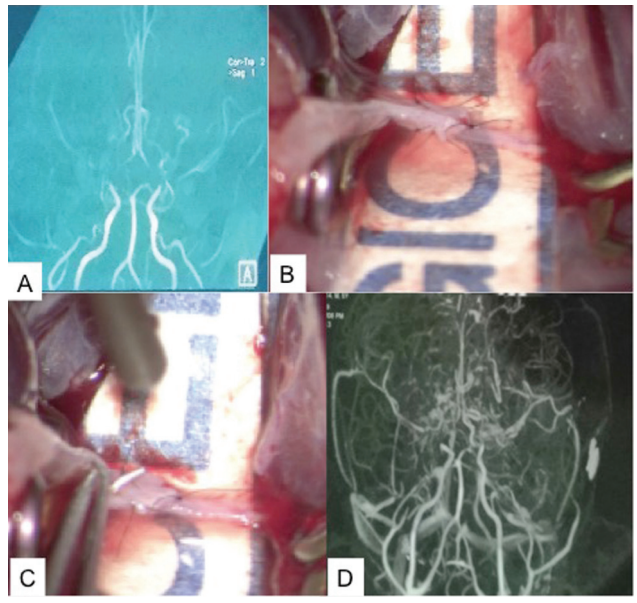

Fig. 5 (A) preoperative MRA of the brain showing bilateral Moyamoya disease. (B & C) Preoperative picture of direct STA-MCA bypass. (D) Postoperative CTA on the 1st POD showing patent STA-MCA anastomosis with increased vascularity.

In two cases STA length was short up to suitable recipient artery on temporal surface due to less available length of STA and also due to falling of brain in deep as a result of cerebro spinal fluid (CSF) drainage. Extra dissection at the root of the zygoma, flushing of the temporal bone and assistant 'holding of donor artery' near the recipient artery helped to make anastomosis with some difficulty.

We procured both branches of the STA and the relatively larger branch was used as donor artery where the other branch was ligated. Where needed, both branches were used as donors in double barrel bypass. In moyamoya disease, we used the frontal branch of the STA for direct STA-MCA bypass, where the parietal branch was used for indirect revascularization (as in EDAS) and the distal end was kept in continuity with the scalp.

Radial artery (RA) Procurement (in High Flow Bypass)

In all cases of high flow bypasses, the left RA was procured after performing the Allen test with a radially placed longitudinal incision from wrist to elbow (20 to 22 cm). We used papaverine solution along with lignocaine solution on the artery during procurement. After procurement, the RA graft was distended with heparin and papaverine solution and then it was suspended in heparin and papaverine mixed solution.

Craniotomy

In most of the cases pterional craniotomy was used for EC-IC bypass. In two cases of moyamoya disease, a suitable recipient artery was found near the bony margin and was prepared for anastomosis, but there were a lot of difficulties (for example, in instrumental movements during stitching) faced by the surgeons due to the bony margin. In the later part of our experiences, when such situations occurred, we cut more bone so that the bony margin did not interfere during instrumental movements

In high flow bypasses, pterional craniotomy was extended down until the root of the pterygoid by removing bone with a rongeur or a drill, so that the RA graft could be brought to the middle fossa through the infratemporal fossa from the cervical wound.

Recipient Selection

In most of the STA-MCA bypasses, the temporal M4 or M3 were used as recipient arteries, which were easy to find and easy to prepare. Finding a suitable recipient artery in moyamoya disease, especially in children, was very challenging. In some cases, deep Sylvian dissection was needed to get a suitable artery. In children, the recipient artery was very thin and fragile, which made anastomosis more difficult. With patience and skill, anastomosis was successfully done in all cases (even in a 4-year-old boy) (►**Figure 5**). In all cases, we had to make the anastomosis with 10/0 nylon with cutting body needle, since there was no alternative suture. The unavailability of appropriate/alternative suture material made anastomosis more complex and difficult.

In high flow bypasses, we did insurance bypass by STA-MCA bypass at first. Then, the temporal M2 was dissected out for quite a distance up to its cortical branches with deep Sylvian dissection. Then deep to the artery triangular background paper (prepared from surgice a package covering) was passed. Both end of background paper was tied with suture to bring the M2 superficially; so that anastomosis became easier. Spongostan was put deep to the background to prevent blood collection in Sylvian fissure from anastomotic leak after release of temporary clips.

The M3/M4 branches of the upper trunk of the MCA were used in 9 cases of double barrel bypasses.

Why the temporal trunk of the MCA and its branches were preferable than the frontoparietal trunk and its branches as recipient artery?

1. The upper trunk supplies more eloquent and important areas (Broca area, primary motor, and primary sensory areas) than the temporal trunk (primary auditory areas

and lower part of the Wernicke area on the left side only, which has overlapping supply from the upper trunk).
2. Occlusion of the upper M2 has more chances of infarction compared with the lower trunk.
3. Infarction of lower trunk areas produce less severe deficits than upper trunk areas.
4. In some cases, the upper trunk supplies the corona radiata.
5. Use of the lower trunk and its branches as recipient arteries is technically easier.

Ischemic Time

From the beginning, we were afraid of infarction of the brain during performance of anastomosis in clinical cases. When we talked to experts (including Prof. Atul Goel) regarding ischemic time, all of them said ischemic time is not a major issue in bypass. But it was our major concern even when we were practicing anastomosis on hen in < 20 minutes.

Realization regarding Ischemic Time

In the first 100 clinical bypasses, we faced no infarction related to temporary occlusion of brain arteries. In the earlier cases, we did not take any protecting measures for the brain parenchyma against ischemia or any talk with anesthesiologist regarding ischemic time. Initially, we took 35 minutes to 40 minutes in STA-M4 anastomosis and 35 to 60 minutes in STA-M3 anastomosis, but, surprisingly, we found no infarct in temporarily occluded arterial territory. In one case, we found infarct that was not related to temporary clamping [►**Figure 6**]. Now, we used to talk regularly with anesthesiologist to keep BP at upper normal level and high dose inj. propofol in high dose. Now, we require 20 to 30 minutes to performing STA-M4 or STA-M3 bypass.

In the later part of our learning curve, we used to take heel and toe suture bites on Donor arteriotomy before applying cross clamps on the recipient artery. This practice decreases ischemic time to some extent.

Preoperative Use of Systemic Heparin

During high flow bypass inj. Heparin 3000 U i.v was used a single dose just before putting a cross clamp 9 on M2. In STA-MCA bypass, no systemic heparin was used.

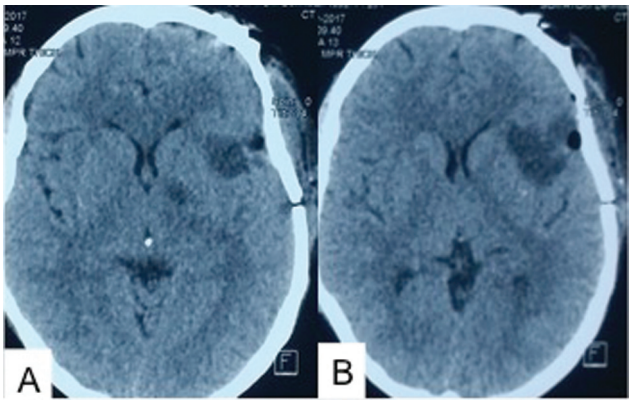

Fig. 6 (**A** & **B**) Postoperative CT scan on the 1st POD showing a fronto-insulo-caudate infarct that was not related to cross clamping of the temporal M3-M4 junction.

Hematoma in Sylvian Fissure

In the initial 3 to 4 cases in which STA-M3 bypass was performed, we found postoperatively hematoma in the sylvian fissure, which was due to initial leaking through anastomotic sites after removal of temporary clips. Later, to prevent this hematoma, we routinely place Spongostan pieces deep to the anastomotic site so that leaking blood should not spread into deep Sylvian spaces.

Common Leaking Sites (►**Figure 7a-7c**)

Leaking is near the heel or toe stitches. To prevent this, we use 'right angle needle pricking direction on recipient' to the needle pricking direction on donor in first stitch near the toe or heel stitch. Anastomotic leaking after removal of temporary clips usually stops spontaneously within 5 minutes; if not, it should stop with round Surgicel packing within the next 5 to 10 minutes. Even with Surgicel, if leaking persists, a temporary clip should be applied on the donor artery for 3 to 5 minutes. If temporary clipping of the donor artery fails to stop leaking, an additional microanastomotic suture will be needed to stop leaking.

In these first 100 EC-IC bypasses, only 3 cases needed additional stiching after removal of the temporary clips and their location was near to toe (anchoring) stich.

Patency Test after Anastomosis

After cessation of leaking through the anastomosis, the anastomotic patency and functionality were checked by inspection, palpation, test occlusion of the donor artery by microforceps or temporary clip and by micro-doppler. We found that the anastomosis was functioning in all cases after completion, except in two cases in which the pathology was giant supraclinoidal ICA aneurysm, and the anastomoses were found occluded after completion of clip reconstruction of the aneurysm. Then, we opened the donor artery just proximal to the anastomotic line with a small arteriotomy and found thrombus at the anastomotic site. Then, we removed it and irrigated with heparinized solution along with systemic heparinization. Blood flow was re-established through the anastomosis. In one case in which the ICA lumen was compromised by aneurysm clips, the total MCA territory was infarcted due to rethrombosis of the STA-MCA bypass (►**Figure 8**). When we reviewed the operating videos, in this case we found that there was overstaining of the endothelial surface of the donor artery at the anastomotic end with 'gentian violet', and we think this might be the cause of thrombosis. Therefore, in subsequent cases, the anastomotic margins of the donor artery were stained carefully after apposing margins, so that the stain should not enter into the luminal surface, and staining of the recipient artery was done before arteriotomy. In another case, we did not find any definitive cause of thrombotic occlusion of the anastomotic site on reviewing the operating video.

In high flow bypasses, we did not face any preoperative or postoperative graft spasm or occlusion.

Dural Closure

In all cases, watertight dural closure was not performed (actually, it was not possible). The wound was closed with

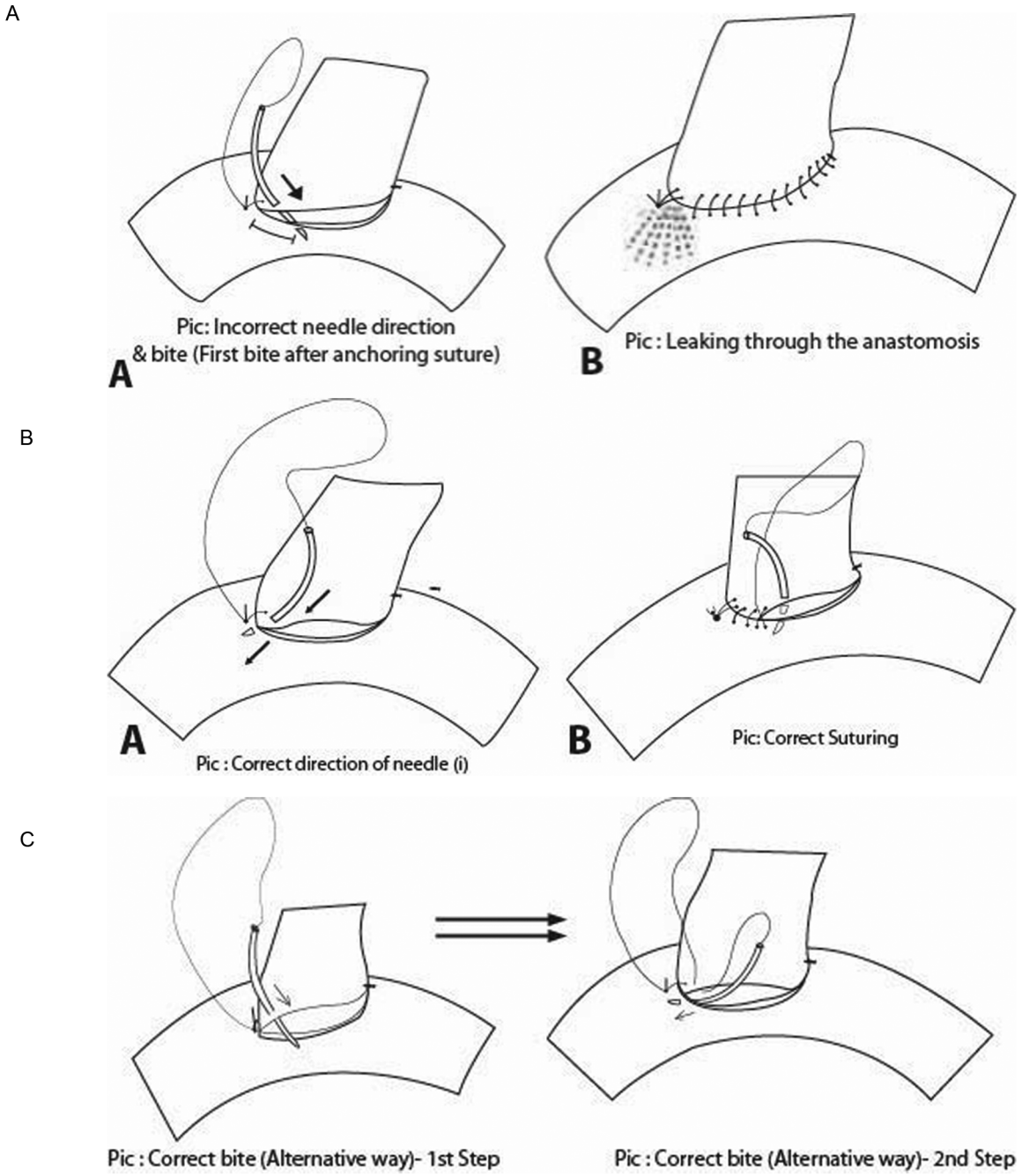

Fig. 7 (A) Schematic drawing showing "incorrect" techniques of 1st bites, needle direction, and suturing after the anchoring suture that results in anastomotic leak after removal of cross clamps. (B) anastomotic leak through the anastomosis (at the 1st suture site) after removal of cross clamps. (**B**) Schematic drawing showing "correct" techniques of 1st bites, needle direction, and suturing after the anchoring suture that prevents anastomotic leak after removal of cross clamps. (**C**) Schematic drawing showing alternative two-step correct techniques of the 1st bites, needle direction, and suturing after the anchoring suture that also prevents anastomotic leak after removal of cross clamps.

drain at the upper end of the wound. In most of the cases, the drain was removed on the 3rd or 4th POD if drain collection was minimum. In only 9 cases in which CSF was coming through the drain after the 4th POD, we continued the drain up to the 8th day and then removed the drain with stitching of the drain site. In four cases, there was subcutaneous collection of CSF that was resolved within 3 weeks in 3 cases; in 1 case, repeated tapping failed to stop collection of CSF and the patient needed readmission followed by lumbar CSF drainage to stop CSF collection at the end of 8 weeks postoperatively.

Patency of Anastomosis on Follow-up (►Figure1b,2f,5 and 9f)

Digital palpation of the STA, doppler checking, CT scan, and CTA of the brain including neck vessels were performed in all

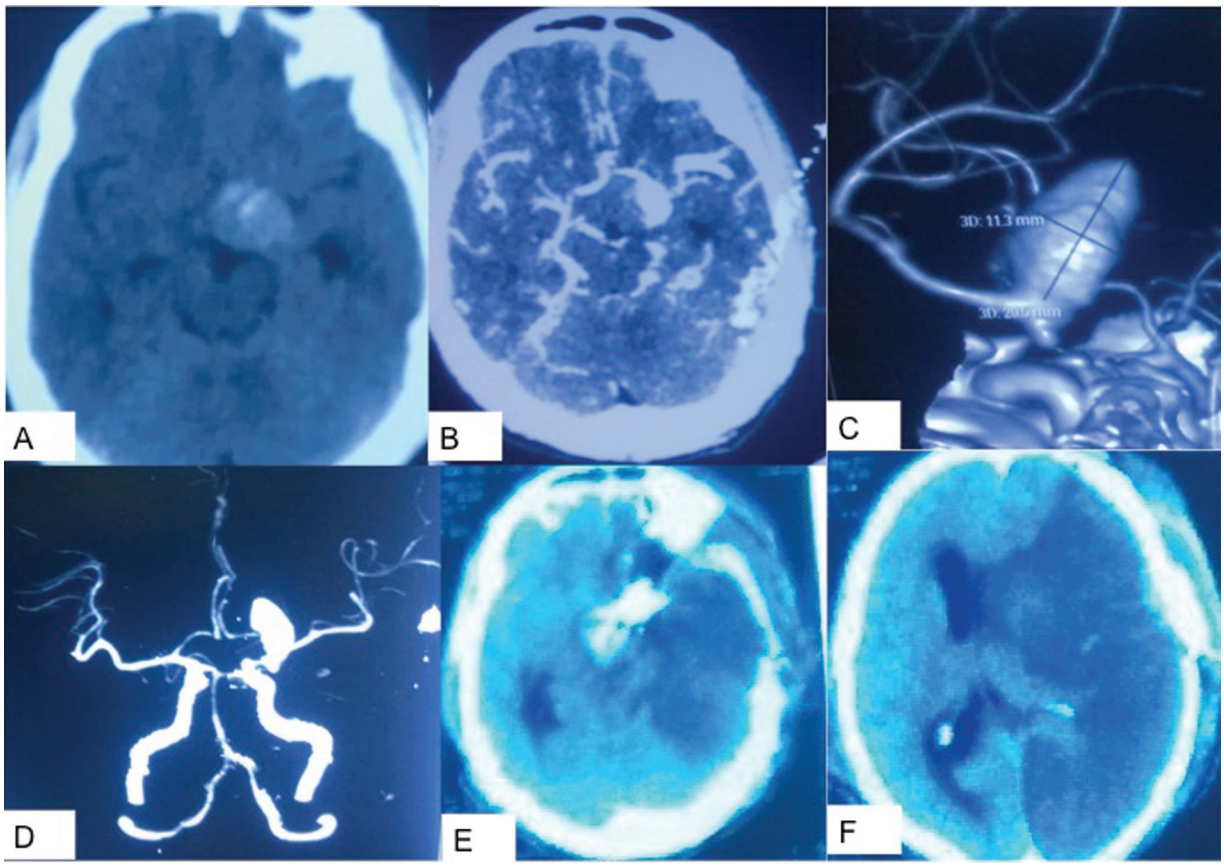

Fig. 8 (A) Preoperative CT scan showing suspected giant left ICA aneurysm. (**B, C and D**) CTA of the brain showing a giant partially thrombosed left ICA aneurysm. (**E and F**) Postoperative CT scan on the 1st POD showing massive left MCA infarct (clip reconstruction of the aneurysm was done with protective STA-MCA bypass, but the bypass was thrombosed preoperatively and it was rescued).

cases on the 1st POD to check anastomotic patency. Computed tomography scan also detects hematomas and infarcts. In one case, infarcts in the caudate nucleus head and in the anterior insula were found, which were not due to cross clamping. Sylvian fissure hematoma was found in two cases on CT scan. In two cases, there were no flows through the STA.

Subsequent follow-up was made by digital palpation and doppler routinely. Computed tomography angiography/ magnetic research angiography [MRA] were performed after 3 months, 9 months, and then at 12-month intervals. No DSA was done in the postoperative follow-up.

At the end of 12 months (69 cases were available for follow-up), all anastomoses were functioning on digital palpation and doppler examination. But CTA/MRA failed to show the anastomosis in 11 cases. All high flow anastomosis were patent on CTA/MRA at the end of 12 months after the operation.

A total of 100 bypasses were done in 83 patients, of which 43 were male and 40 were female. The age range was from 04 to 72 years old (average 32 years old). Eleven patients were lost to follow-up postoperatively after 3 months and they were not even available for telephone follow-up. The follow-up period was from 03 to 120 months (average 18.4 months).

Total number of EC-IC bypasses:100

- High flow bypasses: 08
- Ischemia/infarct (both with ICA occlusion): 02
- Giant ICA aneurysm

  □ Cavernous ICA: 02
  □ Supraclinoidal ICA: 04
- Low flow STA-MCA bypass:
- Single barrel:

  □ Replacement:
- Ischemia/infarct:17
- MCA dissection: 04
- CCF-04:

  ■ Protective/Insurance:

- With high flow bypass: 08
- With aneurysm:

♦ With proximal stenosis: 08
♦ Protective: 16

- Skullbase tumor: 05
- Moya moya: 21
- Double barrel: 08
- MCA stenosis: 05
- Moya moya: 03
- Double barrel (+A3-A3 bypass) [Figure 9a-9f]: 01

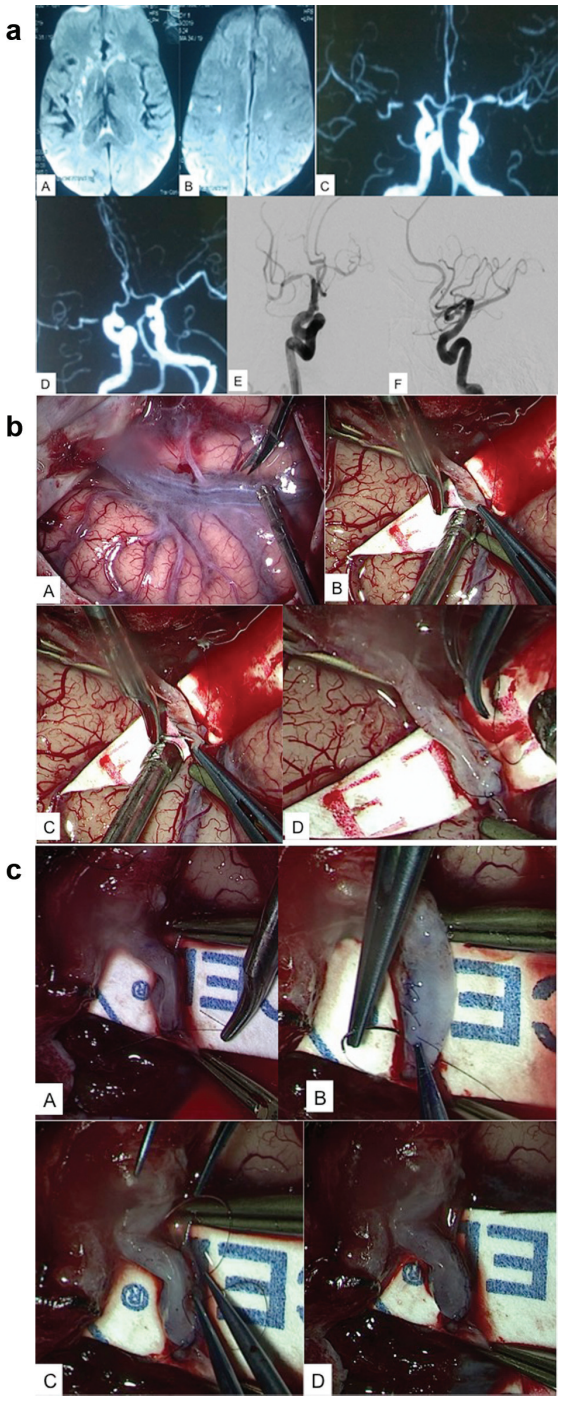

Fig. 9 (a) (**A and B**) MRI of the brain DW images showing the right MCA territory and left ACA ischemia and patchy infarcts. (**C and D**) CTA of the brain showing right M1 stenosis (severe) and left A2 stenosis. (**E and F**) Cerebral DSA showing right M1 stenosis (severe) and left A2 stenosis. (**b**): (**A, B, C, and D**) Preoperative pictures of anastomosis for temporal STA-MCA bypass as a part of double barrel bypass. (**c**) (**A, B, C, and D**) Preoperative pictures of anastomosis for frontal STA-MCA bypass as a part of double barrel bypass. (**d**): (**A, B, C, and D**) Preoperative sequential picture of A3-A3 bypass in the frontal interhemispheric fissure; (**A and B**) Durotomy and interhemispheric dissection. (**C and D**) Identification and preparation of left and right A3 after removal of a small part of the falx. (**e**): (**A, B, C, and D**) Preoperative sequential pictures of A3-A3 side to side anastomosis. (**f**) (**A and B**) Postoperative CTA of the brain showing patent double barrel STA-MCA bypass and A3-A3 bypass (yellow circles indicate anastomosis). Privacy Policy | Disclaimer | Site Map.

Indication of Bypass (83 Cases)

1. Arterial stenosis/occlusion/dissection causing cerebral ischemia:
   - MCA stenosis/occlusion: 05
   - MCA dissection: 04
   - ICA occlusion: 19

   – ICA dissection: 04
   – Thrombotic occlusion of ICA with giant aneurysm: 02
   – Sinonasal infection-induced ICA occlusion: 02
   – Atherosclerotic: 11
2. Intracranial aneurysms: 30
3. Moyamoya disease: 21
   – Ischemia/infarction: 16
   – Haemorrhage: 05
4. Direct CCF- 04 (►**Tables 1** and **2**)

The most common presentation was hemiparesis and dysphasia in the ischemic group with history of transient ischemic attack (H/O TIA). Features of SAH (that is, headache, vomiting and loss of consciousness [LOC]) were the presenting symptoms of the intracranial aneurysm group. Eight cases of intracranial aneurysm had stenosis just proximal to the aneurysm. Middle cerebral stenosis cases presented with TIA and ischemic stroke. In MCA dissection, both ischemic clinical picture and SAH picture were present. All CCF cases were direct and had H/O head injury. Most cases of moyamoya disease presented with symptoms of ischemia. Infection was the etiology of thrombosis in cavernous ICA, in two cases. In one case, orbital cellulitis spread in the CS and caused thrombosis of the ICA (with aneurysm). In the other cases, panrhinosinusitis (by MRSA) spread to both cavernous sinuses (CSs) and both ICAs were occluded. In one interesting case, a giant partially thrombosed ICA bifurcation aneurysm thrombosed totally with distal ICA, A1 and M1. Acute thrombosis of the ICA with aneurysm in CS occurred in 4 cases, one of whom was a 3-month pregnant woman. In one case, there was intractable TIA with impending major stroke in which the whole brain was supplied only by the right-sided ICA, and the patient developed posterior inferior cerebellar artery (PICA) infarct 12 hours before the ‘scheduled urgent’

Table 1 Clinical Presentation of the patients ($n = 83$)

Features	Number	Percentage
Features of SAH (Headache, vomiting, LOC)	33	39.8%
Hemiparesis	36	43.4%
Ophthalmoplegia	06	7.2%
Dysphasia	18	21.7%
Visual disturbance	06	7.2%
Seizure	02	2.4%
H/O TIA	31	37.3%
Red eye and proptosis	04	4.8%

Abbreviations: LOC, loss of consciousness, SAH, subarachnoid hemorrhage; H/O TIA, history of transient ischemic attack.

Table 2 Review of death cases (03) in EC-IC bypass

No.	Age, gender, and diagnosis	Preoperative	Postoperative CT	Time of death
1	31, M, Moyamoya disease	Smoothly functioning bypass	Distant parenchymal hemorrhage	8th POD
2	36, M, giant supraclinoidal aneurysm with atherosclerosis	Preoperative thrombosis of STA-MCA bypass with occlusion of ICA lumen after multiple clip reconstruction	LSA and total MCA infarct	1st POD
3	65, F, giant supraclinoidal aneurysm with atherosclerosis	Preoperative tear of aneurysm neck near bifurcation.	LSA and total MCA infarct	1st POD

Abbreviations: CT, computed tomography; F, female; LSA, lanticulo striate artery; M, male; MCA, middle cerebral artery; STA-MCA, superficial temporal artery-middle cerebral artery bypass; POD, postoperative day.

revascularization operation; high flow EC-IC bypass was done in this case. Postoperatively, the patient developed 'behavioural, intellectual, and psychogenic' symptoms that recovered slowly. The average ischemic time was 28 minutes (range: 20–60 minutes). There was no clamp-related infarction. In one case, the patient developed postoperative insulofrontal infarct unrelated to temporary clamping. One preoperative ambulant patient deteriorated neurologically in the postoperative period and developed hemiplegia. Six months after the operation, she was ambulant with support. In this case, the cause seemed to be hyperperfusion.

Headache resolved in all cases. Transient ischemic attack and seizures were also gone postoperatively. Ophthalmoplegia recovered in all cases in which it was present, except in one case, in which abducent nerve palsy persisted. In one girl, mono-ocular complete blindness developed postoperatively due to ophthalmic artery occlusion, in which high flow bypass with ICA occlusion were performed. Red eye and proptosis were cured in CCF cases. Motor and sensory dysphasia improved in all cases in which it was present, except for one case in which preoperative global aphasia converted to sensory aphasia in the postoperative period.

Three patients died in the postoperative period. The rest of the patients improved postoperatively. All patients were ambulant with static neurostatus without new stroke/TIA until the last follow-up. All bypasses were patent until the last follow-up (clinical, doppler/imaging).

Discussion

As microneurosurgery advanced tremendously, indications for cerebral revascularization expanded to include multi-infarct dementia, acute ischemic stroke, MCA stenosis, MCA dissection, and ischemic retinopathy. To recommend the indications and results of EC-IC bypass, the International Cooperative Study of Extracranial/Intracranial Arterial Anastomosis (EC/IC bypass study) was performed from 1977 to 1985.[18] However, the data of the study showed that EC-IC anastomosis was not superior in preventing stroke in patients with atherosclerotic arteriopathy of the ICA and MCA compared with best medical therapy.[18] The study identified two important subgroups that seemed to do particularly poorly: cases with severe MCA stenosis and those with persistence of TIA or of ischemic symptoms in known ICA occlusion.[19] The subgroups subsequently identified to potentially benefit from surgical cerebral revascularization were those in which hemodynamic changes play a primary role in the precipitation of ischemic stroke. Since then, recent technological advances that were not available at the time of the EC/IC bypass study have made it possible to better identify this potential subgroup of patients.[20–23] One of these parameters (the oxygen extraction fraction [OEF] as determined by positron emission tomography [PET]) identifies cases with hemodynamic susceptibility, which may then benefit from an EC-IC bypass procedure.[24–27]

Currently, EC-IC bypass is either done for cerebral blood flow (CBF) augmentation or replacement. Examples of the first one would be symptomatic cases with ICA occlusion and proven hemodynamic vulnerability or moyamoya disease. Extracranial to intracranial bypass surgery for CBF replacement is most commonly done in complex aneurysm management, such as when an aneurysm is trapped, or in skull base neoplasm surgery associated with arterial sacrifice or injury.[1,2,22,28]

In the following conditions, EC-IC bypass is usually considered:

- an aneurysm or atherosclerotic plaque that is not treatable endovascularly or by other means
- failure of medication to control TIA symptoms or stroke
- imaging tests (angiogram, CTA, MRA) that show arterial stenosis or occlusion
- cerebral blood flow (CBF) studies (CT perfusion, PET, single photon emission computed tomography [SPECT]) that show arterial stenosis is causing insufficient blood flow to the brain

Cerebral bypass may be helpful in restoring blood flow and reducing the risk of stroke in conditions such as:

- Moyamoya disease: a narrowing of the internal carotid arteries at the base of the brain that can cause multiple strokes or hemorrhages. To compensate for the narrowing arteries, the brain creates collateral blood vessels in an attempt to deliver oxygen-rich blood to deprived areas of

the brain. A bypass can restore blood flow to the brain and prevent future strokes.
- Aneurysm: a bulge or ballooning of an artery wall. Some giant, fusiform, or dissecting aneurysms cannot be treated with surgical clipping or endovascular coiling. In such cases, the parent artery must be sacrificed, and the blood flow bypassed for the aneurysm to be effectively treated.
- Skull base tumor: a tumor can grow where the major vessels enter the skull and surround or invade the artery. Removing the tumor may require sacrificing the encased artery and bypassing the blood flow.
- Carotid artery stenosis: a narrowing or blockage of the carotid artery in the neck caused by atherosclerotic plaque deposits in the vessel wall.
- Intracranial arterial stenosis: a narrowing or blockage of an artery inside the skull that supplies blood to specific areas within the brain.[1,2,22,28]

Several techniques for the creation of artificial CBF conduits are available in addition to the arterial graft of the STA-MCA anastomosis. A STA-MCA bypass has a luminal flow patency rate > 95%.[29] Since the first STA-MCA procedure was described by Yasargil,[11,16] many variations have been published, but STA-MCA bypass remains the main workhorse of a neurovascular surgeon. Many of these variations have been developed in dealing with complex intracranial aneurysms and skull base neoplasms. These variations include anastomoses between the bilateral anterior cerebral arteries, the occipital artery to the posterior inferior cerebellar artery (PICA), and the anterior inferior cerebellar artery (AICA). Others include PICA to PICA, vertebral artery (VA) to PICA, STA to SCA or to the posterior cerebral artery (PCA), subclavian artery to PCA, PCA to SCA, and even a tandem occipital artery to AICA and PICA anastomoses.[10]

Other common EC-IC bypasses for cerebral revascularization methods include venous interposition grafts, such as the great saphenous vein, free arterial conduits including the radial artery, and artificial grafts (with polytetrafluoroethylene ePTFE tubes).[30,31]

The great saphenous vein graft has been used in bypasses for giant intracranial aneurysms, skull base neoplasms requiring ICA sacrifice or involving the ICA, or VA occlusive disease.[32,33] Internal carotid artery bypasses include the cervical-supraclinoid ICA, the petrous-supraclinoid ICA, and the cervical–petrous ICA.[34] The radial artery bypass graft has been shown to have long-term patency when used for the management of giant aneurysms of the ICA.[35]

Intracranial-intracranial (IC-IC) bypasses are occasionally necessary (►**Figure 9d** and **9e**). A short interposition graft such as the the saphenous vein of the patient can be used in IC-IC bypasses. Donor vessels in IC-IC bypasses are usually from the ICA, M_1 or A_1 arteries, and the recipients may include the ICA, M1–3, A1–2, P1–2, the basilar artery, and the superior cerebellar artery (SCA).[1]

Very useful and important advancements in monitoring intraoperative blood flow have also been developed. The use of micro-Doppler, and of transit time flowmetry, such as the Charbel microflow probes (Transonic), and indocyanine green (ICG) video angiography have all had a positive impact on cerebral revascularization by EC-IC bypass surgery by ensuring anastomotic and graft patency.[1]

Complications in STA-MCA bypass are limited and include early postoperative TIA, delayed stroke, development of a pseudoaneurysm, and wound dehiscence. High-flow bypass grafts are more prone to develop complications than low-flow STA-MCA bypass. Radial artery grafts may suffer vasospasm or intimal hyperplasia and, eventually, occlude. Proatherogenic changes can occur in SV grafts, which eventually leads to occlusion. After parent vessel occlusion, thromboembolic complications are common in high flow bypass, mainly due to the change in intracranial hemodynamics. Preoperative antiplatelet medications, as well as intraoperative anticoagulation, can prevent these thromboembolic events. In patients without vascular reserve, prolonged temporary occlusion times can lead to territory infarcts without changes in the neuromonitoring. So, it is important to minimize occlusion times in these patients. In longstanding perfusion deficiency, reperfusion hemorrhage may be problematic after revascularization, although its incidence is low. Other complications involve the site of graft harvests, such as infection, ischemic hand, or hematoma.[10]

Cerebral revascularization by EC-IC bypass has evolved from the culmination of several technologies, from the early dawn of vascular surgical techniques in animals to the development and utilization of the surgical microscope, of bipolar coagulation, and of suitable suture material. Major asking regarding the indications and benefits of cerebral revascularization are being addressed. Fascination in further development of this matter to make it safer for the patients remains strong and high. Advanced research into perioperative blood flow assessment will play a key role in determining the positive result of cerebral revascularization. It is logical to hope that, with better understanding of the pathophysiology of cerebral ischemia and better patient selection, cerebral revascularization by EC-IC bypass will remain an indispensable tool in microneurosurgery.[1]

Conclusion

Our initial experiences of 100 cases of EC-IC bypass showed that, even in inexperienced hands, the mortality and morbidity in properly indicated cases were low and that the results were impressive according to the pathology and the aim of the bypass. Lessons learned from these experiences can be very helpful for new and beginner bypass neurosurgeons.

Conflict of Interests

The authors have no conflict of interests to declare.

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Most Frequent Compressive Limb Neuropathies: A Literature Review

Neuropatias compressivas mais frequentes que acometem os membros: Revisão da literatura

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Abstract

Peripheral nerve injuries vary in length and severity, and they can occur secondary to trauma, compression and ischemia, leading to both motor and sensory neurological deficits. Nerve compression can occur in both the upper and lower limbs. These injuries can affect the quality of life, including the total or partial loss of the individual's productive capacity. The diagnostic methods are based on clinical criteria, but they may also include imaging and electroneurophysiological studies. A clinical examination using the Tinel and Phalen tests, for example, may suggest carpal tunnel syndrome. Complementary exams are used to confirm the diagnosis and rule out other possibilities, and the most used are electroneuromyography (ENMG), computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography (US). Depending on the type of injury, recovery may be spontaneous or may require conservative or surgical treatment.

Keywords
- entrapment neuropathy
- median nerve neuropathy
- ulnar neuropathy
- radial neuropathy
- meralgia paresthetica
- peroneal neuropathy

Resumo

As lesões nervosas periféricas variam em extensão e gravidade, as quais podem ocorrer secundárias a trauma, compressão e isquemia, e acarretam déficits neurológicos tanto motores quanto sensoriais. A compressão nervosa pode ocorrer nos membros superiores e inferiores. Estas lesões podem afetar a qualidade de vida, incluindo a perda total ou parcial da capacidade produtiva do indivíduo. Os métodos diagnósticos são baseados em critérios clínicos, mas também podem incluir métodos de imagem e estudos eletroneurofisiológicos. O exame clínico por meio dos testes de Tinel e de Phalen, por exemplo, pode sugerir síndrome do túnel do carpo. Os exames complementares servem para confirmar o diagnóstico e descartar outras possibilidades, sendo os mais utilizados a eletroneuromiografia (ENMG), a tomografia computadorizada (TC), a ressonância magnética (RM) e a ultrassonografia (US). De acordo com o tipo da lesão, a recuperação pode ser espontânea ou necessitar de tratamento conservador ou cirúrgico.

Palavras-chave
- neuropatia por aprisionamento
- neuropatia do nervo mediano
- neuropatia radial
- neuropatia ulnar
- meralgia parestésica
- neuropatia fibular

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Introduction

Peripheral nerve injuries vary in length and severity, and they can occur secondary to trauma, compression and ischemia, leading to both motor and sensory neurological deficits. These injuries can greatly affect the quality of life, including total or partial loss of individual's produtive capacity, which has important economic and social impacts for the population. Depending on the type of injury, recovery can be spontaneous, or conservative therapy or surgical intervention may be required.[1]

Peripheral nerve syndromes can be related to a variety of symptoms, such as: motor weakness, sensory disorders, imbalance, and pain. Nerve compression can occur in both upper and lower limbs.[1]

Among compression neuropathies in the upper limb, carpal tunnel syndrome, characterized by compression of the median nerve, has a higher prevalence in the population.[2]

Other examples are the compressive syndromes of the radial nerve, which present themselves in different ways: they can be purely sensory, motor, or mixed. This group encompasses several syndromes, such as radial tunnel syndrome, Wartenberg syndrome, and posterior interosseous nerve syndrome. As these syndromes affect different compression sites, they may present with different clinical features and have diagnostic intersection with other pathological conditions, such as lateral elbow epicondylitis. The most common compression syndromes are distal to the elbow.[3]

The methods to diagnose these lesions are based on clinical criteria, but they can also include imaging methods and electroneurophysiological studies.[2]

The diagnostic methods used for compressive neuropathies range from clinical examination and anamnesis through semiological tests, such as the Tinel test (percussion over the region of the median nerve, which results in dysesthesia) and the Phalen test (the symptoms are triggered by complete palmar flexion of the wrists for 30 to 60 seconds, causing a characteristic pain) performed in carpal tunnel syndrome. In addition, with the advancement in radiological methods, complementary exams are used to confirm the diagnosis and rule out other possibilities, using electroneuromyography (ENMG), computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography (US).[4]

The present study aims to analyze the factors related to the main compressive neuropathies though a review of articles in databases.

Material And Methods

The present study was performed through bibliographic research cinducted between February and March 2020. The literature review was performed in the PubMed, UpToDate, SciELO and MEDLINE databses. We used the following keywords: *entrapment neuropathy*, *ulnar neuropathy*, *radial neuropathy*, *median neuropathy*, *meralgia paresthetica*, and *peroneal neuropathy*.

The filters were: year of publication, type of article, and text availability. The inclusion criteria were as follows: papers published since 2015, case reports, simple literature reviews, randomized controlled trials, clinical trials, systematic reviews with or without meta-analysis, texts available in full, and adequacy to the topic of the present study. And the exclusion criteria were: articles without the full text available online, animal studies, works published before 2015, and those not available written in Portuguese, English, or Spanish.

A total of 30 articles were selected, which addressed the most prevalent compressive neuropathies of the limbs with involvement of the median, ulnar, radial, fibular and femoral nerves. We excluced the articles that did not meet the inclusion criteria.

Results

In total, 388 potentially-eligible articles were found on the PubMed, UpToDate, SciELO and MEDLINE databases, 30 of which were selected because they addressed the topic of the present review in a comprehensive manner, with pathophysiological description, clinical presentation, diagnostic elements, treatment of the peripheral neuropathies herein discussed, and availability of the full text in English, Spanish and Portuguese. There were 25 articles written in English, and 5, in Portuguese.

Discussion

Pathophysiology

The compression of a nerve results in microvascular lesions, destruction of the myelin, and, eventually, axonal degeneration.[5] This sequence of neural changes will occur depending on the intensity and duration of the compression. Slight compressions can obstruct the venous flow, causing edema, while severe compressions result in ischemia. Persistent compressions result in chronic inflammation and fibrosis, which contributes to mechanical compression.

The histopathological changes caused by chronic nerve compression (►**Fig. 1**) begin with the rupture of the blood-nerve barrier, followed by endoneural edema and perineural thickening. The increase in endoneural pressure will result in changes in microneural circulation and make the nerve susceptible to dynamic ischemia. With increased compression, there will be localized and eventually diffuse demyelination, which decreases the axonal conduction velocity and may cause partial or total blocks of the action potential. The combination of these factors in the long term causes Wallerian axonal degeneration.[6]

Neural changes may not occur uniformly across the nerve and may vary depending on the distribution of compressive forces across the nerve. Superficial fascicles will be affected sooner and it can result in symptoms within a single nerve distribution. For example, in the initial stages of carpal tunnel syndrome, the superficial fascicles of the long finger and ring finger are usually affected before the fascicles of the thumb and the radial side of the index finger.[5]

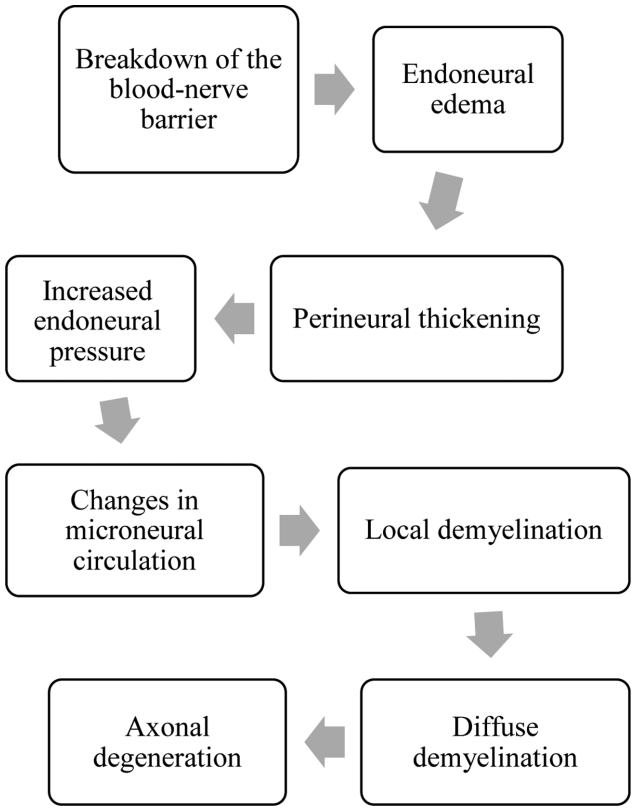

Fig. 1 Histopathological changes in compressive neuropathies.

Electrophysiological studies play an important role in the diagnosis of compressive neuropathies.[6] The initial stage of nerve compression is associated with dynamic ischemic events. Thus, the results of electrodiagnostic studies are generally normal. As the compression progresses, demyelination occurs, and the conduction speed decreases at the site of the compression. Axonal loss does not usually occur until advanced stages of the neuropathy.[7]

Although electrophysiological studies remain the gold standard to confirm compressive neuropathies, neuromuscular ultrasound has gained importance as a tool to assist in their diagnosis. The nerves are usually enlarged at or near the compression site. High-resolution ultrasound confirms the diagnosis by demonstrating edema of the nerve proximal to the compression area, and establishes the presence of dynamic compression, nerve subluxation, or extrinsic compression.[7]

The clinical features differ according to the degree of nerve compression, and the sensory and motor functions may be affected to different degrees, as shown in ►**Table 1**.

Compressive Neuropathies of the Upper Limbs

Median Nerve

Anatomy and Entrapment Sites

The most common and well-known compressive neuropathy is carpal tunnel syndrome (CTS), which results from the compression of the median nerve within the wrist. However, other less common areas of entrapment should be discussed and acknowledged in the differential diagnosis of compressions of the median nerve. Differential diagnosis with radiculopathies and upper-limb plexopathies should be considered.[8]

The median nerve is formed from the medial and lateral divisions of the brachial plexus, receiving contributions from nerve roots from C5 to T1. It follows the path of the brachial artery in the arm medially, without emitting branches. In the proximal forearm, it innervates the pronator teres, the radial flexor of the carpus, and the superficial flexor of the fingers. In this region, a structure that is present in some individuals and that constitutes a rare cause of compression of the median nerve is the Struthers ligament, which lies between the supracondylar process and the medial epicondyle of the humerus.[9]

In the antecubital region, the nerve travels below the bicipital aponeurosis to the elbow and goes between the heads of the pronator teres muscle, which in itself can be a rarer site of compression. Approximately 4 cm before the medial epicondyle, the main trunk of the median nerve gives rise to the anterior interosseous nerve, which innervates the long flexor of the thumb, the deep flexor of the second and third digits, and the square pronator, and is involved in anterior interosseous syndrome.[10]

The median nerve enters the hand when it passes through the carpal tunnel, a restricted anatomical space located in the middle third of the wrist that is formed by the trapezium, trapezoid, capitate, and bamate bones and the transverse carpal ligament (flexor retinaculum). In the distal part of the carpal tunnel, the median nerve divides into motor and sensory branches, and it innervates the pronator muscles of the forearm, as well as most of the flexors of the fingers and wrist in the forearm.[9]

Carpal Tunnel Syndrome

The most common compressive neuropathy of the upper extremity is CTS, with a prevalence of 3% to 5% in the general population, and of 6% among women aged > 40 years. It occurs about five times more in women, with two peaks

Table 1 Clinical degrees of compressive neuropathy

	Mild	Moderate	Severe
Sensitive	Intermittent paresthesia	Persistent paresthesia, numbness, subjective sensory deficit	Objective sensory deficit
Motor	Without changes	Incoordination and subjective weakness	Weakness, paralysis, atrophy

Source: Lee and Lim (2019).[6]

observed in the sixth and 8th decades of life. The risk factors for CTS include obesity, the female gender, coexisting conditions (such as, diabetes, pregnancy, rheumatoid arthritis, hypothyroidism, connective tissue diseases), genetic predisposition, and repetitive use of the wrist.[11]

Carpal tunnel syndrome occurs due to a decrease in the size of the carpal tunnel, leading to compression of the median nerve when the tissues surrounding the flexor tendons in the wrist (synovial sheaths) become inflamed, causing edema.[12] The dimensions of the canal may be compromised by arthritis, tendinopathy, local edema, and the accumulation of substances such as amyloid. Repetitive movements and vibrating tools increase the likelihood of developing carpal tunnel syndrome.[13]

However, other less common areas of entrapment should be mentioned and considered in the differential diagnosis of compressions of the median nerve. Differential diagnosis with radiculopathies and plexopathies of the upper limb should be considered. For this, in addition to the differences in the sensory and motor involvement of each neuropathy, complementary exams can be performed, especially electroneuromyography, which is the gold standard for any compressive mononeuropathy.[8]

Patients affected with this mononeuropathy have numbness, tingling, or other paresthesias that affect the first to the third fingers and the lateral region of the fourth finger, exacerbated by wrist flexion. Muscle weakness occurs in the most advanced cases, manifested by weakness in opposition and thumb abduction accompanied by atrophy of the thenar region.[14]

The electrodiagnostic evaluation proved to be useful to identify lesions of the median nerve in the wrist and to differentiate those from lesions of the proximal median nerve, brachial plexus, and roots of the cervical nerve. Although the results of electrodiagnostic tests are considered the gold standard for the diagnosis of CTS by some authors,[13] the test is not 100% sensitive.

The treatment of CTS consists of conservative therapy with a wrist splint, especially at night or during activities that exacerbate the symptoms. In case of failure, injecting steroids into the wrist is usually helpful in relieving symptoms (at least temporarily, in most cases). Surgical release of the flexor retinaculum is indicated, with excellent results, for patients with persistent symptoms who do not respond to conservative therapy.[15] The flexor retinaculum in the carpal tunnel consists of three segments (►**Fig. 2**).[31]

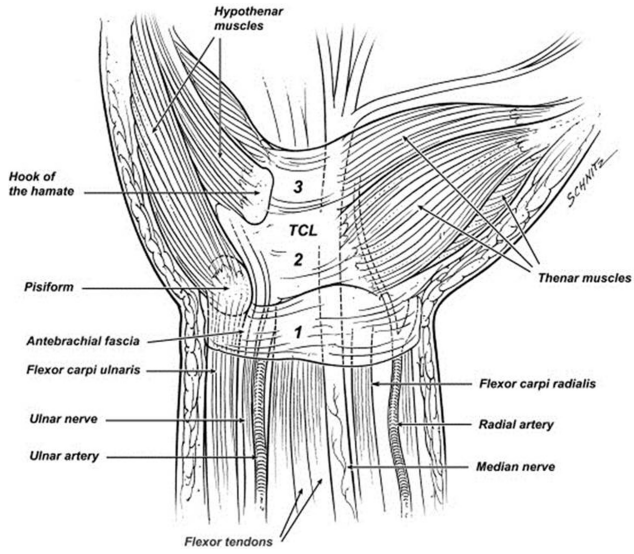

Fig. 2 The flexor retinaculum in the carpal tunnel consists of three segments: The proximal segment (**1**) is inseparable from the antebrachial fascia, whereas the transverse carpal ligament (TCL) makes up the second portion (**2**). The distal segment (**3**) consists of the aponeurosis between the thenar and hypothenar muscles. Source: Koo J, Szabo R (2004).[31]

Proximal Median Nerve Neuropathies

Injuries to the median nerve at or above the elbow are uncommon. The causes include fracture of the humerus, and compression in a supracondylar region, in the Struthers ligament, or within the pronator teres muscle, as well as iatrogenic causes, such as brachial artery catheterization or creation of an arteriovenous fistula for hemodialysis. The pattern of electrodiagnostic abnormalities expected in lesions near or close to the elbow are reduced amplitudes of sensory and motor nerve conduction responses, normal distal latencies, and possibly a slight deceleration of the forearm conduction speed.[13]

Anterior Interosseous Nerve (AIN) Syndrome

Lesions on this branch of the median nerve are uncommon. The most common clinical presentation is unilateral weakness of the flexor digitorum prufundus muscles (digits I and II), with preservation of the thumb abduction and opposition. Flexion of the wrist tends to be spared, but there may be demonstrable weakness of the pronator quadratus muscle.[16] The common sites of compression in AIN syndrome are shown in ►**Fig. 3**.[31]

The expected electrodiagnostic pattern includes median nerve normal motor and sensory conduction studies. In electromyography, it is expected to be abnormal in the flexor pollicis longus, pronator quadratus, and median part of the flexor digitorum profundus muscles. The thenar muscles remain normal, as well as the pronator teres and the flexor

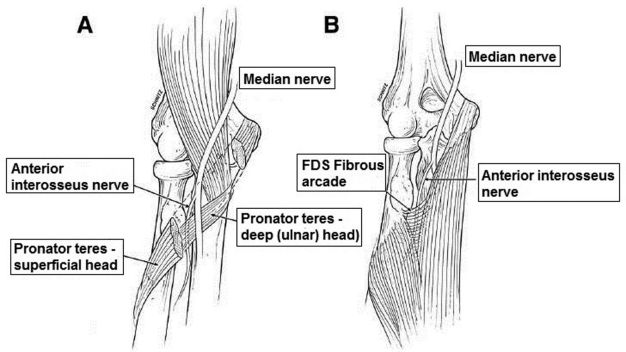

Fig. 3 Common sites of compression in anterior interosseous nerve (AIN) syndrome. (**A**) Deep head of the pronator. (**B**) Fibrous arcade at the proximal margin of the flexor digitorum superficialis (FDS) to the middle finger. Source: Koo and Szabo (2004).[31]

carpi radialis. The expected pattern of results includes reduced amplitude of motor response and slight elongation of latency from the elbow to the muscle.[16]

Ulnar Nerve

Anatomy and Entrapment Sites

Due to anatomical features, the ulnar nerve is more vulnerable to compression in the elbow and wrist. The cubital tunnel in the elbow is the most common site of entrapment of the ulnar nerve, and, less commonly, the Guyon canal in the wrist.[17] The common sites of compression of the ulnar nerve are shown in ►**Fig. 4**.[32]

The ulnar nerve is formed from the lower trunk and medial fascicle of the brachial plexus, receiving contributions from the nerve roots of C8 and T1. It continues medially in the arm, crosses the medial intermuscular septum, and passes through the brachial fascia and fibers of the medial head of the biceps that form the arcade of Struthers.

At the level of the elbow, the ulnar nerve crosses superficially between the medial epicondyle and olecranon, a region called the groove for the ulnar nerve. The ulnar nerve enters the cubital tunnel distally at the elbow. The tunnel is formed by the Osborne ligament (a ligament between the two heads of the flexor carpi ulnaris muscle), the joint capsule and the collateral ligament of the elbow, the medial epicondyle, the olecranon, the medial collateral ligament, and the fascia between the two heads of the ulnar flexor carpi muscle.[17]

In the region of the elbow, the main sites that may compress the ulnar nerve are the arcade of Struthers, the medial intermuscular septum, the medial epicondyle, the cubital tunnel through the Osborne ligament, and the fascia of the flexor-pronator muscle group of the forearm.[13]

In the forearm, the ulnar nerve is located medially and above to the flexor digitorum profundus, and deep into the flexor carpi ulnaris, providing branches to innervate these muscles along its course. The ulnar nerve is lateral to the flexor carpi ulnaris muscle and medial to the ulnar artery.

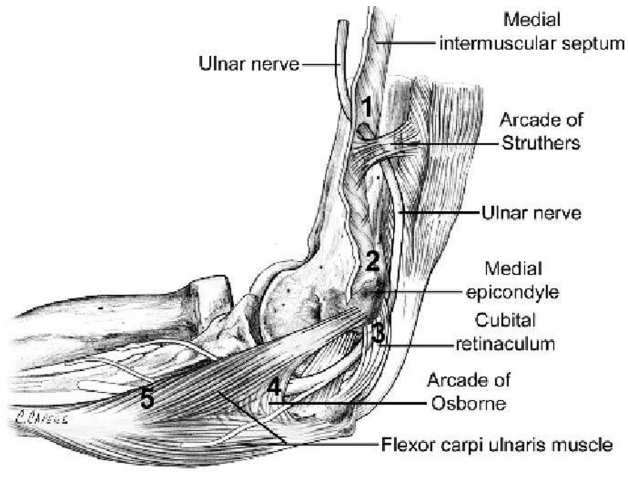

Fig. 4 Common sites of compression of the ulnar nerve: medial intermuscular septum, arcade of Struthers, medial epicondyle, cubital tunnel, arcade of Osborne and flexor-pronator muscle group. Source: Terry and Zeigler (2002).[32]

At the level of the wrist, the ulnar nerve and artery enter the Guyon canal, which is fibro-osseus canal formed by the transverse ligament of carpus, hypothenar muscles, carpal volar ligament, pisiform, pisohamate ligaments and the hook of the hamate.[17,18]

The ulnar nerve originates two branches, one dorsal (sensitive) and one palmar (mixed) branch. The palmar branch enters the Guyon canal with the ulnar artery and originates a sensory branch (which goes to the little finger and the ulnar side of the ringer finger) and a motor branch (which innervates the intrinsic muscles of the hand).

Ulnar Neuropathy in the Elbow

The elbow is the second extremity of the upper limb most affected by compressive neuropathies, with several places of entrapment. One of these sites, the cubital tunnel, is formed by the ulna, the collateral ligament, and the aponeurosis of the flexor carpi ulnar muscle joint. The ulnar nerve is also susceptible to compression immediately proximal to the medial epicondyle. The impact mechanism is still undefined. There is some evidence to suggest that elbow subluxation may decrease the chance of developing ulnar neuropathy.[13]

Patients affected with this mononeuropathy present numbness, tingling, and other paresthesias that affect the territory of the ulnar nerve (fourth and fifth fingers), and that usually worsen at night. In severe cases, weakness and atrophy of the intrinsic musculature of the hand may be evident. The Duchenne sign (ulnar claw) due to weakness of the third and fourth lumbrical muscles, and the Wartenberg sign (patient with the fifth finger abducted when at rest) due to weakness of the third palmar interosseous muscle, may be present. The Froment sign is evidenced by the flexion of the thumb to compensate for the weakness of the adduction during the grip of an object.[17]

An injury to the ulnar nerve in the elbow can be diagnosed by finding a deceleration in the conduction velocity of the elbow segment. According to the American Association of Neuromuscular and Electrodiagnositic Medicine (AANEM), the deceleration of the elbow segment speed to less than 50 m/s with the elbow at 90° of flexion is the first abnormality criterion.[19]

An ulnar lesion in the elbow can also be diagnosed by decelerating the speed of the elbow in relation to the forearm by 10 m/s. This is the second AANEM criterion for abnormality.[20]

Studies of ulnar sensory conduction can contribute to the location of the lesion. In C8-T1 radiculopathy, the ulnar sensory action potential is normal because the lesion is preganglionic. The ulnar sensory response of the fifth finger remains normal if the elbow injury is purely demyelinating, because the axons distal to the elbow remain intact. When axonal damage is present, the amplitude of the sensory nerve action potential (SNAP) is reduced or absent.[19]

Non-ulnar muscles of the C8 myotome (abductor pollicis brevis, extensor indicis proprius) should be tested to exclude C8 radiculopathy or lower trunk/brachial plexopathy of the medial cord.[13]

The conservative treatment is indicated for patients with mild to moderate ulnar neuropathy in the elbow, characterized by intermittent or persistent sensory loss and weakness, and without structural damage.[21]

The surgical treatment is recommended for patients with convincing clinical and electrophysiological evidence of moderate to severe ulnar neuropathy in the elbow caused by trauma, structural abnormality, or nerve compression. The surgical treatment is chosen for those who show moderate to severe progressive symptoms and signs lasting six months, despite conservative measures.[21]

The two main categories of surgery currently performed for ulnar neuropathy in the elbow are in situ decompression of the ulnar nerve and ulnar transposition.[21]

Simple decompression for ulnar neuropathy in the elbow is usually performed by cutting the aponeurosis of the flexor carpi ulnaris (humeroulnar arcade) to decompress the ulnar nerve. Transposition of the ulnar nerve can be achieved by first cutting the humeroulnar arcade, and then mobilizing the ulnar nerve from the retrocondylar sulcus to a more anterior position.[22]

Ulnar Neuropathy in the Distal Forearm and Hand

Ulnar nerve injury in the distal forearm and hand is uncommon. Proximal to the wrist, the cutaneous palmar and cutaneous ulnar dorsal nerves branch off. When the nerve enters the hand through the Guyon Canal, it divides into deep and superficial terminal branches. The deep branch innervates all the muscles of the ulnar hand, except the palmaris brevis muscle. The superficial branch innervates the palmaris brevis muscle and then provides sensory innervation to the palmar aspects of the fourth and fifth fingers. Lesions can involve any of these branches individually or together.[13]

The nerve may be trapped or traumatized in the Guyon canal when it enters the hand. Ganglion cysts are a common cause. The most common clinical pattern is weakness sparing the hypothenar muscles, but involving all other muscles supplied by the ulnar nerve. An injury that produces only sensory deficits is rare.[13]

The electrodiagnostic assessment should include ulnar motor conduction to the hypothenar and first dorsal interosseous muscles, and sensory conduction to the fingers. The dorsal ulnar skin branch that appears in the region of the distal forearms should be tested if the sensory study of the fingers is abnormal. The results include prolongation of the distal motor latency. The amplitude of the Compound Muscle Action Potential (CMAP) test will be reduced if the axon is lost.[13]

Conduction velocities in the elbow and forearm segments should be normal. Sensory studies of the fourth or fifth fingers may show prolonged distal latency and reduced amplitude of response, if the superficial terminal branch is involved. The dorsal ulnar skin study should be normal. Electromyography will show abnormalities in the hypothenar muscles, the first dorsal interosseous or both, depending on the injury site. The forearm muscles innervated by the ulnar nerve must be normal.[13]

Conservative treatment is suggested as an initial treatment for patients with mild to moderate ulnar neuropathy in the wrist, characterized by intermittent or persistent loss and sensory weakness, and without structural damage. In addition, conservative treatment is recommended as an initial treatment for patients with moderate to severe but stable ulnar neuropathy, lasting less than six months.[22] For the less common condition of ulnar neuropathy in the wrist, surgery consists of decompression of the ulnar tunnel.[22]

Radial Nerve

The radial nerve is rarely affected by chronic compressions, but it is a common target for acute compressions. The most common etiology of radial neuropathies is trauma usually related to fracture of the humerus. Nerve entrapment usually occurs in the groove for the radial nerve in the humerus.[9] The common sites of compression of the radial nerve are sown in ►**Fig. 5**.[33]

The radial nerve receives innervation from C5 to T1 through the posterior divisions of the three trunks of the brachial plexus to form the posterior fascicle, which then gives rise to the subscapular, axillary and radial nerves. In the arm, the radial nerve emits three branches: the posterior cutaneous nerve, the lower lateral cutaneous nerve, and the posterior cutaneous nerve of the forearm. Then, it goes along with the brachial artery deeply between the long head of the triceps and the humerus, and through the groove of the radial nerve. At the level of the elbow, the nerve then forks into two terminal branches, a superficial sensitive and a deep motor branch, called the posterior interosseous nerve.[8]

The posterior interosseous nerve passes through the arcade of Fröhse, which is formed by the fibrous arch that arises from the superficial head of the supinator muscle at its connection to the lateral epicondyle. It innervates the muscles responsible for supination of the forearm, wrist extension, finger extension, and thumb extension. The superficial sensitive branch is responsible for the cutaneous innervation of the dorsolateral region of the hand.[23]

Radial Neuropathy in the Arm (Saturday Night Paralysis)

Compression of the radial nerve is often described at the Arcade of Fröhse, but it can occur in the arm pit, in the spiral groove of the humerus. The entrapment of the radial nerve at the level of the radial groove of the humerus is the most common site. It can occur due to prolonged immobilization or direct compression of the nerve on the humeral bone (Saturday night paralysis). In this syndrome, the patient presses the middle third of the arm against a surface (for exemple, arm outstretched against crutches or back of a chair) mainly during sleep, intoxication or sedation.[13]

This part of the nerve can also be traumatized by humeral fractures, gunshot wounds, and intramuscular injections. Weakness of the wrist and finger extension occurs along with a sensation of disturbance on the dorsolateral aspect of the hand. Partial elbow flexion weakness may also be present due to brachioradial involvement. Elbow extension generally remains normal because the branches of the triceps leave the main proximal nerve trunk at the level of the humerus.[13]

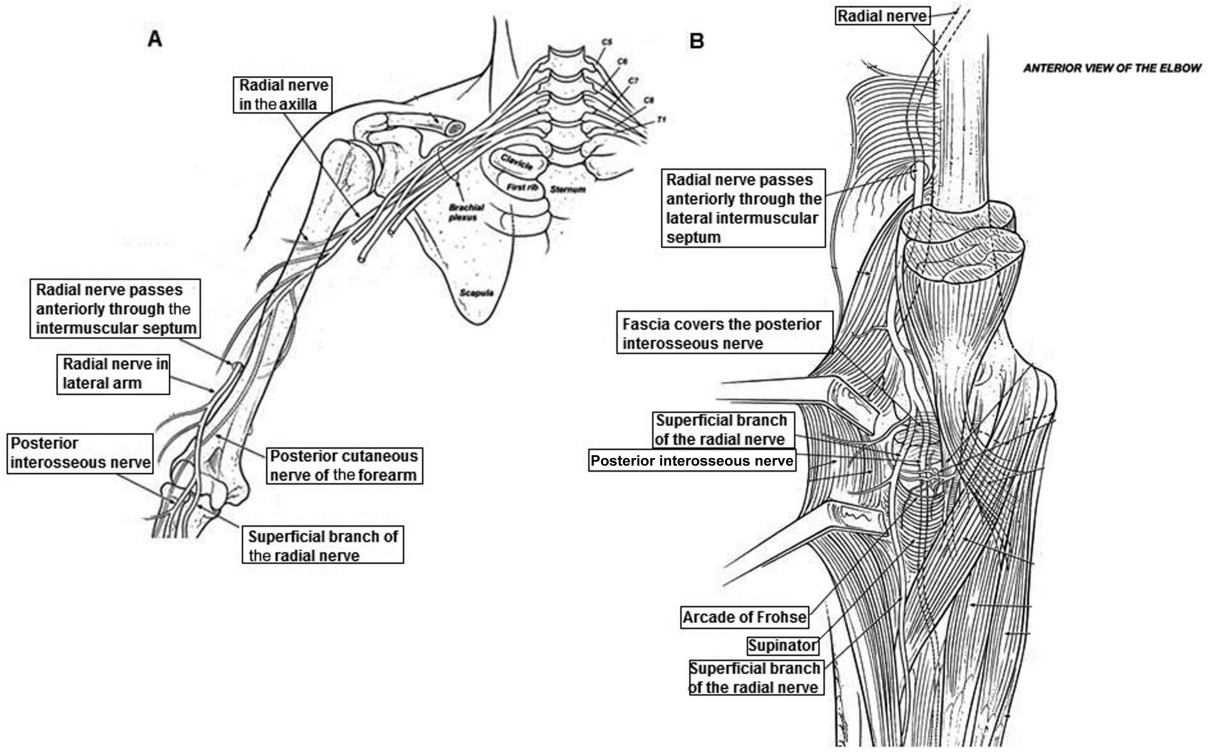

Fig. 5 Common sites of compression of the radial nerve: (**A**) axilla, groove for the radial nerve in the humerus. (**B**) Posterior interosseus nerve at the arcade of Fhronse. Source: Markiewitz and Merryman (2005).[33]

The results of radial conduction studies by electromyography can help locate the lesion site and also assist in the design of local demyelinating components versus axonal components. The sensory response of the superficial radial nerve remains normal if demyelination is the predominant pathology in lesions above the nerve bifurcation in the sensitive and motor branches of the elbow. A low amplitude or absent response indicates loss of the axon.[24]

The triceps muscles are spared when the lesion is below the humerus.[24]

Conservative treatment is usually the rule for patients with a single compression injury to the radial nerve, and its most important features are physical therapy, wrist splint (to maintain function), and pain control. The prognosis for full recovery is generally good.[7]

Posterior Interosseous Syndrome

Posterior interosseous syndrome is a pure motor neuropathy which results from compression of the posterior interosseous nerve in the arcade of Fröhse related to excessive supination movements, trauma, and compressive injuries at the site, such as cysts and aneurysms. This syndrome presents with weakness in the extension of the fingers and, to a lesser extent, in the extension of the wrist. There is no sensory deficit.[23]

Low amplitudes of the indicator extensor, thumb extensor, extensor digitorum communis or extensor carpi ulnaris in the CMAP test are expected when the axon is lost.[13]

The non-radial muscles of the forearm should always be tested when the manifestations are predominantly radial. Multifocal motor neuropathy can also involve this nerve more prominently than other nerves in the forearm or hand.[13]

►**Table 2** summarizes the provocative tests related to injuries to the main nerves in the upper limb. ►**Table 3**, on the other hand, shows the main sites of compression of the median, ulnar and radial nerves.

Compressive Neuropathies of the Lower Limb

Fibular Nerve

The common peroneal nerve (CPN), or common fibular nerve, consists of nerve fibers from the medullary roots of L4, L5, and S1. These fibers pass through the lumbosacral plexus, later forming, together with the neurons destined for the tibial nerve, the sciatic nerve. The path of the sciatic nerve runs through the posterior thigh, branching immediately above the popliteal fossa in its two primary branches: the tibial and common peroneal nerves. Then, the CPN follows distally and laterally, entering deeply into the lateral compartment of the leg, where it involves the fibular head anteriorly. Due to the close contact with this bone protuberance in the proximal and lateral regions of the leg, the nerve is more susceptible to excessive stretching or compressions that culminate in the development of compressive neuropathies.[25–27]

Inferior to the fibular head, the CPN is subdivided into superficial and deep branches. The superficial fibers are responsible for the sensitivity of the instep and the latero-distal portion of the leg, as well as for the motricity of the peroneus brevis and longus muscles (both responsible for eversion of the foot). The deep fibers are responsible for the

Table 2 Provocative tests for nerve compression[34]

Nerve	Compression site	Provocative testing	Conservative management
Median	Carpal tunnel	Pressure proximal to the carpal tunnel	Wrist splint in neutral position at night
		Phalen test	
		Reverse Phalen test (wrist hyperextension)	
	Proximal forearm	Pressure on the proximal forearm in the region around the pronator muscle, with the forearm in supination	Use of stretching exercises for the pronator teres muscle
		Resistance to elbow flexion, pronation, and finger flexion	
Ulnar	Guyon canal	Pressure proximal to the Guyon canal	Wrist splint in neutral position at night
		Reverse Phalen test	
	Cubital tunnel	Flexion and pressure of the elbow proximal to the cubital tunnel	Education about elbow position: position elbow in extension, and direct decrease in pressure on nerve
Radial (posterior interosseous)	Arcade of Fröhse	Pressure on the supine	Supine position and avoid repetition of pronation and supination activities
		Supination resistance	
		Finger extension and resisted wrist extenstion test (Cozen's test)	
Radial (sensitive)	Forearm	Pressure on the brachioradial junction/carpal radial extensor tendon	Avoid repeated pronation and supination activities
		Pronation of the forearm with ulnar flexion of the wrist	

Source: Mackinnon and Novak (2005).

sensitivity of the first interphalangeal region of the foot, and for the motricity of the anterior tibial muscles (dorsiflexion of the foot), the fibular third (dorsiflexion and eversion of the foot), and the short and long extensors of the hallux and toes (responsible for dorsiflexion of the toes).[25–27]

Peroneal or Fibular Neuropathy

The clinical picture of peroneal neuropathy (PN) usually leads to a dropped foot, decreased muscle strength for dorsiflexion of the foot, hallux and foot eversion, paresthesias, and loss of sensation on the anterolateral portion of the lower leg and on the instep. Other signs and symptoms that can be observed are: pain at night when the sheets touch the anterior side of the affected leg, antalgic gait, and slapping gait. Therefore, the physical examination of these patients must include a complete assessment of sensitivity (pain, touch, and vibration), motor skills, and motor coordination of the lower limbs, performing the Romberg test to identify a possible proprioceptive disorder and assessing the presence or absence of pathological gait.[25–27] The common site of compression in fibular (peroneal) nerve entrapment is shown in ►**Fig. 6**.[35]

Peroneal neuropathy is the most common compressive neuropathy of the lower limb.[26,27] Its onset may be acute, as in trauma episodes (such as in proximal fractures of the fibula), or due to chronic external compressive processes. The causes of chronic PN can be masses (such as ganglion cysts) or pressures exerted during prolonged periods of immobilization (such as procedures with the use of anesthetics, use of orthoses, or during the usual leg crossing). The main risk factors are related to the decrease in subcutaneous cell tissue, as in patients with low body mass index (BMI), or in those who have experienced episodes of rapid weight loss, since they make the nerve more susceptible to compression injuries. Diabetic neuropathy should be considered in this context, since the accumulation of sorbitol in the tissue of the CPN can lead to its engorgement. Another factor predisposing to common peroneal neural injury is excessive prolonged squats.[25,26]

Table 3 Nerve compression sites in the upper limbs

Nerve	Compression site
Median	Wrist (carpal tunnel syndrome)
	Anterior interosseous
	Elbow (pronator syndrome)
Ulnar	Elbow (cubital tunnel syndrome)
	Guyon canal
Radial	Armpit
	Groove for the radial nerve of the humerus
	Posterior interosseous
	Superficial sensitive branch (meralgia paresthetica)

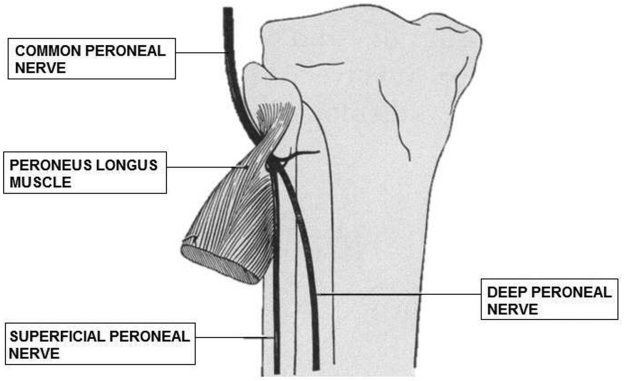

Fig. 6 Common site of compression in fibular (peroneal) nerve entrapment. The common peroneal nerve wraps around the head of the fibula in the proximal lateral lower leg. Source: Kopell and Thompson (1960).[35]

The main differential diagnoses for peroneal neuropathy are more proximal lesions of the sciatic nerve, lumbosacral plexus, or nerve roots from L4 to S1.[25,26] Weakness of foot plantar flexors (mediated by the gastrocnemius muscles innervated by the tibial nerve [L5-S2]) or of the hip abductors (mediated by the middle gluteal muscle, innervated by the upper gluteal nerve [L5-S1]), as well as the involvement of the patellar and achilles reflexes should alert to other causes of dropped feet that are not peroneal mononeuropathy.[26] Electrophysiological studies are particularly useful in the assessment of peroneal neuropathy. Electroneuromyography and nerve conduction studies enable the delimitation of the topography of the neurological lesion as exclusive to the peroneal nerve, and they provide evidence of focal compressions at the level of the fibular head, and are able to determine the extent of the axonal lesion, therefore enabling a prognostic assessment.[26,27] Electrophysiological studies should be performed in all patients with onset of foot drop, and repeated every three months to assess the improvement or worsening of the disease. In cases of trauma or postoperative neuropathy, these tests should be postponed for two to six weeks. Monitoring by neurophysiological tests can dictate the course of the treatment, including the surgical indications. The finding of an important nerve conduction delay along the CPN ($>$ 50%) and ENMG showing significant impairment of motor innervation are used in some centers as criteria for surgical decompression.[27]

Imaging tests, such as US and MRI, are not routinely used; however, they are useful in complementing the clinical evaluation, especially in those individuals with suspected compressive mass.[26]

The prognosis of peroneal mononeuropathy is in most cases favorable. The treatment is generally conservative, consisting of supportive measures, such as patient education, removal of predisposing factors, indication of support equipment (such as orthoses for dropped feet, splints for nightly use, padding of the region of the fibular head), and physiotherapy. The predictors of a worse prognosis are advanced age, severe paresis at the beginning of the presentation of the disease, and evidence of denervation on ENMG. Surgical decompression is still controversial, due to the excellent results of the conservative treatment, and is therefore limited to those individuals who do not improve after three months of conservative treatment or who show progressive symptoms in the absence of a clear cause for nerve compression.[26,27]

Femoral Nerve

The lateral femoral cutaneous nerve (LFCN) originates from the lumbar plexus, consisting of fibers from the nerve roots of L2 and L3.[26,28,29] The nerve appears approximately at the level of the lateral margin of the psoas major muscle, then acquiring an oblique path along the abdomen toward the inguinal ligament on the anterior surface of the iliac muscle, a region in which it is surrounded by the dense layer of iliac fascia tissue.[28] The exit point of the LFCN from the abdomen presents considerable anatomical variation, with some configurations showing a greater predisposition to the development of compressive neuropathies, such as those in which the nerve is located within the inguinal ligament, within the tendon insertion of the sartorius muscle, or in those in which the nerve courses above the iliac crest.[26]

The close anatomical relationships of the LFCN with the pelvic margins is the main factor predisposing to compressive injuries.[26] In 85% of the individuals, the nerve leaves the abdominal region medially to the sartorius muscle; however, even in these situations, it has different proximity relations with the anterosuperior iliac crest (ASIC). The average distance from the LFCN to the ASIC is of $\sim$ 8 mm, which can vary from a minimum of 0 mm to a maximum of 40 mm. It is postulated that the closer proximity of the nerve to ASIC, as well as the other abnormal trajectories (the remaining 15%), increase the chance of developing meralgia paresthetica (MP).[28]

Meralgia Paresthetica: Neuropathy of the Lateral Femoral Cutaneous Nerve

Meralgia paresthetica is the second most common mononeuropathy of the lower limbs, with $\sim$ 30 to 40 new cases per 100 thousand inhabitants per year.[26,28,30] The main risk factors for this pathology are obesity, diabetes, and the male gender. Its symptoms include sensory disturbances (pain, discomfort, numbness, paresthesia, burning, and hypersensitivity to touch) in the anterolateral region of the affected thigh. An important characteristic of MP is the lack of involvement of the patient's degree of muscle strength, since the LFCN is not constituted by any motor fibers; thus, MP is an exclusively sensitive disease.[26,28–30] There are numerous reported causes of MP, which are classified as spontaneous or iatrogenic.[28] Among the spontaneous etiologies, the following can be highlighted: intense compressions and excessive stretching of the nerve due to the use of external clothing and accessories (very tight pants and belts or fanny packs for heavy objects), increased abdominal weight (in obese, pregnant, and ascitic individuals), and acute trauma caused by the seat belt during automobile accidents.[26,29] One of the most frequent iatrogenic injuries to the LFCN in the clinical practice are spine surgeries in which the patient remains in prone position (the incidence of

MP ranges from 12% to 24%); obese patients or those with long periods of immobilization during surgery are at higher risk; however, in these cases, the injury is temporary, with spontaneous regression of symptoms.[28] Other invasive procedures that involve an iatrogenic risk of developing MP are the anterior approaches to the hip and pelvis, external fixations of the pelvis with insertion of screws in the ASIC, and techniques for removing bone grafts from the iliac crest.[26] The common site of compression of the LFCN is shown in ►**Fig. 7**.[36]

The diagnosis of MP is eminently clinical, through anamnesis and physical examination. These should demonstrate a well-defined sensory disturbance in the anterolateral thigh region, extending from the femoral trochanter to the upper margin of the patella.[26] Most patients report the sensation of numbness in the affected limb; however, burning and tingling are also frequently reported. The history of the disease can vary from intermittent symptoms with spontaneous resolution in a short time (~ 25% of individuals show spontaneous improvement) to continuous symptoms for long periods of time (with reports of up to 30 years in duration).[28,29] Any conditions that generate greater pressure or stretching of the LCFN can worsen the symptoms, such as, long periods of standing or excessive extensions of the hip joint when driving or walking.[28] The pelvic compression test, performed at the level of the inguinal ligament, is a non-invasive semiological tool which is useful in the diagnosis of

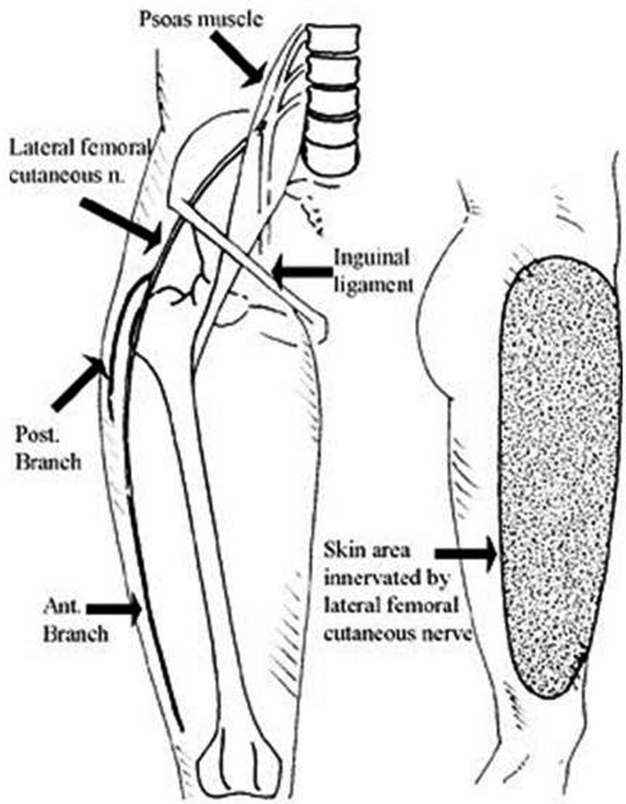

Fig. 7 Common site of compression of lateral femoral cutaneous nerve (LFCN). The close anatomical relationships of the LFCN with the pelvic margins are the main factor predisposing to compressive injuries. Source: Goulding et al. (2010).[36]

MP, with a study[28] showing a sensitivity of 95% and a specificity of 93.3%. The presence of concomitant motor abnormalities makes it necessary to investigate other etiologies. The presence of paresis of the iliopsoas muscle, in particular, identified by the decrease in muscle strength in hip flexion, suggests the involvement of the medullary level of L2 (as in the case of high lumbar disc hernias), and is an important differential diagnosis to be considered.[26,29]

Ultrasonography is extremely useful to locate the LFCN, for it enables the identification of atypical nerve pathways and acts as a guide to perform interventions such as anesthetic blocks. However, its importance in the diagnosis of MP remains poorly established by scientific evidence. Some studies correlated data such as the presence of hypoechoic or swollen LFCN with MP, and have stated that certain parameters, such as the cross-sectional area and the maximum diameter of the nerve, can be used as diagnostic criteria. However, larger and more methodologically-elaborate studies are still needed to establish US as a diagnostic method.[28]

Other imaging exams, such as the MRI, the CT, and radiography, have limited usefulness in the diagnosis of LFCN mononeuropathy, and are indicated in an attempt to evaluate other neurological diseases that are part of the differential diagnosis of MP (such as lumbar disc herniation and tumors located in the region of the lumbar plexus).[28]

Electrophysiological studies help confirm the diagnosis, although they are not routinely performed and present technical difficulties due to the intense anatomical variability of the neural pathway among patients.[26] Motor conduction studies must be normal, which makes it possible to rule out spinal cord and nerve root diseases, or polyneuropathies. The two main tests available to assess MP are somatosensory evoked potentials (SSEPs) and sensory nerve conduction tests.[28–30] The SSEPs have the main advantage of their greater accessibility and easy performance, especially in obese patients; however, despite its good specificity (76%), the test has a sensitivity of only 52%. This results in a high rate of false-negatives and, consequently, in the underdiagnosis of the population with MP. Sensitive nerve conduction tests, on the other hand, enable the calculation of the sensitive nerve action potential (SNAP) and the side-to-side amplitude ratio (SSAR), with better accuracy. Amplitudes of the SNAP below 3 diagnose PM in 73.3% of the patients, whereas a SSAR of 2.3 has a specificity greater than 98.75%.[28]

The therapeutic approaches for this pathology can be divided into three main modalities: conservative treatment, the use of nerve blocks, and surgical interventions.[28,30] Currently, there is still little scientific evidence to indicate the superiority of one modality in relation to another; however, the majority of patients are submitted to conservative treatment due to the lower risks involved and the good rate of improvement of the symptoms. The conservative management includes general supportive measures, reduction of risk factors (such as weight loss for obese patients and avoiding the use of tight clothing or accessories around the waist), and use of non-steroidal anti-inflammatory drugs, anticonvulsants, and antidepressants to alleviate the

neuropathic pain.[26,28,29] As a good number of individuals report improvement with the aforementioned measures, interventional therapies, anesthetic and corticosteroid injections, and surgical decompression remain as exceptional approaches (second option, depending on the risks and benefits) for MP.[26]

The two main surgical approaches to MP are neurolysis and neurotomy. In the former, the surgeon's objective is to relieve the compression points of the NCFL along its path, and the main technique consists of three steps: cutting the inguinal ligament in its portion on the nerve, cutting the iliac fascia that surrounds the nerve, and making distal cuts in the thigh fascia for each division of the nerve. The average success rate for this procedure is of 80% (range: 60% to 99%). Neurotomy, on the other hand, consists of direct injury to the LFCN, providing relief from unpleasant sensory symptoms at the cost of remaining numb in the affected region as a sequela of the procedure. The success rate is higher than that of neurolysis, varying from 85% to 100% of the cases, with studies even showing that most individuals were not bothered by the sequelae of the operation. Therefore, it is up to the physician to inform the patient of the therapeutic options, and together they can decide on the best strategy in surgical cases.[28,30]

Conclusion

The present review showed the importance of better understanding regarding clinical presentation and more accurate diagnostic methods to assist in the management of compressive neuropathies of the limbs.

Conflict of Interests

The authors have no conflict of interests to declare.

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Nontraumatic Intracranial Epidural Hematoma: Systematic Review of the Literature

Hematoma epidural intracraniano não traumático: revisão sistemática da literatura

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Abstract

Introduction Epidural hematoma (EDH) is generally a direct sequela of head injury. Spontaneous EDH is rarely described in the literature. Spontaneous EDH can be caused by infections of adjacent regions, vascular malformations of the dura mater, metastases to the bone skull, and disorders of blood coagulation. The preferred treatment is surgical. The prognosis is directly related to the size, location, and Glasgow Coma Scale score on admission and the underlying disease.

Methods A systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We performed the search in the PubMed/MEDLINE, Embase, and Scopus databases. Abstracts and articles were screened according to our inclusion and exclusion criteria.

Results The literature review yielded 1,156 records from the databases, of which a total of 164 full-text articles were included in the final synthesis, plus 22 additional relevant studies. A total of 89 case report studies were included, providing 95 unique patients. There was a predominance of coagulopathies as the main etiology of spontaneous EDH. A total of 45.3% of the patients presented lesions in >1 brain lobe. The frontal lobe was the most prevalent location of EDH. The most used neuroimaging exam was computed tomography (CT). Surgical intervention was the most common treatment performed. A total of 24.2% of the patients died.

Conclusion Nontraumatic EDH represents an uncommon manifestation of several pathologies. Clinical investigation should be aware of such a possibility. Healthcare professionals should value the physical examination and clinical history of the patient. Given the scarcity of information on the pathogenesis of spontaneous EDH, further studies are needed to better define intervention strategies and therapies for these patients.

Keywords
- spontaneous epidural hematoma
- intracranial
- nontraumatic
- extradural hematoma

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Resumo

Introdução Geralmente, o hematoma epidural (HED) é decorrente de traumatismo cranioencefálico. O HED espontâneo tem sido ocasionado por infecção de áreas adjacentes, malformação vascular na dura-máter, metástases para osso do crânio e doenças da coagulação sanguínea. Seu prognóstico está diretamente relacionado com o tamanho, a localização, o escore na escala de coma de Glasgow na admissão e a doença de base.

Metodologia Uma revisão sistemática da literatura foi conduzida e seguiu as diretrizes Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA, na sigla em inglês). Realizamos a pesquisa nos bancos de dados PubMed/MEDLINE, Embase e Scopus. Os resumos e artigos foram selecionados de acordo com os nossos critérios de inclusão e exclusão.

Resultados A revisão da literatura resultou em 1,156 registros nas bases de dados, dos quais um total de 164 artigos com texto completo foram incluídos na síntese final; mais 22 estudos relevantes foram adicionados. Um total de 89 estudos de caso foi incluído, fornecendo 95 pacientes únicos. Havia uma predominância de coagulopatias como a principal etiologia do HED espontâneo. Um total de 45,3% dos pacientes apresentava lesões em >1 lobo cerebral. A intervenção cirúrgica foi o tratamento mais comum realizado. Um total de 24,2% dos pacientes morreu.

Conclusão Hematoma epidural não traumático representa uma manifestação incomum de várias patologias. A investigação clínica deve estar atenta a tal possibilidade e os profissionais de saúde devem valorizar o exame físico e a história clínica do paciente. Dada a escassez de informações sobre a etiopatogenia do HED, mais estudos são necessários para melhor definir estratégias de intervenção e terapias para estes pacientes.

Palavras-chave

- hematoma epidural espontâneo
- intracraniano
- não traumático
- hematoma epidural

Introduction

The most common cause of epidural hematoma (EDH) is a traumatic brain injury and skull fracture.[1] Spontaneous EDH can arise from various pathological conditions, and its incidence still uncertain in the literature.[2] The first reported case of spontaneous EDH in the literature was in 1951, published by Schneider et al.[3] There have been several reports published since then.

Spontaneous EDH is typically associated with four etiological categories: pericranial infections, dural vascular malformations, cranial metastases, and coagulation disorders.[4,5] The present study is a systematic review of the literature that aims to identify, compile, and analyze the case reports on EDH of a nontraumatic cause.

Methods

Inclusion Criteria

Abstracts were screened and selected according to the following inclusion criteria: articles published with full text, articles that report at least one case of EDH, and articles published in any language and year.

Exclusion Criteria

We excluded studies following our defined exclusion criteria: articles that did not report at least one original case report of EDH, case reports of spinal EDH, case reports of traumatic EDH, case reports published in conference proceedings, letters to the editor, book chapters, articles that had not been peer-reviewed, and EDH due to any neurosurgical procedure.

Literature Search

We conducted a systematic review of the literature based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)guidelines.[6] We performed the search in the PubMed/MEDLINE, Embase, and Scopus databases in December 2020. Ethical approval and patient consent were not required as this is a systematic review based on published studies. Additional studies identified through the selected articles were analyzed and included according to the inclusion and exclusion criteria.

Study Selection

The search yielded 1,039 potentially relevant articles after the removal of duplicates. Two authors (Souza Junior J. F. and Medeiros L. E. D. Q.) independently reviewed and selected the studies using Rayyan QCRI (https://rayyan.qcri.org) software.[7] We performed a selection with the reading of the title and abstract of the articles, followed by full-text reading, and the final inclusion depended on the agreement with all the inclusion and exclusion criteria. The research included a total

of 89 articles, representing 95 reported patients. The included studies in our systematic review were published between 1951 and 2020.

Data Extraction

The demographic data extracted from the reported patients were: age (in years), gender, etiologic cause of the hematoma, location, modality of imaging exams, treatment adopted, and outcome.

Results

The literature review yielded 1,156 records in the databases. After duplicates were removed, 1,039 were screened, 164 full-text articles were assessed for eligibility, and 67 were included in the final synthesis, plus 22 additional relevant studies, providing data on 95 individual patients. The summary of the selected reports is presented in ►**Table 1**. A total of 89 case report studies were included (►**Fig. 1**). The median age of the patients was 24.3 years old, the oldest patient was 70 years old, and the youngest was 28 days old. A total of 65.2% of the patients were male, and 34.7% were female.

Among the etiologies of spontaneous EDH, there was a predominance of coagulopathies (40%), followed by pericranial infections (19%), neoplasms (14.7%), eosinophilic granuloma (7.4%), dural vascular abnormalities (2.1%), kidney disease (5.3%), medication (3.1%), systemic lupus erythematosus (2.1%), cardiac surgery (1%), hysterical crying (1%), intracranial hypotension (1%), and intradiploic epidermoid cyst (1%). The etiology of EDH was unknown in 2 cases (2.1%). A total of 45.3% of the patients presented lesions in >1 brain lobe. The most prevalent location of spontaneous EDH was the frontal lobe (37.9%), followed by the parietal lobe (29.5%), the temporal lobe (17.9%), and the occipital lobe (8.4%). Other locations, such as cerebellar (1%) and retroclival (1%), were less frequent; the location was not reported in 2 cases (2.1%).

The most used neuroimaging exam was computed tomography (CT) (88.4%), followed by magnetic resonance imaging (MRI) (23.1%), cerebral angiography (12.6%), simple radiography (9.5%), and angio-MRI (2.1%). The treatment performed most frequently was surgical intervention (81%), followed by conservative treatment (14.7%), and not reported (4.3%). Among the cases, 23 patients (24.2%) died and 75.8% progressed satisfactorily with total or partial symptom remission.

Discussion

Epidural Space and Epidural Hematoma Formation

The epidural space is located between the inner layer of the skull bones and the dura mater and is closely adhered to the skullcap and cranial sutures (EDHs are usually limited in their extent by the cranial sutures). The majority of the blood supply of the dura mater arises from the middle meningeal artery. Spontaneous EDH is associated with four etiological categories[1,4,5]: pericranial infections, dural vascular malformations, skullcap metastasis, and coagulation disorders. In the present study, we observed other infrequent etiologies:

Table 1 Summary of reported cases of nontraumatic epidural hematomas, age/gender

Author, year	Age/gender
Pericranial infections	
Schneider et al., 1951[3]	21/M
Schneider et al., 1951[3] Novaes et al., 1965[40]	21/M 26/M
Kelly et al., 1968[28]	11/M
Clein,1970[39]	18/M
Sanchis et al.,1975[1]	13/M
Marks et al., 1982[29]	31/M
Ataya, 1986[30]	31/M
Sakamoto, et al., 1997[31]	16/F
Hamamoto et al., 1998[4]	15/M
Papadopoulos et al., 2001[32]	17/M
Griffiths et al., 2002[34]	17/M
Moonis et al., 2002[33]	21/M
Chaiyasate et al., 2007[35]	14/F
Knopman et al., 2008[71]	11/M
Takahashi et al., 2010[36]	10/F
Cho et al., 2011[37]	12/F
Spennato et al., 2012[38]	12/F
Neoplasm	
Anegawa et al., 1989[74]	32/F
Kuga et al., 1990[73]	65/M
Nakagawa et al., 1992[84]	52/M
Simmons et al., 1999[75]	67/M
Hayashi et al., 2000[85]	70/M
Dufour et al., 2001[76]	36/F
Hassan et al., 2009[26]	55/F
Kanai et al., 2009[81]	56/M
Kim et al., 2010[80]	53/M
Woo et al., 2010[82]	46/M
Mahore et al., 2014[72]	12/M
Kim et al., 2016[79]	41/M
Ramesh et al., 2017[77]	40/F
Zhao et al., 2020[78]	45/F
Coagulopathies	
Cooper et al.,1979[55]	6 w/F
Kuwayama et al.,1985[53]	21/F
Grabel et al., 1989[59]	2/M
Karacostas et al., 1991[42]	19/M
Resar et al., 1996[43]	14/M
Ganesh et al., 2001[44]	11/M
Okito et al., 2004[67]	12/M
Okito et al., 2004[67]	2/M

Table 1 (*Continued*)

Author, year	Age/gender
Ng et al., 2004[61]	52/M
Dixit et al., 2004[86]	17/M
Dahdaleh et al., 2009[62]	18/M
Iliescu et al., 2009[60]	28/F
Pati et al., 2009[57]	32/F
Pallotta et al., 2010[69]	21/M
Vural et al., 2010[51]	7/F
Azhar et al., 2010[87]	12/M
Arends et al., 2011[45]	19/M
Bölke et al., 2012[46]	19/M
Babatola, et al., 2012[2]	18/M
Page, et al., 2014[88]	7/F
Page et al., 2014[88]	20/M
Serarslan et al., 2014[89]	19/F
Ilhan et al., 2014[70]	15/M
Kilit et al., 2014[56]	13/F
Farah et al., 2014[52]	2/M
Hettige et al., 2015[63]	7/F
Oka et al., 2015[64]	19/M
Zhang et al., 2015[58]	21*/F
Ewane et al., 2016[68]	20/M
Saul et al., 2017[66]	18/M
Mishra et al., 2017[65]	18/M
Komarla, et al., 2018[47]	18/F
Komarla et al., 2018[47]	17/M
Banerjee et al., 2018[48]	-/M
Saha et al., 2019[49]	20/F
Prabhu et al., 2019[54]	21/F
Tomboravo et al., 2019[50]	21/M
Ntantos et al., 2020[27]	44/F
Eosinophilic granuloma:	
Cho et al., 2001[8]	2/M
Chen et al., 2002[9]	2/M
Mut et al., 2004[10] Bhat et al.,2010[11]	9/M 10/M
Sadashiva et al., 2016[12]	15/M
Bakhaidar et al., 2016[13]	7/M
Al-Mousa et al., 2020[14]	3/M
Renal disease	
Hamamoto et al., 1998[4]	12/F
Shahlaie et al., 2004[5]	16/M
Zheng et al., 2009[15]	54/F
Khan et al., 2017[16]	40/M
Yadav et al., 2016[17]	39/M
Medication	
Ruschel et al., 2016[18]	39/M
Khan et al., 2017[16]	30/F
Fukai et al., 2019[19]	27/F
Systemic lupus erythematous	
Song et al., 2015[20]	29/F
Yin et al., 2019[21]	45/F
Vascular and dural abnormalities	
Sanchis et al.,1975[1]	59/F
Hasegawa et al., 1983[83]	11/F
Cardiac surgery	
Ahmad et al., 2005[22]	4/M
Hysterical crying	
Chen et al., 2018[23]	19/F
Intracranial hypotension	
Cho et al., 2009[24]	36/M
Intradiploic epidermoid cyst	
Wani et al., 2008[25]	60/M
Unknown etiology	
Ng et al., 2004[61]	23/F
Bolliger et al., 2007[41]	67/M

Abbreviations: F, female; M, male; w, weeks.
*Age of admission differs from the age of onset of epidural hematoma.

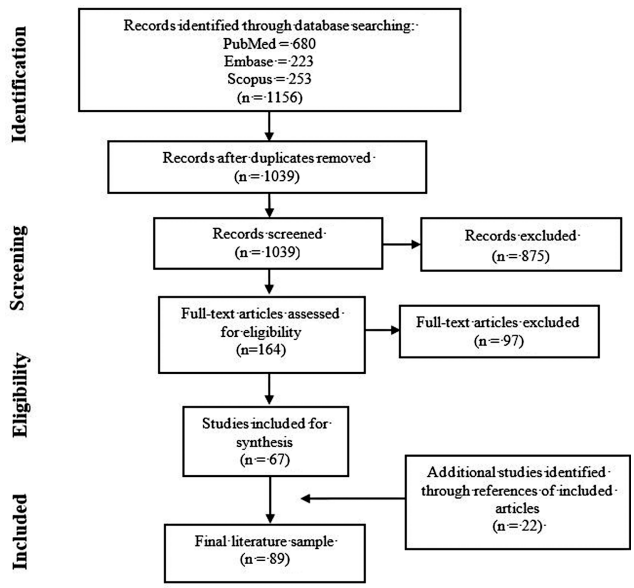

Fig. 1 Flowchart of the present systematic literature review.

eosinophilic granuloma,[8,9,10,11,12,13,14] kidney disease,[4,5,15,16,17] associated with drug therapy,[16,18,19] systemic lupus erythematosus,[20,21] cardiac surgery,[22] historical crying,[23] intracranial hypotension,[24] and intradiploic

epidermoid cyst.[25] Hassan et al.[26] suggest that the term nontraumatic is more appropriated than spontaneous to refer to EDH because this kind of EDH is invariably associated with a primary cause. Despite this discussion, we used both expressions as synonyms in the present study.

The CT image of an EDH is an extra-axial collection in the shape of a biconvex lens.[22] The mechanisms involved in each etiology are different. There are three propositions about the pathophysiological mechanisms described in the literature:[27] cranial injury leading to elevation of the periosteum and rupture of the cortical bone margin and consequent hemorrhage in the epidural space, abnormal anatomy caused by a pathological process of chronic medullary hematopoiesis, and insufficient venomous drainage leading to cerebral edema and hemorrhage. The occurrence in the population is rare, with a very uncertain incidence in the literature.

Pericranial Infections

Among the EDH cases associated with pericranial infections, sinusitis[28,29,30,31,32,33,34,35,36,37,38] was the most common etiology (►**Table 2**). Schneider et al.,[3] reported in 1951the first case in the literature of 2 patients with distinct pericranial infections. These authors also recognized errors in the management of one of the patients, who died, partially in consequence of a failure to consider that the intracranial lesion presented could be of any nature, except an inflammatory condition, as well as a mistake in not having properly associated the findings of the physical examination and of the topography of the lesion.

There are two possible explanations for epidural bleeding and hematoma formation in patients with pericranial infections: a) extension of the infectious process to the external surface of the dura mater, promoting vasculitis and rupture of epidural vessels, thus causing blood leakage; and b) progressive detachment of the dura mater from the internal bone surface and vascular injury due to excessive accumulation of exudate or air from the infected area.[4] The first mechanism is justified based on radiological, operative, and histological evidence available, which observed proximity of the bone structures to the infectious process (focal osteitis).[1,28,32,39] The second possible mechanism is shown by a progressive displacement of the dura mater from the internal bone surface due to excessive accumulation of purulent exudate or air from the infected area, leading to vascular injury and to the development of EDH.[1]

It is known that a mechanism involved in EDH formation in patients with pansinusitis involves infection by a retrograde route through the valveless vessels or diploic vascular channels, leading to inflammation weakening the vessel walls, which, in turn, leads them to rupture, as reported by Chaiyasate et al.[35] The typical clinical presentation of EDH associated with craniofacial infection occurs with headache, vomiting, and decreased level of consciousness preceded by signs and symptoms of the primary site of infection.[34]

Table 2 Summary of reported cases of spontaneous epidural hematoma associated with pericranial infection

Author, year	EDH etiology	EDH site	Diagnostic imaging exam					Surgery	Outcome
			CT	MRI	AG	Rx	Others		
Schneider et al., 1951[3]	Otitis media	Right temporal					Autopsy	No	Died
Schneider et al., 1951[3]	Otitis media	Right frontotemporal				x	EEG	Yes	Recovered
Novaes et al., 1965[40]	Otitis media	Temporal			x	x		Yes	Recovered
Kelly et al., 1968[28]	Frontal sinusitis	Left frontal				x	T-99 BS	Yes	Recovered
Clein,1970[39]	Otitis media	Left frontoparietal					Autopsy	No	Died
Sanchis et al.,1975[1]	Otitis media	Right temporal			x	x		Yes	Recovered
Marks et al., 1982[29]	Sinusitis	Right frontal	x			x		Yes	Recovered
Ataya, et al., 1986[30]	Chronic sinusitis	Left frontal	x			x		Yes	–
Sakamoto et al., 1997[31]	Maxillary sinusitis	Left frontal	x					Yes	Recovered
Hamamoto et al., 1998[4]	Pansinusitis	Left frontal	x			x		Yes	Died
Papadopoulos et al., 2001[32]	Frontal sinusitis	Right frontal	x					Yes	Recovered
Moonis et al., 2002[33]	Sphenoid sinusitis	Left temporal	x	x				Yes	Partially recovered
Griffiths et al., 2002[34]	Frontal sinusitis	Frontal	x					Yes	Recovered
Chaiyasate et al., 2007[35]	Pansinusitis	Right frontal	x					Yes	Recovered
Knopman et al., 2008[71]	Otitis media	Right temporal	x	x				Yes	Recovered
Takahashi et al., 2010[36]	Sphenoid sinusitis	Right temporal	x	x	x			Yes	Recovered
Cho et al., 2011[37]	Sphenoid sinusitis	Right temporal	x	x				Yes	Recovered
Spennato et al., 2012[38]	Frontal sinusitis	Right frontal	x		x*			Yes	Recovered

Abbreviations: AG, angiography; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; RX, radiography; T-99 BS, technetium-99m brain scan.
*Angio-CT.

The most frequent symptoms presented by the patients with pericranial infections (►**Table 2**) were: headache, fever, nausea/vomiting, and drowsiness. Among the reports with ocular involvement, the most common sign among the patients was periorbital edema (38.9%),[3,28,29,30,31,35,38] anisocoria,[3,40] exophthalmos (11.1%), [31,38] and papilledema (1%).[4]

Spennato et al.[38] reported the following data in a series of cases with pericranial infections: the mean age observed was 20 years old, most common in males (8:2), and frontal location EDH was the most frequent. These data were similar to the findings of Cho et al.[37] In Asia, case reports of spontaneous EDH associated with sinus infections were more frequent due to the higher incidence of chronic pericranial infection cases among Asians.[37]

The most commonly used imaging exam in patients with pericranial infections was CT, followed by x-ray. These imaging exams contribute to evaluate the anatomy of the paranasal sinuses and verify the existence of fractures. The treatment performed in most cases was that of the infection etiology, associated with craniotomy and drainage of the hematoma.

Coagulopathies

It is known that coagulopathies may be responsible for spontaneous bleeding, including epidural bleeding.[41] In the present study, the observed coagulopathies (►**Table 3**) were: sickle cell anemia (SCA),[2,42,43,44,45,46,47,48,49,50] coagulation factor XIII deficiency,[51,52] hypofibrinogenemia,[53,54] vitamin K deficiency,[55] congenital afibrinogenemia,[56,57] immune thrombocytopenic purpura,[27,58] myelodysplastic syndrome,[59] disseminated intravascular coagulation (DIC),[60] and liver disease[61]. Coagulation disorders and pericranial infections are the two major categories of pathologies with which EDH is associated. In the present literature review, among all the included cases of spontaneous EDH, coagulopathies were predominant. Sickle cell anemia was the most common coagulopathy observed.

The first reported case in the literature was in 1979 by Cooper et al.,[55] of a 6-week-old patient with vitamin K deficiency who required surgical intervention for hematoma evacuation. The most frequent etiology of spontaneous EDH observed in the present study was SCA, accounting for 27.4% of all 95 patients listed in ►**Table 1**. Sickle cell anemia, characterized by changes in the shape of red blood cells and intermittent intravascular obstruction of blood flow, represents a common genetic disorder, especially among African Americans (1:600).[62,63]

Epidural hematoma is the most common neurosurgical emergency complication in patients with SCA[48]; however, it still is a rare manifestation. Nevertheless, in patients with SCA, EDH should be suspected if the patient starts presenting with sudden headaches or other signs of intracranial hypertension, leading to a search for bone lesions and hemostatic disorders, such as thrombocytopenia.[64]

The symptoms presented by SCA patients differ from the classical symptoms of EDH caused by trauma, which often have a lucid interval in clinical condition, as suggested by Babatola et al.[2] Among homozygous patients, chronic hemolytic anemia may occur, with increased susceptibility to infections, vaso-occlusive crises, and cerebrovascular disorders (especially cerebral ischemia), which can worsen the clinical conditions of the patient.[63]

A SCA crisis may increase the hematopoietic demand on cranial medullary tissue, predispose to bone margin disruption and subsequent hemorrhage. All patients reported by Mishra et al.[65] had an SCA crisis that preceded the EDH. The exact mechanism of EDH in patients with SCA is unknown, but it is possibly related to bone infarction.[64] Bone infarction has been related to hematoma cases, possibly due to periosteal elevation and disruption of the bone margin.[2] Bone infarction has been reported in long bones, the spine, the sternum, and the ribs and is commonly associated with adjacent edema and hemorrhage.[66]

A literature review conducted in 2015 noted an anatomical correlation between bone infarction and EDH location, but the direct cause has not yet been established.[63] In contrast, studies hypothesized that cases of spontaneous EDH are not associated with bone infarction and may occur due to abnormalities in cranial anatomy,[2] so that chronic expansion of hematopoietic tissue may rupture the inner and outer margins of the bone, causing extravasation of blood and medullary tissue into the subgaleal or epidural spaces. Another proposed mechanism has been less discussed and considers that the insufficient venous drainage in sickle cell pathology is possibly responsible for edema and hemorrhage.[67]

The combination of MRI and angio-MRI is typically performed in patients with SCA to investigate headache, weakness, and vision changes associated with symptoms of a possible stroke, especially in children.[47] An extradural heterogeneous hypodense lesion presenting on imaging exams can be interpreted as a chronic EDH or an acute EDH with noncoagulated blood due to a low hemoglobin level.[65] Crisis prevention occurs through adequate hydration, folic acid consumption, and regular rest.[65] This prevention is essential in the care of SCA patients and prevents neurosurgical events.

There is no cure reported for this condition, and the management of symptomatic events involves the administration of fluids, appropriate analgesia, intravenous antibiotics (in case of isolated focal infection), and low molecular weight heparin as a prophylactic treatment, which can contribute to the prevention of crises due to the reduction of blood flow in the small circulation.[63] Studies have shown that general anesthesia and surgical trauma can precipitate red blood cell sickling factors, resulting in postoperative complications previously described in between 25 and 30% of patients.[68] Therefore, patients with SCA should be evaluated regarding surgical intervention by neurosurgeons, anesthesiologists, and hematologists, to ensure patient safety. In this scenario, early intervention and adequate imaging tests can modify the evolution of the patient.[69]

Another coagulopathy reported as the underlying etiology for EDH formation is factor XIII deficiency.[51,52] Coagulation factor XIII deficiency is a rare phenomenon of low incidence

Table 3 Summary of reported cases of spontaneous epidural hematoma associated with coagulopathy

Author, year	EDH etiology	EDH site	Diagnostic imaging exam					Surgery	Outcome
			CT	MRI	MRA	Rx	Others		
Cooper et al., 1979[55]	Vitamin K deficiency	Temporoparietal (bilateral)	x			x		Yes	Recovered with sequels
Kuwayama et al.,1985[53]	Hypofibrinogenemia	Temporal (bilateral)	x					Yes	Recovered
Grabel et al., 1989[59]	Myelodysplastic syndrome	Left frontal	x					No	Recovered
Karacostas et al., 1991[42]	Sickle cell anemia	Left parietal and frontal (bilateral)	x	x				No	Recovered
Resar et al., 1996[43]	Sickle cell anemia	Right occipitotemporal	x			x		Yes	Died (renal failure)
Ganesh et al., 2001[44]	Sickle cell anemia	Frontal (bilateral)	x					No	Recovered
Okito et al., 2004[67]	Sickle cell anemia	Right frontotemporal	x					Yes	Died
Okito et al., 2004[67]	Sickle cell anemia	Left temporal	x					No	Died (septicemia)
Ng et al., 2004[61]	Hepatopathy	Left frontoparietal	x					Yes	Recovered
Dixit et al., 2004[86]	Sickle cell anemia	Left frontal	x					No	Recovered
Dahdaleh et al., 2009[62]	Sickle cell anemia	Right frontal and parietal (bilateral)	x					Yes	Recovered
Iliescu et al., 2009[60]	DIC	Right frontoparietal	x					Yes	Died
Pati et al., 2009[57]	Afibrinogenemia	Frontal (bilateral)	x					Yes	Recovered
Pallotta et al., 2010[69]	Sickle cell anemia	Right frontal	x	x				Yes	Recovered
Vural et al., 2010[51]	Factor XIII deficiency	Right parietooccipital	x					Yes	Recovered
Azhar et al., 2010[87]	Sickle cell anemia	Left frontal	x					Yes	Partially recovered
Arends et al., 2011[45]	Sickle cell anemia	Right parietal	x	x				No	Recovered
Bölke et al., 2012[46]	Sickle cell anemia	Left parietal	x					Yes	Recovered
Babatola et al., 2012[2]	Sickle cell anemia	Left frontal	x					Yes	Died (renal failure)
Page et al., 2014[88]	Sickle cell anemia	Infratentorial suboccipital (bilateral)	x					Yes	Died
Page et al., 2014[88]	Sickle cell anemia	Left frontal	x	x				No	Recovered
Serarslan et al., 2014[89]	Sickle cell anemia	Right temporal	x					Yes	Partially recovered
Ilhan et al., 2014[70]	Sickle cell anemia	Left parietal	x					Yes	Recovered
Kilit et al., 2014[56]	Afibrinogenemia	Right frontal	x	x				No	Recovered
Farah et al., 2014[52]	Factor XIII deficiency	Right frontal and occipital lobe*	x					Yes	Recovered
Hettige et al., 2015[63]	Sickle cell anemia	Parietal (bilateral)	x	x				Yes	Died (renal failure)
Oka et al., 2015[64]	Sickle cell anemia	Occipital lobe	x	x				No	Recovered
Zhang et al., 2015[58]	Immune thrombocytopenic purpura	Right frontoparietal	x	x				Yes	Recovered
Ewane et al., 2016[68]	Sickle cell anemia	Frontal (bilateral)	x					Yes	Died

Table 3 (*Continued*)

Author, year	EDH etiology	EDH site	Diagnostic imaging exam					Surgery	Outcome
			CT	MRI	MRA	Rx	Others		
Saul et al., 2017[66]	Sickle cell anemia	Parietooccipital (bilateral)	x	x				–	–
Mishra et al., 2017[65]	Sickle cell anemia	Right parietal	x			x		Yes	Recovered
Komarla et al., 2018[47]	Sickle cell anemia	Right cerebral hemisphere		x	x			Yes	Recovered
Komarla et al., 2018[47]	Sickle cell anemia	Frontal (bilateral)	x					Yes	Died
Banerjee et al., 2018[48]	Sickle cell anemia	Frontal (bilateral)	x	x	x			No	Recovered
Saha et al., 2019[49]	Sickle cell anemia	Right frontal	x					Yes	Recovered
Prabhu et al., 2019[54]	Hypofibrinogenemia	Right frontoparietal	x					Yes	Died
Tomboravo et al., 2019[50]	Sickle cell anemia	Right frontal	x				Eco-doppler	Yes	Recovered
Ntantos et al., 2020[27]	Immune thrombocytopenic purpura	Parietal (bilateral)	x					Yes	Died

Abbreviations: CT, computed tomography; DIC, disseminated intravascular coagulation; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; RX, radiography.
*At different times

worldwide, defined as an autosomal recessive disorder.[46] Farah et al.[46] reported the first case of EDH in a child with coagulation factor XIII deficiency. The diagnosis of coagulation factor XIII deficiency can be performed by quantitative analysis of the plasma levels of factor XIII in both the patient and family members.

Hypofibrinogenemia is a rare disorder defined by a deficiency in bloodstream fibrinogen levels (< 2 g/L), but not by its complete absence.[54] The frequency of intracranial bleeding in patients with hypofibrinogenemia is known to be between 7.3 and 13%.[36,37] Medical professionals must pay attention to the immediate correction of the coagulation profile. This correction is possible through transfusion of fresh frozen plasma and cryoprecipitate, preoperatively or intraoperatively. Tranexamic acid can also be added to the therapy.[54]

A coagulopathy that is similar to hypofibrinogenemia is afibrinogenemia.[56,57] Afibrinogenemia is considered a rare coagulation disorder with an estimated prevalence of 1/1,000,000 worldwide. Half of the congenital afibrinogenemia cases reported in the literature result from a consanguineous marriage in the family history. Pati et al.[70] suggested that the ideal level of fibrinogen in the bloodstream should be > 1 g/L, while Kilit et al.[63] suggested that these levels should be ~ 1.5 g/L.

Disseminated intravascular coagulation (DIC) has been reported as a cause of EDH, either alone or associated with SCA. Iliescu et al.[60] reported one case of a pregnant woman who underwent curettage after spontaneous termination of pregnancy and evolved with spontaneous EDH and subsequent death due to DIC. Intrauterine fetal demise is often responsible for the onset of severe DIC, and according to the medicolegal literature, several forms of intracerebral hemorrhage may be complications of this hematologic entity.[60] Other studies reported the same condition secondarily to metastatic processes[66,68] or SCA.[11,12,48] Saha et al.[49] observed 100% mortality in patients with spontaneous EDH who suffered from DIC, which is similar to that observed in the present study.

Immune thrombocytopenic purpura (ITP) is another coagulopathy correlated with the occurrence of spontaneous EDH. However, its pathophysiological role has been explained by different mechanisms. Zheng et al.[15] reported a patient with spontaneous EDH with chronic evolution who, although presenting only with headache, had large volume and advanced calcification. Thus, thrombocytopenia may be directly associated with chronic bleeding. Ntantos et al.[27] reported a case of acute development with multiple neurological deficits in a patient with ITP refractory to pharmacological treatment. It is relevant to consider that the escalating therapy in these cases uses thrombopoietin receptor agonist drugs, assuming the risk of cerebral thrombotic events. Given this, hypercoagulability and venous stasis may be the connective link between ITP and spontaneous subdural and epidural hemorrhages, by venous rupture and dissection of the periosteal layer of the meningeal, respectively.[27,71]

There is a case report in the literature of spontaneous EDH associated with myelodysplastic syndrome (MDS) described

by Grabel et al.[59] in a child on daily warfarin use. The cause of bleeding remains obscure due to the previous coagulopathy of the patient. Grabel et al.[59] recommended the regular use of CT to evaluate pediatric patients with coagulopathy who presented altered mental status.

Neoplasms

Spontaneous EDH caused by neoplasms is a rare condition, with the most common lesions being hepatocellular carcinomas.[72] In the present literature review, among the patients who presented neoplastic lesions (►**Table 4**),[26,72,73,74,75,76,77,78] reports involving metastasis from hepatocellular carcinoma prevailed (50%), followed by metastasis from lung carcinoma. The reason why cranial metastases derived from hepatocellular carcinoma cause EDH more often than other tumors still uncertain, but it is known that they may frequently contribute to intracranial bleeding[79]; what is already known is that carcinomas should be considered as a differential diagnosis in the evaluation of patients with EDH.[80]

The first report of spontaneous EDH involving a primary tumor was described by Mahore et al.,[72] and the lesion located in the patient was an angiosarcoma. The most common location of hematomas in patients with neoplastic lesions is intratumoral or intraparenchymal, and rarely epidural.[80] Among EDHs caused by neoplastic disease in the present study (►**Table 3**), the most common location observed was in the parietal region (78.6%); the hematoma was present overlapping > 1 brain lobe in 50% of the cases. Based on the report by Hassan et al.,[26] the possible mechanism involved in the formation of HE in patients with dural metastasis is the rupture of cerebral blood vessels from micrometastases.

In a pediatric case reported in India,[72] the authors concluded that the possible triggering factor for intracranial bleeding and EDH formation would be the fragility and dysplasia of the thin vessels in the tumor tissue, associated with tissue necrosis. Similar observations were made by Anegawa et al.,[74] who suggested that hemorrhages initiated in a small intratumoral artery accelerate the displacement of the dura mater.

Cranial metastases due to hepatocellular carcinoma are rare among patients with this neoplasm, ranging from 0.4 to 1.6%.[81] In most EDH cases due to hepatocellular carcinoma, the bleeding derives from the middle meningeal artery, the emissary veins, and the venous sinus.[80] Woo et al.[82] reported the case of a patient with hepatocellular carcinoma located at the base of the skull, and the authors demonstrated that the bleeding arose from the diploic space and that the liver dysfunction was an intensifying factor of the bleeding.

Lung carcinomas, especially small cell carcinomas, commonly metastasize to the central nervous system (CNS) and account for between 60 and 70% of CNS metastases, being rarer in the epidural space, with a frequency of < 3.6%.[75]

Simmons et al.[75] suggested that the treatment of neurological involvement in patients with metastasis should have an aggressiveness proportional to the oncologic treatment, justified in the high potential for deterioration of the clinical picture. In the present review, 57.1% of the patients with a neoplastic lesion died due to failure in the primary tumor organ or went into a permanent vegetative state. Among the other case reports, the prognosis ranged from the partial improvement of the clinical status to complete improvement and return to chemotherapy.

Table 4 Summary of reported cases of spontaneous epidural hematoma associated with neoplastic disease

Author(s), year	EDH etiology	EDH site	Diagnostic imaging exam				Surgery	Outcome
			CT	MRI	AG	Rx		
Anegawa et al., 1989[74]	Metastasis of ovarian carcinoma	Right parieto-occipital	x				Yes	Recovered
Kuga et al., 1990[73]	Metastasis of hepatocellular carcinoma	Right parietal	x		x		Yes	Died
Nakagawa et al., 1992[84]	Metastasis of hepatocellular carcinoma	Occipital	x				Yes	Died
Simmons et al., 1999[75]	Lung carcinoma metastasis	Right parietal	x				Yes	Partially recovered
Hayashi et al., 2000[85]	Metastasis of hepatocellular carcinoma	Right parietal	x	x	x		Yes	Died
Dufour et al., 2001[76]	Meningioma	Parietal	x	x	x		No	Recovered
Hassan et al., 2009[26]	Lung carcinoma metastasis	Right parieto-temporal	x				Yes	Partially recovered
Kanai et al., 2009[81]	Metastasis of hepatocellular carcinoma	Left parieto-occipital	x				Yes	Died
Kim, et al., 2010[80]	Metastasis of hepatocellular carcinoma	Right temporal	x				Yes	Died
Woo et al., 2010[82]	Metastasis of hepatocellular carcinoma	Right parieto-temporal	x				Yes	Vegetative state
Mahore et al., 2014[72]	Angiosarcoma	Left cerebellar hemisphere	x	x			Yes	Recovered
Kim et al., 2016[79]	Metastasis of hepatocellular carcinoma	Left parieto-occipital	x				Yes	Died
Ramesh et al., 2017[77]	Peripheral nerve sheath metastasis	Right parietal	x			x	Yes	Recovered
Zhao et al., 2020[78]	Gastric carcinoma metastasis	Parietotemporal	x				Yes	Died

Abbreviations: AG, angiography; CT, computed tomography; MRI, magnetic resonance imaging; RX, radiography.

Eosinophilic Granuloma

The case reports of spontaneous EDH due to eosinophilic granuloma (EG) represented 7.3% of all patients in the present study (►**Table 5**). Eosinophilic granuloma is related to Langerhans cell histiocytosis, a rare immunological disorder characterized by histiocytic proliferation in multiple organs. In this context, EG represents the local form of histiocytosis and occurs predominantly in children and adolescents.[12] In our literature review, we observed, among the EG group, that the mean age of the patients was 6.8 years old, ranging from 2 to 15 years old, which reinforces the occurrence among young patients.

Al-Mousa et al.[14] reported a case of a 3-year-old child who presented an EDH associated with EG, verified through CT in an osteolytic lesion closely associated with the hematoma and histopathological analysis confirming the type of lesion. The association between EG and HE is rare, and the pathogenesis is explained in several ways: stretching of the dura mater during granuloma growth, bleeding of dural neovascularization, erosion of dural surface vessels, and intradiploic erosion.[12] We observed in the present study that the highest occurrence of EG was in the parietal region, followed by the occipital region. In all cases, CT was performed for diagnosis. Surgical intervention was also performed in all patients. All patients listed in ►**Table 5** were male.

Chronic Renal Disease

Chronic renal disease is currently a worldwide public health problem, with an increasing incidence, and it is known that intracranial hemorrhages are a rare but possible presentation, usually spontaneous.[17] In some case reports,[4,5] renal disease was considered the etiology of spontaneous EDH. The exact mechanism by which chronic renal disease causes bleeding is not understood, but it is comprised that platelet

Table 5 Summary of reported cases of spontaneous epidural hematoma associated with other causes

Author, year	EDH etiology	EDH site	Diagnostic imaging exam				Surgery	Outcome
			CT	MRI	AG	Rx		
Hamamoto et al., 1998[4]	Kidney disease	Right occipitotemporal	x			x	Yes	Died
Cho et al., 2001[8]	Eosinophilic granuloma	Left occipital	x				Yes	–
Chen et al., 2002[9]	Eosinophilic granuloma	Left occipital	x				Yes	–
Mut et al., 2004[10]	Eosinophilic granuloma	Occipital (bilateral)	x	x			Yes	Recovered
Shahlaie et al., 2004[5]	Chronic kidney disease	Left temporoparietal	x				Yes	Died
Ahmad et al., 2005[22]	Cardiac surgery	Posterior fossa	x				Yes	Recovered
Wani et al., 2008[25]	Intradiploic epidermoid cyst	Left parietooccipital	x				Yes	Recovered
Cho et al., 2009[24]	Intracranial hypotension	Retroclival region		x	x		No	Recovered
Zheng et al., 2009[15]	Chronic kidney disease	Left temporoparietal	x		x		No	Recovered
Bhat et al., 2010[11]	Eosinophilic granuloma	Right parietal	x				Yes	
Song et al., 2015[20]	Systemic lupus erythematosus	Right frontal and right temporoparietal	x				Yes	Recovered
Yadav et al., 2016[17]	Chronic kidney disease	Frontal (bilateral)	x				Yes	Recovered
Ruschel et al., 2016[18]	Drug therapy	Left parietal	x				Yes	Partially recovered
Sadashiva et al., 2016[12]	Eosinophilic granuloma	Right temporoparietal	x	x			Yes	Recovered
Bakhaidar et al., 2016[13]	Eosinophilic granuloma	Right parietal	x				Yes	Recovered
Khan et al., 2017[16]	Chronic kidney disease	Frontal (bilateral)	x				No	Recovered
Khan et al., 2017[16]	Drug therapy	Frontoparietal	x				Yes	Recovered
Chen et al., 2018[23]	Hysterical crying	Left frontal and right frontal*	x				Yes	Recovered
Fukai et al., 2019[19]	Drug therapy	Right frontal	x	x	x		Yes	Recovered
Yin et al., 2019[21]	Systemic lupus erythematosus	Left temporoparietal. Frontal and left occipital*	x				Yes	Died
Al-Mousa et al., 2020[14]	Eosinophilic granuloma	Left parietal	x				Yes	Recovered

Abbreviations: AG, angiography; CT, computed tomography; MRI, magnetic resonance imaging; RX, radiography.
*At different times.

dysfunctions have been documented in patients with uremia, a condition that predisposes to the appearance of spontaneous bleeding.[15] Shahlaie et al.[5] reported a case of a patient in end-stage renal disease in the absence of hemodialysis, associating the pathogenesis to the uremia or hypertension of the patient. In an attempt to elucidate the pathogenesis of EDH in the light of chronic renal disease, Khan et al.[16] reported the following causes: fluctuations in ICP during hemodialysis, associated arterial hypertension, uremic platelet dysfunction, use of heparin during hemodialysis, and direct activation of tissue plasminogen activator as a result of hemodialysis.

It is not understood in the literature whether hematoma drainage and brain decompression contribute significantly to the bleeding process in patients with an evident propensity for epidural bleeding,[5] but it is known that early diagnosis and treatment of coagulopathies should be done if available.[17] Thus, signs such as sudden and severe headache associated with nausea and vomiting, despite the absence of trauma, should be investigated, and spontaneous EDH must be taken into consideration.[17]

Medication

Among the reports of spontaneous EDH, some case reports[16,18,19] have been related to drug therapy. Ruschel et al.[18] reported a case of EDH in a 39-year-old patient using rivaroxaban. The use of rivaroxaban poses a risk of developing hematomas that is 40% lower than the risks posed by the use of Warfarin.[18] Khan et al.[16] reported a patient in treatment for tuberculosis, which led to decreased renal function and consequent EDH formation. As in reports of EDH resulting from renal disease, the exact mechanism for hematoma formation is still not widely understood.

Fukai et al.[19] reported a patient using fingolimod who developed EDH, which may cause arterial vasospasm and reversible posterior encephalopathy syndrome. In this report, the patient had multiple sclerosis, and it is known that this group of patients is more vulnerable to vascular damage, especially those who use fingolimod, which may induce hemorrhage or ischemia, either by vasospasm or vascular rupture, but this fact is still controversial.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) constitutes an autoimmune disease characterized by clinical heterogeneity. In patients with SLE, EDH can result from thrombocytopenia, hypertension, hemorrhagic infarction, hyperlipidemia, coagulation disorder, and cerebrovascular disease, presenting as a severe comorbidity among these patients.[21] Song et al.[20] also suggested that EDH secondary to SLE may regress more rapidly than EDH of traumatic origin and that increasing the dosage corticotherapy drugs is a relevant condition in the treatment of these patients. The thrombocytopenia presented can derive from several situations, such as platelet destruction by antibodies, therapy with immunosuppressive agents, antiphospholipid antibody, thrombotic microangiopathy, medullary depression, and disorder in the maturation of megakaryocytes.[21]

Vascular and Dural Abnormalities

Dural vascular malformations are considered rare lesions with an infrequent occurrence of EDH. In 1983, Hasegawa et al. reported a case of spontaneous EDH associated with a pseudoaneurysm of the middle meningeal artery, and the patient also had frequent reports of otitis media.[83] Sanchis et al.[1] reported a case of a patient with a saccular aneurysm of the right middle meningeal artery and parietal dural angioma associated with an EDH. Both patients in the reported cases reported no history of trauma. Dural vascular malformations rarely lead to hematoma formation, but when they occur, they can be seen in the epidural space.[4]

Other Etiologies

Besides the already mentioned reports, Chen et al.[23] reported an uncommon case of spontaneous EDH due to a hysterical crisis; the authors associate the formation of the hematoma to hyperventilation during the crisis. The patient described by Chen et al.[23] presented to the emergency room twice, at 2-year intervals, both times with EDH due to hysterical crying. In the first admission, the EDH was located in the left frontal lobe, and 2 years later, during the second admission, the EDH was located in the right frontal lobe. In the report, the patient did not have any comorbidities or clinical, laboratory, and imaging findings that would explain the bleeding. The authors further reported that crying induces hypertension and microbleeding of the dural vessels, which may cease spontaneously under normal conditions. Hysterical crying may be followed by acute hyperventilation, hypocapnia, and arterial constriction, which leads to a reduction in cerebral blood flow. The decrease in cerebral flow leads to decreased ICP, promoting dural detachment from the bone tissue, thereby triggering the formation of EDHs.

Ahmad et al. reported a case of a patient with EDH following cardiac surgery. Deterioration of the neurological status after cardiac surgery usually occurs due to cerebral edema or embolization. Patients with deteriorating neurological conditions after cardiac surgery should also be investigated for the presence of a hematoma. The cause may be heparinization during the procedure or even hypotension during cardiac arrest23. In the present review, one report[24] considered that the formation of EDH was due to intracranial hypotension and possibly resulted from a systemic condition. This latter event may cause the rupture of vessels in the dura mater with the variation in brain volume.[22]

Wani et al.[25] reported the case of an EDH secondary to an intradiploic epidermoid cyst. Intradiploic epidermoid cysts can elevate ICP or eventually evolve into malignancy. Imaging examination can define well the radiolucent lesion with sclerotic borders centered in diploe. The mechanism suggested by the authors[25] consists of continuous dural detachment and consequent bleeding from dural vessels or of

bleeding from diploid vessels and extravasation from unnoticed trauma.

Evaluation and Diagnosis

The signs and symptoms of acute EDH involve neurological impairment, sometimes indicating the need for surgical intervention. Sudden headache and consciousness disturbances are the main manifestations of EDH.[50] In the present study, the clinical picture of the patients varied according to their underlying etiology, location, and EDH volume.

Regarding the evaluation of the patients with spontaneous EDH, clinical examination is the main form of exploring the complaints of the patients. We should pay special attention to the physical examination of the sinuses, the ears, and the chest. Other methods of investigation are sinus radiography (sinus infection), lung radiography (lung mass), abdominal CT (liver neoplasms or other vascular changes), coagulogram (coagulopathies), and histological analysis of hematomas and abnormal tissues.[26] Among the imaging examinations, CT remains the most widely used because of the lower cost and the ease and quickness of image acquisition. The diagnosis of EDH is confirmed with CT, and if specific findings associated or not with clinical deterioration are found, emergency surgery should be performed.[17]

Epidural hematomas present at CT as an extra-axial collection in the shape of a biconvex lens.[22] In the evaluation of the CT, the size and the mass effect of the hematoma and the deviation of midline structures should be observed. The CT has also been useful to evaluate osteolytic lesions in the skull cap.[9] Magnetic resonance imaging (MRI) has been indicated in case of doubt in the diagnosis and in the differential diagnosis.[35] Magnetic resonance imaging examination can reveal cranial convexity infarcts where the EDH is located, a common condition among EDH secondary to SCA.[63]

Treatment

The choice between conservative treatment and a surgical intervention depends not only on the size of the hematoma but also on the severity of symptoms and disease progression.[76] Deterioration of neurological conditions is a relevant factor influencing surgical indication.

In our study, the most common treatment was surgery, representing 81% of the cases. Among the surgical interventions, osteoplastic craniotomy followed by hematoma drainage was the most common procedure. Conservative treatment represented 14.7% of the cases and is related to the management of the underlying disease that triggered the formation of the hematoma. Deaths were more frequent among patients who presented neoplastic lesions as the etiology for the formation of the hematoma. The time course of the patients in each study was different, ranging from observation during hospital discharge to a 4-year prospective follow-up.

Conclusion

Nontraumatic EDH represents an uncommon manifestation of several pathologies. A clinical investigation should be attentive to such a possibility since this condition is amenable to medical intervention and presents a good prognosis when diagnosed early. Health professionals must pay attention to the physical examination and to the clinical history of the patient to better understand and approach the patient with EDH. In this sense, it is also important to study the pathogenesis of spontaneous EDH in each etiology, due to the scarcity of precise information about the nature of these events. These strategies may improve the therapies for the treatment of this condition, especially in prevention.

Conflict of Interests

The authors have no conflict of interests to declare.

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Neurological Patients during the Covid-19 Pandemic

Pacientes neurológicos durante a pandemia de Covid-19

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Abstract

With the current pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), measures of social isolation were necessary, and this resulted in the interruption of several treatments. Regarding neuro-oncological patients, especially those with central nervous system (CNS) disorders, this interruption can cause serious damage or even compromise the success of the treatment in the future. It is essential that each case be evaluated separately to decide how to continue treatment during the pandemic, always considering the risk of SARS-CoV-2 infection and the benefits that the treatment will bring. The policy of not prescribing potentially toxic drugs, chemotherapy, and immunosuppressive therapies, as well as the use of techniques like stereotactic biopsy and telemedicine are important strategies at this time.

Keywords
- coronavirus
- neuro-oncology
- treatment

Resumo

Com a atual pandemia causada pelo coronavírus da síndrome respiratória aguda grave 2 (*severe acute respiratory syndrome coronavirus 2*, SARS-CoV-2, em inglês), foram necessárias medidas de isolamento social que resultaram na interrupção de alguns tratamentos médicos hospitalares. Em relação aos pacientes neuro-oncológicos, principalmente aqueles com distúrbios do sistema nervoso central (SNC), uma interrupção pode causar sérios danos ou até mesmo comprometer o sucesso do tratamento no futuro. Assim, de acordo com a literatura encontrada, é de fundamental importância que cada caso seja avaliado individualmente, para que se decida como prosseguir com o tratamento durante a pandemia, sempre considerando o risco de infecção por SARS-CoV-2 e os benefícios relacionados ao tratamento. São estratégias importantes neste momento a política de não prescrição de medicamentos potencialmente tóxicos, quimioterapia e terapias imunossupressoras, além do uso de técnicas como biópsia estereotáxica e telemedicina..

Palavras-chave
- coronavírus
- neuro-oncologia
- tratamento

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The current coronavirus disease 2019 (Covid-19) pandemic has brought about measures of social isolation which have resulted in the interruption of several health treatments. Regarding neuro-oncological patients, especially those with central nervous system (CNS) disorders, this interruption can cause serious damage or even compromise the success of the treatment in the future, since surgical resections are being avoided as much as possible, and several rehabilitation services are not available due to the closure of units and the reorientation of teams to combat Covid-19. Therefore, certain information on how to organize these treatments in the current scenario is extremely relevant and should always be followed with due precautions, as these patients are more likely to develop the most severe forms of Covid-19, especially if they have undergone chemotherapy or surgery recently.[1,2]

First, it is essential that each case be evaluated separately to decide how to continue treatment during the pandemic, always considering the risk of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the benefits that the treatment will bring. In addition, emergency cases or those with a high chance of cure should not be extended.[3] It is essential to consider the reuse of available drugs to treat and prevent brain diseases associated with Covid-19.[4] However, more than ever, the policy of not prescribing potentially toxic drugs, systemic chemotherapy, and immunosuppressive therapies is mandatory, such as re-irradiation combined with steroids, for which the evidence of benefit is not clinically relevant in the current scenario. In situations in which there are no immediate urgent needs and long-term treatment is likely to bring benefits, such as in patients with low-grade astrocytomas or oligodendrogliomas, a more conservative dose of chemotherapy should be considered.[5]

The use of stereotactic biopsy has already been described, which at least offers a definitive diagnosis for severe conditions and can elucidate malignant tumor characteristics, with the advice that the best possible treatment should be followed in view of the current incapacity for maximum tumor resection. At the Mount Sinai Hospital, in New York, patients are always considered positive for Covid-19 until proven otherwise, and maximum precautions have been taken, including regarding the patients in need of intubation and in the postoperative setting.[2]

Another factor to be considered is telemedicine. In Brazil, the Federal Council of Medicine already recognizes the possibility of remote medical care during the fight against Covid-19, as well as in other countries in which the performance of these virtual consultations is made available when feasible.[6] However, for face-to-face procedures, patients should be tested for Covid-19. In institutions in which the test is not available, there should be a questionnaire regarding symptoms, and patients should be tested when available.[7] In addition, some processes must remain accessible, such as ambulatory radiology, with the establishment of protocols that limit the number of patients in the waiting room and provide protective masks for everyone.[8]

It is also necessary to consider during this period the frequency of clinical follow-up at regular intervals for patients who have been stable and without intervention for years, as is the case of many individuals with brain tumors. Visits to the hospital environment can be divided into defined populations with more severe cases.[4]

Concluding, clinical follow-ups differ in relation to the conditions of the patients, according to the severity of each case. That is why the benefits and risks that the continuity of treatment will bring must be considered, with precaution and engagement on the part of the entire team involved.

Conflict of Interests

The authors have no conflict of interests to declare.

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Intracranial Teratoma in Young Adult Female: Case Report

Teratoma intracraniano em mulher adulta jovem: Relato de caso

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Abstract

Intracranial teratoma corresponds to a type of germ cell tumor (GCT) of the central nervous system which is characterized by the presence of tissues derived from the germinal layers, which may have hair and adipose tissue inside, for example. The literature on the subject is scarce, and the T2 magnetic resonance imaging (MRI) pattern commonly found is that of a heterogeneously hyperintense mass and, after contrast, teratoma presents heterogeneous enhancement. Therefore, the present case report aims to present atypical results of a GCT in a young adult woman. Data analysis and compilation were performed from medical records, as well as the neuroimaging study. Thus, the present case report demonstrates neuroimaging findings with homogeneous postcontrast enhancement in an adult patient, with an unusual age profile when compared with most of the studies published so far. This demonstrates that it is possible to have atypical neuroimaging findings for mature teratomas and that they can behave in a less aggressive way, not requiring adjuvant postoperative therapies.

Resumo

Teratoma intracraniano corresponde a um tipo de tumor de células germinativas (TCG) do sistema nervoso central que se caracteriza pela presença de tecidos derivados das camadas germinativas que podem conter pelos e tecido adiposo no seu interior, por exemplo. A literatura sobre o assunto é escassa e o padrão de ressonância magnética (RM) T2 comumente encontrado é o de massa heterogeneamente hiperintensa e, após contraste, o teratoma apresenta realce heterogêneo. Pensando nisso, o presente relato de caso tem como objetivo apresentar resultados atípicos de TCG em uma paciente mulher adulta jovem. Para isso, foi realizada a análise e a compilação dos dados em

Keywords
- germ cell tumor
- intracranial germ cell tumor
- mature teratoma

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Palavras-chave
- tumor de células germinativas
- tumor intracraniano de células germinativas
- teratoma maduro

prontuário, assim como um estudo de neuroimagem. Assim, o presente relato de caso demonstra achados de neuroimagem com realce homogêneo pós-contraste em indivíduo adulto com perfil etário incomum ao descrito na maioria dos estudos até o momento. Isto demonstra que é possível a confirmação dos achados de neuroimagem atípicos para os teratomas maduros e que eles podem se comportar de forma menos agressiva, dispensando terapias adjuvantes no pós-operatório.

Introduction

Germ cell tumors (GCTs) of the central nervous system are relatively rare, comprising 0.5 to 3% of all intracranial tumors.[1] Germ cell tumors are divided into the following classes: germinomas, nongerminomatous (teratoma, embryonic carcinoma, endodermal sinus tumor, and choriocarcinoma), and mixed GCT. Teratomas are a subtype of GCTs characterized by the presence of somatic tissues derived from two or three germ layers (the ectoderm, the endoderm, and the mesoderm), which commonly affect the child population[2] and, when they affect adults, they are commonly derived from gonadal tissues.[3] They can be divided into mature teratomas, immature teratomas, and teratomas with malignant transformation. Mature teratoma is characterized exclusively by mature adult tissue, while immature teratomas demonstrate components similar to fetal tissue, and teratomas with malignant transformation are very rare and differ because of the malignant transformation of somatic tissue.[4]

Primary intracranial teratomas have a clear male predominance (4:1) and occur predominantly in childhood and adolescence, with only a few cases reported in adulthood.[2,5–7] These tumors tend to appear in the midline structures of the brain, mainly in the pineal and suprasellar regions, possibly due to the great potential of these areas for displacement of progenitor germ cells.[1,8]

Reports of the image pattern of teratomas are scarce in the literature. Most of the knowledge we have are from case reports or from a few small series. Most tumors are solid cystic or predominantly cystic with a mural nodule and show mixed signs derived from different tissues. On T1-weighted images, most lesions show multilocularity or cysts, with or without hyperintensities. On T2-weighted images, most teratomas are shown as heterogeneously hyperintense masses. After the administration of contrast agents, teratomas are usually visualized with a heterogeneous enhancement. But a homogeneous enhancement is possible, as demonstrated in our case.[9,10] With that in mind, the present report aims to present a rare case of CGT in a young adult woman with atypical neuroimaging.

Case Report

The description of the present case report was approved and accepted by the research Ethics Committee (CEP – Plataforma Brasil), under opinion number 4.869.499. The present report refers to a female patient, 36 years old, white, who was admitted to the health system at the emergency service with a complaint of chronic periorbital headache associated with photophobia, phonophobia, nausea, and vomiting – there was a clinical picture of facial paresthesia associated with the headache episodes. According to the patient, she had no previous history of pathologies and did not use continuous medication. There were no complications during the physical and neurological examination.

Through the analysis of neuroimaging by magnetic resonance imaging (MRI) of the skull, there was evidence of an extra-axial mass with expansion to the right middle fossa, with a mass effect in the right temporal lobe. Postcontrast T1 neuroimaging (T1C +) showed a homogeneous hyperintense mass. On the other hand, at T2, the lesion had heterogeneous hyperintensity and diffuse effects of susceptibility, and when at gradient echo (GRE), hypointensity was observed, thus suggesting the existence of calcification or hemorrhage. Therefore, the main initial diagnostic hypothesis was meningioma (►**Figs 1** and **2**).

There was an investigation to exclude the possibility of arteriovenous malformation and cerebral angiography was performed, which indicated absence of vascular and/or flow alterations, discarding the possibility of aneurysm (data not shown). After the complementary examinations, resection of the tumor was performed for further confirmation by anatomopathology. The mass was removed with a size of $\sim 35 \times 30 \times 9$ mm. The resection was performed by right frontotemporal craniotomy and step-by-step debulking using a microsurgical technique. When the tumoral mass was seen during the resection procedure, we instantly identify the presence of a reddish-brown mass with the presence of hairs and heterogeneous-looking histological components (►**Fig. 3**).

After the removal of the tumor, the specimen was sent for histopathological examination, which was confirmed by an anatomopathological report to be a mature teratoma, which contained histological constituents derived from the epidermis, from trabecular bone tissue, and from mature white adipose tissue (►**Fig. 4**).

In the clinical evolution after the surgical period, the patient did not present any neurological deficit and there was a medical record description in which she presented a significant improvement regarding the complaint of headaches. After integrated follow-up with an oncologist, there was no indication of chemotherapy or radiotherapy, and the patient was then submitted to regular radiological follow-up.

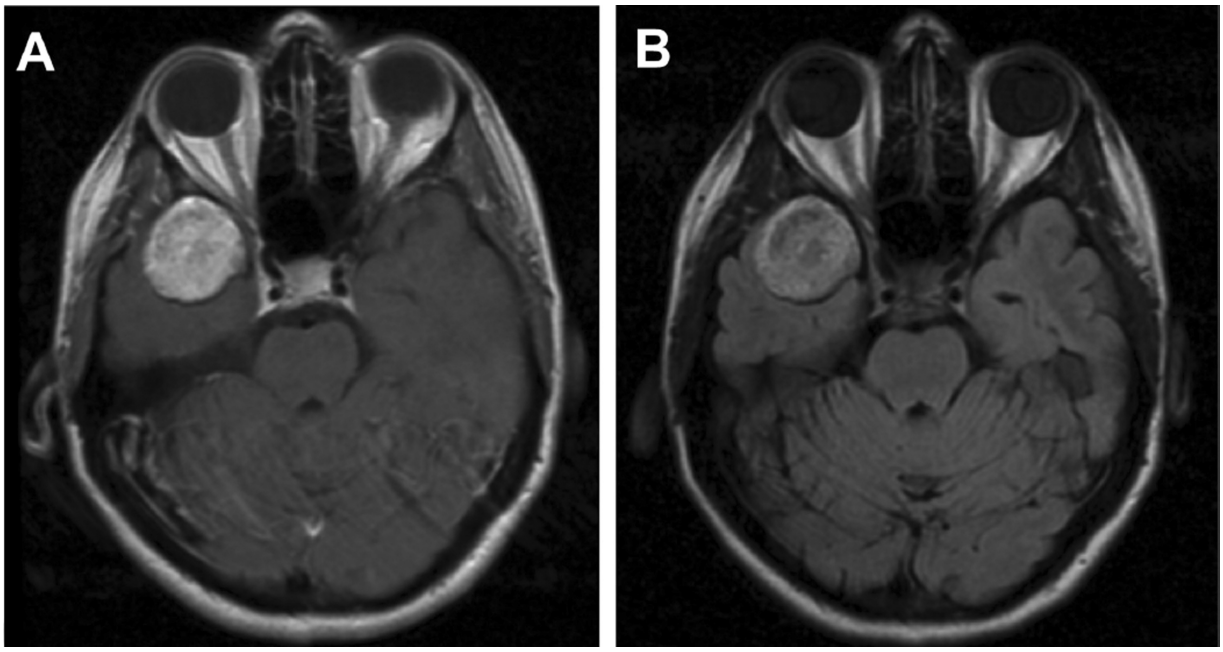

Fig. 1 A. Magnetic resonance imaging in T1C+ – homogeneous and hyperintense mass in the right middle cranial fossa. B. T2 magnetic resonance imaging showing the same mass with a heterogeneous appearance.

Discussion

Mature intracranial teratomas are rare, with 90% of the cases occurring in young individuals < 20 years old.[11] The description of the present case differs from what is most often found in the literature, because in addition to distinguishing from biological aspects for affecting adult women, it also exposes that this extra-axial intracranial teratoma presented atypia in neuroimaging exams.[12–14]

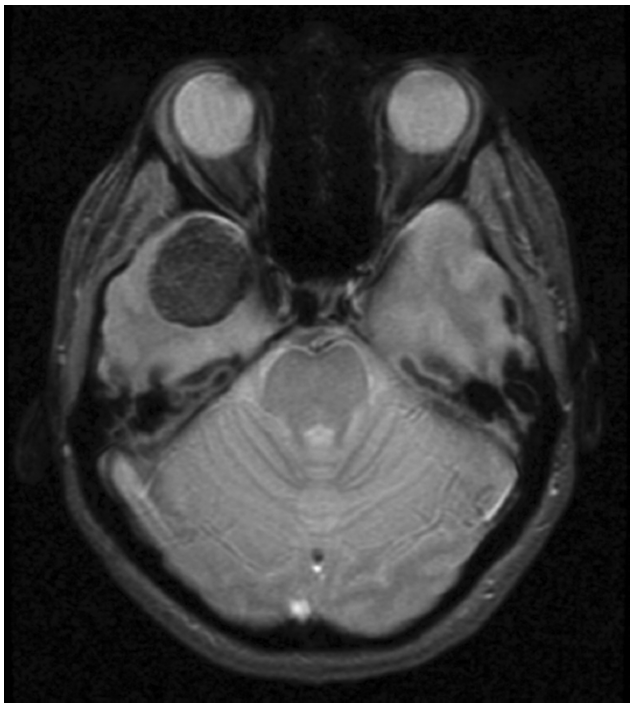

Fig. 2 Gradient echo showing the mass with hypointensity, suggestive of calcification or hemorrhage.

Therefore, knowing that the findings in the literature on the neuroimaging pattern of this type of GCT is scarce, it is recognized that the diagnosis is based on findings in which the results of MRI neuroimaging transmit a mixture of intensity signals in T1 and T2 MRI scans.[15,16] However, in the present case, the results of neuroimaging exams presented as a homogeneous mass in T1C+ and in GRE with hypointensity suggestive of calcification or bleeding. This last finding is identified in approximately half of the cases of mature teratoma, in which there is calcification in its interior[15] as it was also confirmed in the present case through the presence of mature trabecular bone tissue (►**Fig. 4**).

In addition, as expected, according to the histopathological examination, the GCT of the case presented here was also in line with the literature, mostly with tissues derived from the three embryonic leaflets (the endoderm, the mesoderm, and the ectoderm).[14] Specifically, the GCT presented mature tissues such as hair (ectoderm), bone tissue, and white adipose tissue (mesoderm).[17]

As mentioned initially in the discussion of the evolution of the clinical record, the diagnostic hypothesis of an intracranial tumor was mentioned; specifically, it could be of the meningioma type. For this hypothesis, there are clinical findings that lead to such assumption, since, in addition to extra-axial meningiomal formations, MRI showed homogeneous postcontrast characteristics and, also considering that this is the most common primary intracranial tumor with the biological characteristics of the tumor detected in our patient.[18] However, as explained above, the actual diagnosis was different from the initial assumption after the debulking of the tumor *in locu* and the histopathological report.

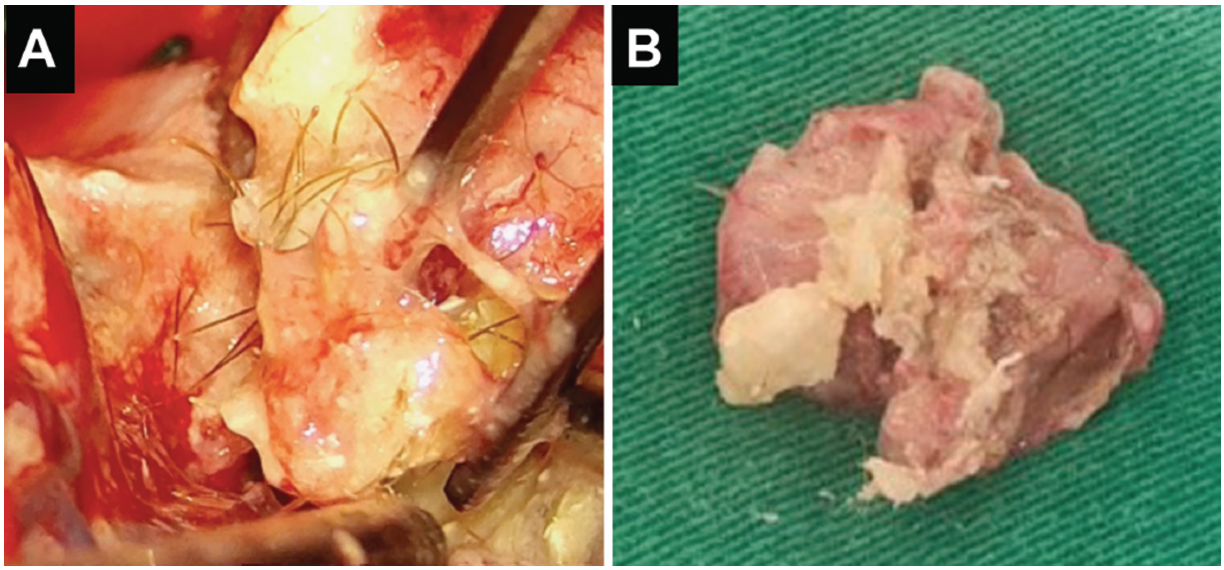

Fig. 3 A. Note the moment of visualization of the tumor by microsurgical technique showing hair strands. B. Tumor mass that was removed, measuring 35 × 30 × 9mm, with a reddish-brown appearance and the possibility of visualizing tissue with histological features similar to those of bone tissue.

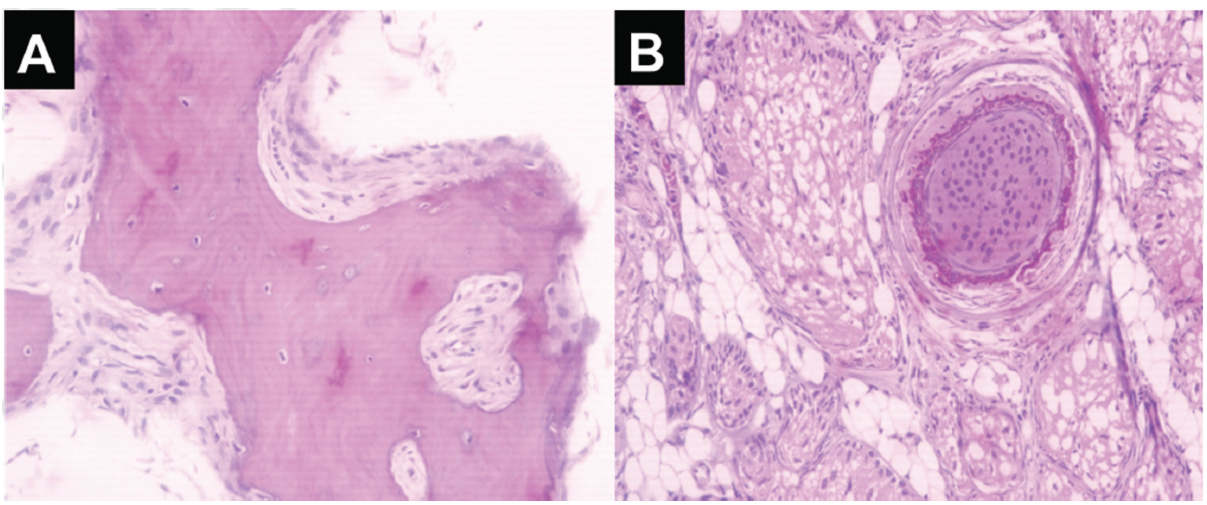

Fig. 4 . View of epidermal and bone tissue in histopathological section. B. Histopathological section showing adipose tissue and trabecular bone.

Regarding the symptomatology of intracranial teratomas, there is no specific and reliable clinical picture, which varies according to the size of the tumor, its location, and course, with findings of intracranial hypertension.[9,19] In the present case report, the manifestation of chronic periorbital headache is justified only by the presence of intracranial hypertension in the patient, as the other symptoms, such as: photophobia; phonophobia; nausea and vomiting together with facial and limb paresthesia were totally unspecific considering the location of the tumor lesion. In addition, nonspecific signs and symptoms are considered since there was no optic nerve compression or intraocular injury, considering that the tumor was located in the anterior portion of the temporal lobe; therefore, far from the posterior occipital portion. Thus, in this scope, one of the possibilities of the symptomatology associated with intracranial pressure would be the existence of a picture of papilledema, as this represents a significant warning sign when there is high intracranial pressure, thus causing not only the potential loss of vision, but also a variety of other visual signs and symptoms such as the ones our patient presented with.[20]

Facial paresthesia may be a finding that is justifiable due to the anxiety of the patient, or it could be explained by compression of the fibers of the cranial nerve root. In both conditions, the literature presents findings in case reports with this sign and symptom; for example, it is known that anxiety can induce hyperventilation, and the resulting hypocapnia and hypocalcemia can cause paresthesia and tetany,[21] just like idiopathic intracranial hypertension.[22]

Generally speaking, CGTs differ in terms of classification and, consequently, in their treatment. In addition to surgical resection of the GCT, options such as chemotherapy and radiotherapy are possible and combinable alternatives.[4] In the present report, the mature teratoma was resected and radiological follow-up was preferentially chosen to optimize

the postoperative period. According to the follow-up of the medical record up to the writing of the present report (~ 12 days after surgery), there was no evidence of recurrence.

Conclusion

This is a case of intracranial teratoma with atypical imaging in a 36-year-old patient. Characteristics such as the age and gender of the patient are uncommon for this type of GCT. Regarding the neuroimaging exams performed in the present case, the homogeneous contrast enhancement – although rare – was a radiological finding and it becomes possible. The treatment of choice presented here was the one most suitable for the case, according to the most accepted protocols, which should preferably be surgical with radiological follow-up, added to chemotherapy and radiotherapy, if necessary, to optimize the postoperative period. With this in mind, we emphasize here that the presentation of a mature teratoma at an advanced age reflects the ideology that these tumors are histologically less aggressive than immature ones.

Ethics

The description of this case report was approved and accepted by the Research Ethics Committee (CEP – Plataforma Brasil), under opinion number 4,727,152.

Conflict of Interests

The authors have no conflict of interests to declare.

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Intradiploic Epidermoid Cyst of the Posterior Fossa – Case Report and Review of the Literature

Cisto epidermoide intradiploico da fossa posterior – Caso clinico e revisão da literatura

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Abstract

Intracranial epidermoid cysts represent ~ 0.2 to 1.8% of all intracranial tumors. These tumors are most frequently encountered in the cerebellar pontine angle or in the parasellar region. Rarely, they arise from the cranial diploe, being able to affect every flat bone of the cranium.

We report a case of a 63-year-old male who presented with progressively worsening headache and vertigo with 6 months of evolution. Neuroimaging identified a probable occipital intradiploic epidermoid cyst with mass effect on the cerebellar hemispheres. This lesion was approached using a suboccipital craniotomy, followed by total resection of the tumor and cranioplasty with titanium plate placement. The histological evaluation confirmed the diagnosis of intraosseous epidermoid cyst. The patient had a successful recovery, without complications or neurologic dysfunction.

Being benign lesions, commonly remaining asymptomatic and rarely presenting as a bony lump in the skull bone, it could be straightforward to assume a conservative management with planned follow-up. On the other side, a more aggressive strategy with surgical excision has been advocated, especially in lesions that tend to enlarge and erode the cranial bone with possible consequent epidural extension and mass effect symptoms. A preoperative diagnosis is extremely helpful in proper surgical planning. Diffusion weighted imaging facilitates a straightforward diagnosis.

As was observed in our case, the largest reviews on intradiploic epidermoids available in the literature mostly demonstrated a benign clinical course. However, malignant transformation can occur. Some patients develop permanent neurologic deficits from mass effect or tumor infiltration. However, surgical approach of the tumor is curative in most cases. Nonetheless, from our experience, it is important to maintain clinical and imaging follow-up with regular monitoring to prevent possible tumor recurrences.

Keywords

- epidermoid cyst
- craniotomy
- cranioplasty
- titanium mesh

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Resumo

Os cistos epidermoides intracranianos representam cerca de 0,2 a 1,8% de todos os tumores intracranianos. Esses tumores são mais frequentemente encontrados no ângulo pontocerebeloso ou na região parasselar. Raramente surgem na diploe, no entanto podem afetar todos os ossos do crânio. Relatamos o caso de um homem de 63 anos que apresentou agravamento progressivo da cefaleia e vertigem e desequilíbrio com 6 meses de evolução. O estudo de imagem realizado identificou um provável cisto epidermoide intradiploico occipital com efeito de massa nos hemisférios cerebelosos. A lesão foi abordada por craniotomia suboccipital, seguida de ressecção total do tumor e cranioplastia com colocação de placa de titânio. A avaliação histológica confirmou o diagnóstico de cisto epidermoide intraósseo. O doente teve uma recuperação bem sucedida, sem complicações ou disfunção neurológica. Sendo lesões benignas, que geralmente permanecem assintomáticas, pode-se assumir um tratamento conservador com seguimento clínico. Por outro lado, uma estratégia mais agressiva com excisão cirúrgica tem sido preconizada, principalmente em lesões que tendem a aumentar e invadir as estruturas ósseas cranianas com possível extensão peridural e sintomas causados pelo efeito de massa. Um diagnóstico pré-operatório é extremamente útil no planeamento cirúrgico adequado. A imagem ponderada por difusão facilita um diagnóstico direto. Como observado no nosso caso, as maiores revisões sobre epidermoides intradiploicos disponíveis na literatura demonstraram, na sua maioria, um curso clínico benigno. No entanto, a transformação maligna pode ocorrer. Alguns doentes desenvolvem déficits neurológicos permanentes por efeito de massa ou infiltração tumoral. A abordagem cirúrgica do tumor é curativa na maioria dos casos. Consideramos importante manter o seguimento clínico e imagiológico regular para prevenir possíveis recidivas tumorais.

Palavras-chave

- ► cisto epidermoide
- ► craniotomia
- ► cranioplastia
- ► rede de titânio

Introduction

First described in 1838 by Müller, intracranial epidermoid cysts represent ~ 0.2 to 1.8% of all intracranial tumors.[3] Most of these tumors arise from the cerebellopontine angle or from the parasellar region. The diploe of the skull is an uncommon location for the presentation of an epidermoid cyst, although this type of lesion can affect every flat bone of the cranium. Primary intradiploic epidermoid cysts of the central nervous system (CNS) are considered rare, with a few more than 200 cases reported so far.[11] The nature of theses lesions is primarily congenital, presumed to occur due to inclusion of ectodermal cells in the bony tissue during neural tube closure in the embryonic life.

We share our experience on a case of primary intradiploic epidermoid cyst in the occipital bone with compression of the dura in the posterior fossa and review the literature on intradiploic epidermoid tumors.

Case Presentation

A 63-year-old male presented to our department with progressively worsening headache, intermittent dizziness, and imbalance, with 6 months of evolution. The vital signs were stable. Personal medical history included arterial hypertension on pharmacological control with aldosterone receptor antagonist and calcium channel blocker, benign prostate hyperplasia, and peripheral venous insufficiency. No relevant familial history was found, namely regarding neurocutaneous disorders.

Physical examination revealed an elevation of the occipital cranial bone region, hard and fixed on palpation, with no obvious redness, swelling or tenderness of the superficial scalp. A cranial computed tomography (CT) scan (►**Fig. 1**) showed a paramedian occipital osteolytic intradiploic expansive lesion with left lateral extension, with smooth bone remodeling and focal bony defects.

Complementary brain magnetic resonance imaging (MRI) was performed (►**Fig. 2**), documenting the large, well-delimited heterogenous intradiploic lesion, mostly hyperintense on T2/FLAIR and hypointense on T1, with no contrast enhancement and demonstrating a characteristic restricted diffusion pattern, suggestive of intradiploic epidermoid cyst. The lesion measured ~ $72 \times 30 \times 40$ mm (transverse, anteroposterior, and rostrocaudal axis, respectively). Intracranial extradural extension and mass effect on the cerebellar parenchyma were also evident.

Surgery was performed under general anesthesia with the patient in ventral decubitus, with the head fixed in the Mayfield head. A midline incision was performed for posterior fossa craniectomy with bilateral enlargement. The tumor eroded both the external and internal laminae of the cranial bone. It was solid, soft, tender, pale yellow, with poor blood

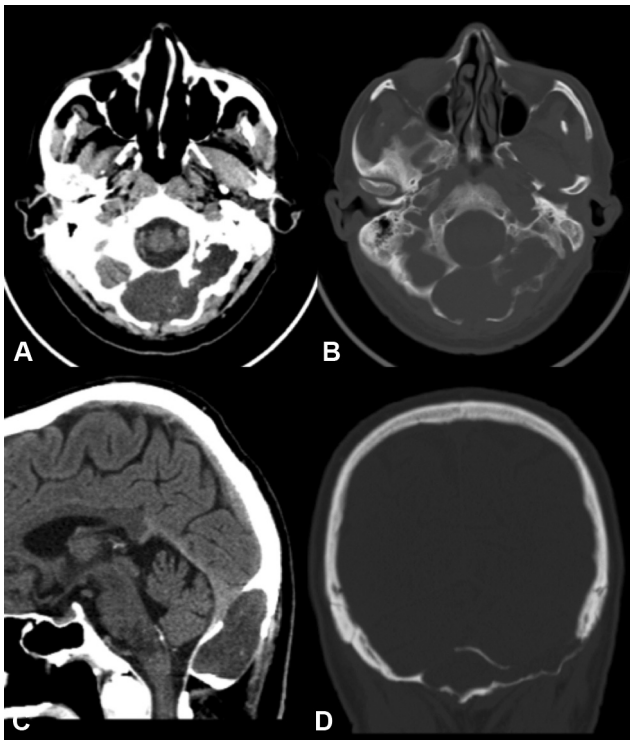

Fig. 1 Head computed tomography scan showing an occipital osteolytic hypodense intradiploic expansive lesion. Note the widening of the diploic space with smooth bone remodeling, thinning of the inner and outer tables, and associated bony defects.

supply, and presented clear margins. There was a slight adhesion to the underlying dura mater, still intact, protecting the underlying parenchyma of the cerebellar lobes.

During lesion resection, hemorrhage was satisfyingly controlled. We performed cranioplasty with a titanium mesh with good results, without complications up to follow-up data. A CT scan performed 1 day after the operation (►**Fig. 3**) showed complete resection of the lesion and absence of immediate complications.

The postoperative histological diagnosis reported epidermoid cyst, (►**Fig. 4**) the first with bone and lining of the cyst and the second with the lining (keratinized stratified squamous epithelium) and the content (keratin).

The patient was discharged 3 days after the operation, with no record of complications or neurological deficits. Headache and vertigo progressively improved during the period of hospitalization. At the 1-month follow-up consultation, the patient was asymptomatic.

A 6-month follow-up brain MRI (►**Fig. 5**) was performed, documenting lack of recurrence.

Discussion

Representing 5% of all intracranial epidermoid cysts, intradiploic epidermoid cysts are considered rare.[1] The nature of these lesions is mostly congenital, arising from sequestration of ectodermal cells, although acquired etiology, namely post-traumatic, has been reported.[2] The slow growth rate of the

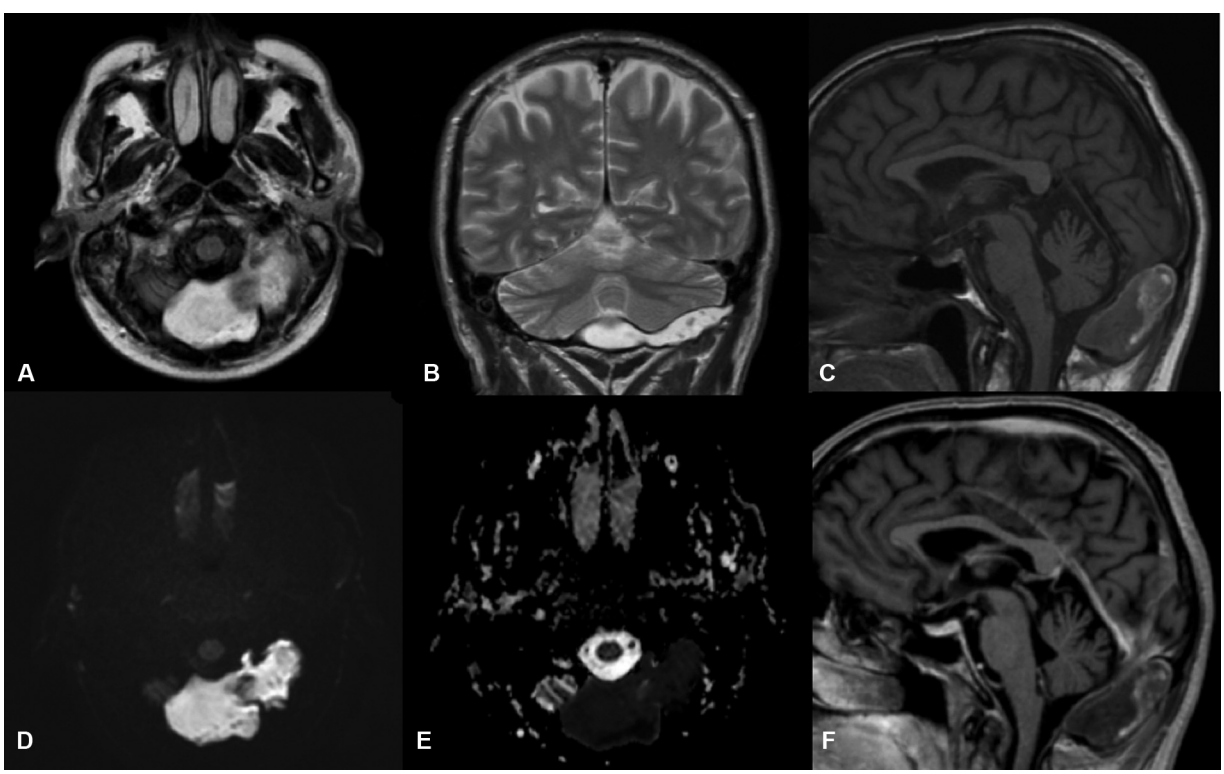

Fig. 2 Brain magnetic resonance imaging A. Axial FLAIR sequence; B. Coronal T2 weighted sequence; C. Sagittal T1 weighted sequence; D. DWI; E. ADC map. F. Sagittal T1 contrast enhanced weighted sequence showing the well-delimited intradiploic lesion in the posterior fossa, with intracranial extradural extension molding the cerebellar parenchyma. The lesion presents T2/FLAIR hyperintensity (images A and B), heterogeneous signal on T1, mostly hypointense with small areas of hyperintensity arrow head (image C), and no contrast enhancement (image F). Finally, note the characteristic restricted diffusion pattern (images D and E). This is an intradiploic epidermoid cyst.

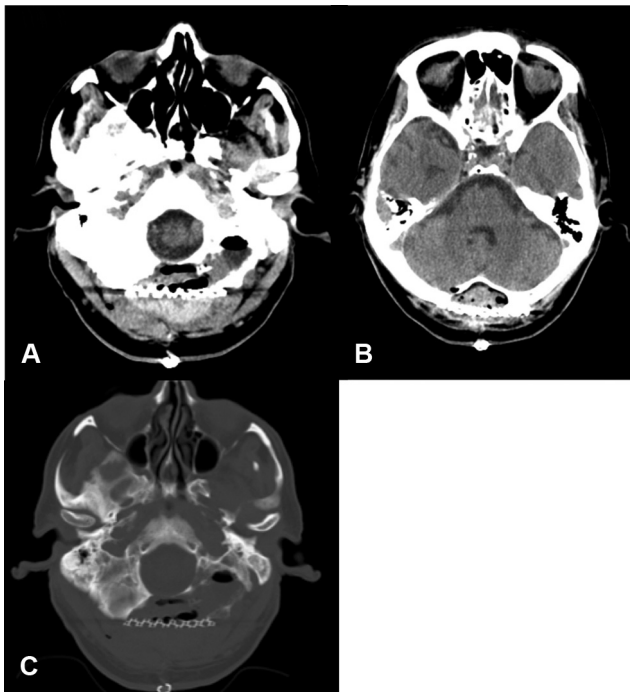

Fig. 3 1-day postoperative head computed tomography scan showing no major complications. In the bone window, we can observe the correct placement of the cranioplasty titanium mesh.

cyst causes expansion of the inner and outer tables of the skull and, through continuous enlargement, it may achieve gigantic dimensions, originating exuberant images, such as in our case. Giant intradiploic epidermoids, however, are exceptionally rare.

A preoperative diagnosis is extremely helpful in proper surgical planning. At times posing as a diagnostic challenge on neuroimaging, current developments in MRI sequences have assisted in obviating this problem[11].

On CT imaging, intradiploic epidermoids typically present as nonenhancing hypodense osteolytic lesions with smooth margins and associated bony defects, causing widening of the diploic space and preferential erosion of the inner table. Differential diagnoses of lytic bone defects with expansion of the diploic space include dermoid cyst, intraosseous hemangioma, eosinophilic granuloma, and fibrous dysplasia. Dermoid cysts usually present in childhood and are located in the midline along suture lines. Intraosseous hemangiomas show characteristic intralesional spicules or trabeculae and homogenous enhancement after contrast administration. Differently from epidermoids, they generally erode the outer table, with a relative sparing of the inner table. Eosinophilic granulomas have a characteristic appearance in the skull as punched-out lytic lesions without a sclerotic rim. Sometimes, a double contour or beveled edge appearance may be seen due to asymmetrical involvement of the inner versus the outer table (the classic "hole within a hole sign"). If there is a small sequestrum of devascularized bone, this will result in a typical "bull's eye" or "button sequestrum" appearance. Fibrous dysplasia lesions generally have more ill-defined margins. There is expansion of the diploic space, but usually both tables are intact, with no bony defects. There is loss of

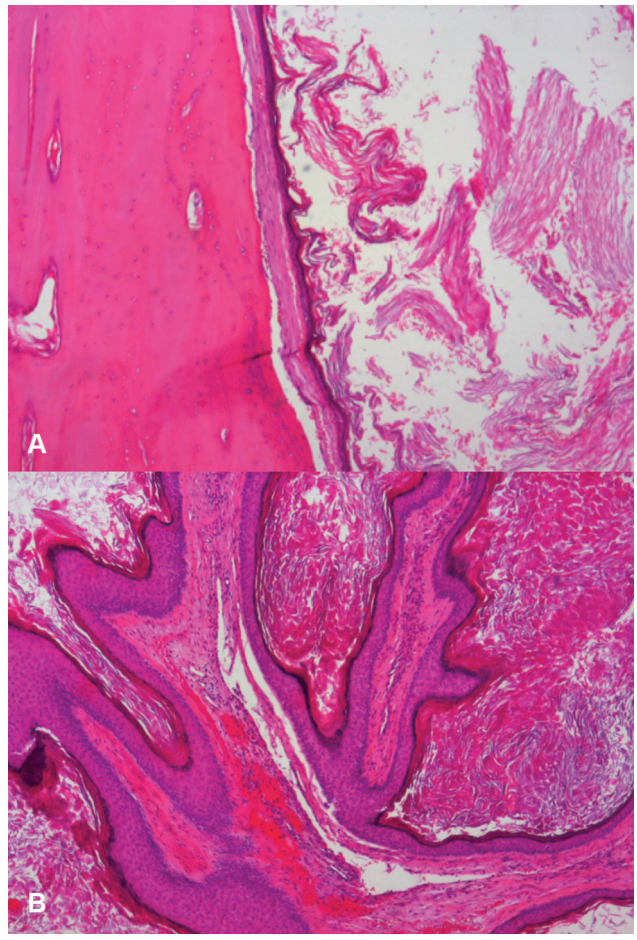

Fig. 4 A. Histologic examination, corresponding to coating (keratinized stratified pavement epithelium) and the content (keratin). B. Histologic examination, corresponding to bone and cyst lining.

the normal corticomedullary differentiation, with a typical homogeneous ground glass appearance.[3]

On MRI imaging, we usually find a mildly T1 hyperintense lesion, with iso/hyperintensity on both T2 and FLAIR images, restricted diffusion pattern, and no contrast enhancement. The differential diagnosis does not pose much of a challenge. Nonetheless, rare, atypical "white epidermoids" with high protein content that show reversed signal intensity on MRI images and have no restricted diffusion have been reported.[1,4]

A review of 8 cases of infratentorial giant intradiploic epidermoids found a mean age at the onset of symptoms of 55 years old and a predilection for males (male:female ratio 8:0).[2] Reported cases of giant intradiploic epidermoids usually course with cranial hypertension symptoms, probably explained by compression or thrombosis of the venous dural sinuses. Other expected signs and symptoms include headaches, which are the most common, cranial nerve deficits, cerebellar symptoms, and seizures. Several case reports found painless subcutaneous scalp swelling to be common. Our patient presented with occipital localized headache, dizziness, and loss of balance, explained by the mass effect on the left cerebellar hemisphere. Despite clear intradiploic expansion, thinning and disruption of both tables, the

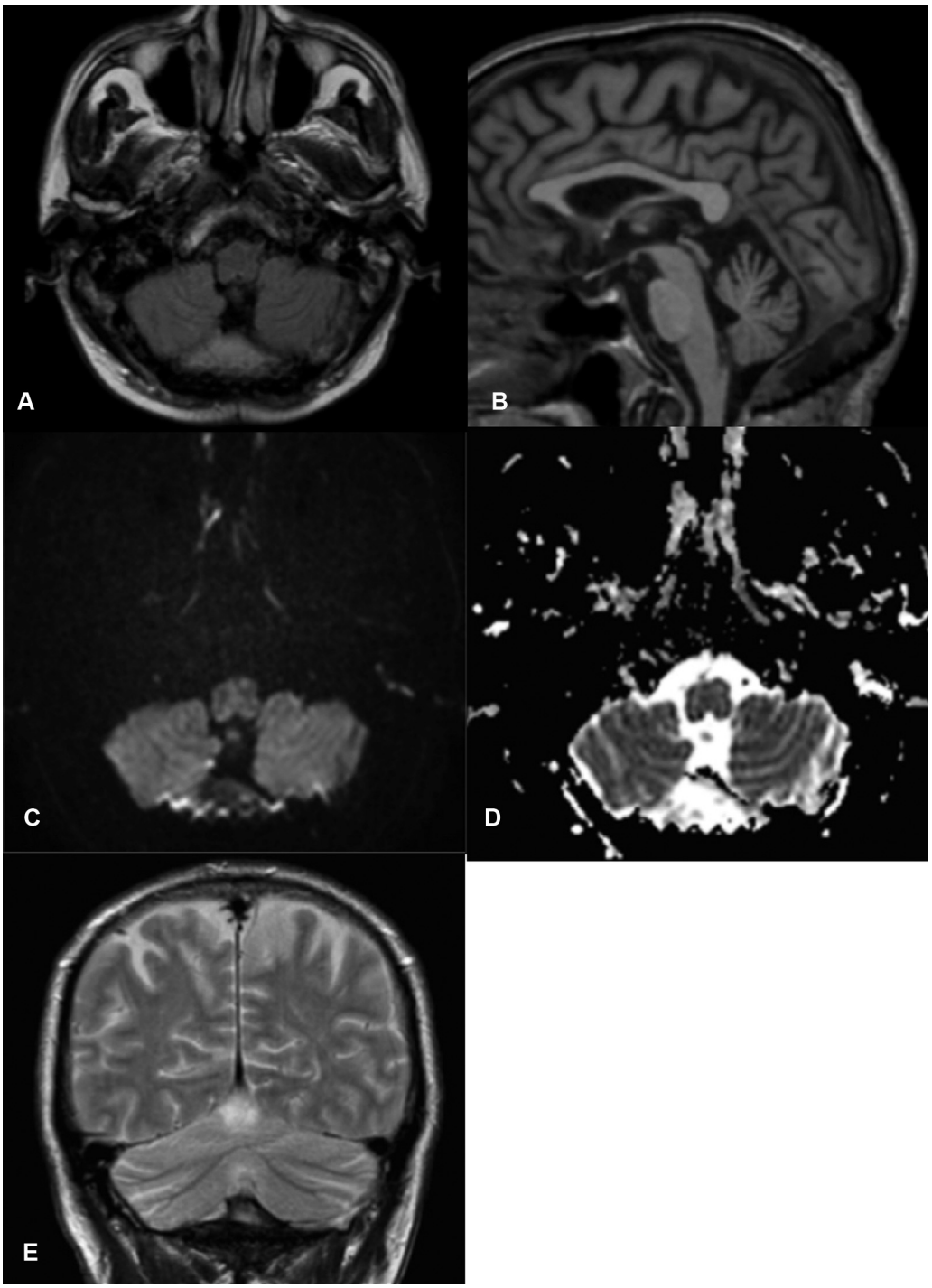

Fig. 5 6-month follow-up brain magnetic resonance imaging documenting lack of recurrence.

epidermoid mostly insinuated intracranially and no scalp swelling was noted. Despite achieving an exuberant size with intracranial expression, there was no significant affection of the cerebrospinal fluid pathways or venous system. These aspects are characteristic of our case, making it unique. Fortunately, there were no complications associated with the lesion itself, since, in particular, the rupture of the cyst, a possible complication, that can may worsen the case's evolution.

Spontaneous cyst rupture may complicate intradiploic epidermoid tumors, producing granulomatous meningitis.[4] Although very rare, malignization might occur, especially in cases of recurrence due to incomplete resection.[3,5,6]

Surgery with total removal of the epidermoid cyst is advocated.[7] Despite its size, total removal of the lesion along with its capsule leads to definite treatment with very low morbidity and mortality.[2,8–12] Conservative resection can also be considered given the slow growing nature of this tumor, especially when its localization near crucial neurovascular structures poses a threat. Excision of the eroded bone and cranioplasty, as performed in our case, may be necessary. As in other pathologies, the advantage of surgical

excision is the possibility of obtaining a sample to confirm the diagnosis.

Intraosseous epidermoid cysts must be included in the differential diagnosis for osteolytic of calvarian and skull lesions.[13]

Conclusions

Intradiploic epidermoid cysts are rare congenital lesions. They present a characteristic dormant clinical course. The slow growth rate of the cyst causes expansion of the inner and outer tables of the skull, being able to achieve gigantic dimensions and originating exuberant images, such as in our case. Neuroimaging shows typical findings, particularly the characteristic restriction diffusion pattern on diffusion weighted imaging (DWI), providing a straightforward diagnosis. Imaging is also extremely helpful in surgical planning.

Despite their benign histology, epidermoid tumors may enlarge and cause lytic destruction of the cranial bone, sometimes invading the dura mater and underlying structures. Fortunately, this was not present in our case. Surgical resection should be considered for selected patients as early as possible to avoid progression-related deficits and more extensive surgery with potential complications or sequelae. Surgical management with noncomplicated total removal of these lesions is the treatment of choice, which also establishes the diagnosis and can provide a good long-term outcome. Nonetheless, from our experience, it is important to maintain clinical and imaging follow-up with regular monitoring to prevent possible tumor recurrences.

Conflict of Interests

The authors have no conflict of interests to declare.

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Oncocytic Meningioma: Case Report of a Rare Meningioma Variant

Meningioma oncocítico: Relato de caso de variante rara de meningioma

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Abstract

Oncocytic meningioma has been first identified in 1997 as a rare meningioma variant, composed predominantly of large meningothelial cells with abundant intracytoplasmic mitochondria. Here, we describe a 34-year-old male patient presenting with 2 weeks of progressive holocranial headache. Brain magnetic resonance imaging (MRI) revealed an extra axial solid-cystic expansive lesion in the left parieto-occipital parasagittal region, with intense vascularization. Histological and immunohistochemical analysis established the diagnosis. We also review briefly the pathological and radiological findings of this rare variant of meningioma as described in the literature.

Keywords
- meningioma
- mitochondria
- pathology

Resumo

O meningioma oncocítico foi identificado pela primeira vez em 1997 como uma variante rara do meningioma, composta predominantemente por grandes células meningoteliais com abundantes mitocôndrias intracitoplasmáticas. Aqui, descrevemos um paciente do sexo masculino de 34 anos apresentando cefaleia holocraniana progressiva de 2 semanas. A ressonância magnética (RM) do cérebro revelou lesão expansiva sólido-cística extra-axial em região parassagital parieto-occipital esquerda, com intensa vascularização. A análise histológica e imuno-histoquímica estabeleceu o diagnóstico. Também revisamos brevemente os achados patológicos e radiológicos desta variante rara de meningioma, conforme descrito na literatura.

Palavras-chave
- meningioma
- mitocôndrias
- patologia

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Introduction

Oncocytic meningioma is a rare histological meningioma variant, characterized histologically by large meningothelial cells, with a ground-glass oncocytic appearance due to abundant intracytoplasmic mitochondria.[1,2] Oncocytic changes are rare in tumors of the central nervous system and are generally limited to neoplasms of the choroid plexus and neurohypophysis.[3,4] This variant of meningioma has been included in the description of the World Health Organization (WHO) classification of tumors of the central nervous system (4th edition, 2016), but its clinical, radiological, and histopathological characteristics are still poorly understood, due to a very limited number of descriptions in the literature.

The first case was reported by Roncaroli et al. in 1997.[5] Sassagawa et al.[6] reported a case with intratumoral bleeding as the main clinical-radiological finding, an unusual feature in meningiomas.[7] The diagnosis of oncocytic differentiation of meningioma has been later associated by some authors with a worse clinical prognosis and greater risk of recurrence.[7] However, most cases do not present invasion of the adjacent brain parenchyma or other major criteria of atypia; therefore, oncocytic differentiation has not been defined as a high-grade neoplasm.[8]

Histological criteria for the diagnosis of oncocytic meningioma require at least 75% of the tumor cell population presenting the characteristic oncocytic pattern.[8] Immunohistochemical evaluation of the reported cases also demonstrate positivity for antimitochondrial antigens.[6] In its first description, oncocytic meningioma was described as having an aggressive behavior, indicating worse prognosis, despite its apparently benign histological presentation.[6]

Here, we describe a case of oncocytic meningioma from the Hospital das Clínicas of the Universidade de São Paulo, São Paulo, state of São Paulo, Brazil. To our knowledge, this is the first case of oncocytic meningioma reported in the American continent.

Clinical Summary

Clinical History

Male patient, 34 years old, engineer, previously healthy, complained of progressive headache for 14 days. Pain was reported as holocranial, intense, and unresponsive to analgesics, sometimes associated with nausea and vomiting. Family members reported that the patient presented with episodes of behavioral arrest for seconds, without loss of consciousness, motor alterations, or sphincter dysfunction. He denied any comorbidities, use of medications, alcohol, smoking, or use of illicit drugs. At the initial neurological evaluation, the patient was alert, lucid, and oriented in time and space, with muscle strength preserved on the four limbs. He presented tactile hypoesthesia on the right upper limb and lower quadrantopsia on the right side. Speech was fluent, able to name objects; however, with some writing difficulty.

Magnetic resonance imaging (MRI) showed a large, solid-cystic extra-axial parietal lesion in the left side, with lobulated contours, presenting accentuated vascularization and heterogeneous contrast enhancement, without restriction to diffusion of water molecules. In addition, the perfusion evaluation demonstrated a marked increase in the relative cerebral blood volume in relation to the contralateral normal white matter.

There was perilesional edema in addition to a large cystic content adjacent to the lesion, without contrast enhancement, which, together with the lesion, determined left lateral ventricle compression and subfalcine herniation (►**Fig. 1**).

A complementary study of the whole vertebral spine showed no changes. Laboratory tests on admission did not detect hematological, hepatic, or renal dysfunctions. Integrating all imaging findings, clinical history, age and gender of the patient led to hemangiopericytoma as the main diagnostic hypothesis, followed by primary meningeal neoplasia, dural metastases, lymphoma, and inflammatory diseases as differential diagnosis. Since the lesion showed intense vascularization, the patient was submitted to arteriography to attempt preoperative embolization 1 day before surgery. Despite the embolization, the tumor showed exuberant vascularization during the surgery as well as areas of internal bleeding. The lesion was completely removed surgically. The patient was discharged from the hospital 4 days after the surgery, being followed-up by the neurosurgery group.

Pathological Findings

We received multiple irregular fragments of brownish tissue with frequent reddish spots and fibroelastic consistency alternating with friable areas (►**Fig. 2**–A).

The entire specimen was fixed in 10% buffered formalin and embedded in paraffin. Then, 5-µ-thick sections were cut and stained with hematoxylin and eosin (H&E). Immunohistochemical staining was performed on an automated immunostaining system Ventana BenchMark Ultra (Ventana, Oro Valley, AZ, USA) with negative and positive controls. The antigens searched were: epithelial membrane antigen (EMA, clone E29; Ventana, Oro Valley, AZ, USA), SSTR2 (Clone UMB1; Abcam, Cambridge, UK), STAT6 (Clone 426R-16; Cell Marque, Rocklin, CA, USA), S100 protein (polyclonal; Ventana, Oro Valley, AZ, USA), progesterone receptor (1E2; Ventana, Oro Valley, AZ, USA), glial fibrillary acidic protein (GFAP, EP672Y, Cell Marque, Rocklin, CA, USA), CD34 (clone QBEnd/10, Ventana; Oro Valley, AZ, USA), anti-mitochondrial antibody (clone 113–1; BioGenex, Fremont, CA, USA) and K_i-67 (clone 30–9; Ventana, Oro Valley, AZ, USA).

Microscopic examination revealed a predominant solid pattern, with high cellular areas intermingled with prominent large intratumoral vascular spaces. The prevailing cell pattern was well-defined epithelioid cells with marked pleomorphic, irregular, and vesicular nuclei, with frequent nuclear pseudoinclusions, and broad eosinophilic granular cytoplasm (►**Fig. 3**). We observed the presence of neutrophilic infiltrate predominantly in areas of ischemic pattern necrosis and frequent areas of intratumoral hemorrhage. The mitotic count was 2 mitoses in 10 high power fields (400x

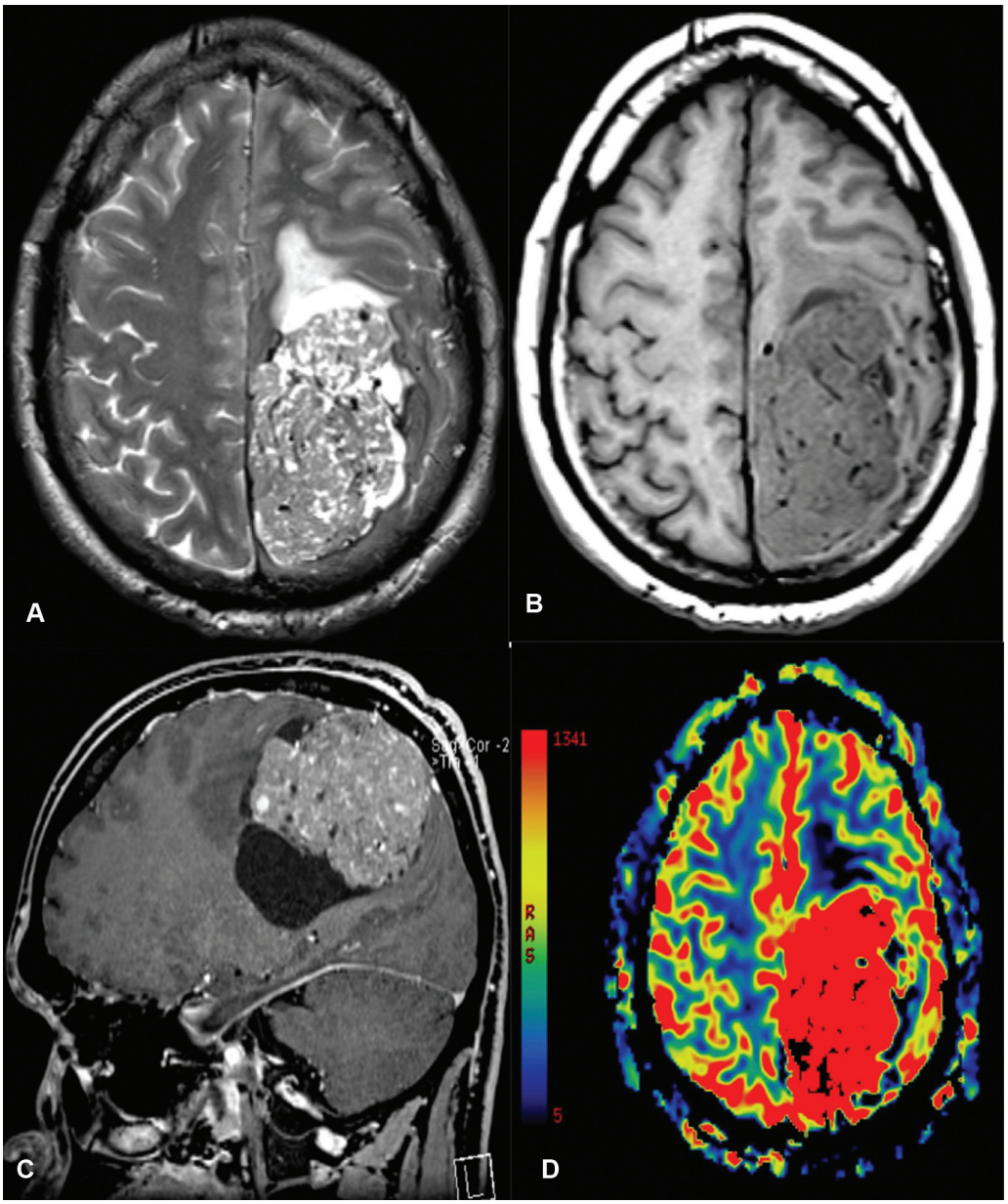

Fig. 1 Axial T2-weighted (**A**), axial T1-weighted precontrast (**B**) and sagittal T1- weighted postcontrast (**C**) Magnetic resonance imaging (MRI) shows a large, solid-cystic extra-axial lesion in the left parieto-occipital region, presenting accentuated vascularization and heterogeneous contrast enhancement. Perfusion MRI (**D**) exhibits marked increase in the relative cerebral blood volume in relation to the contralateral normal white matter.

magnification/0,196 mm^2). The proliferation index, measured by Ki67 immunoreactivity, ranged from 4 to 10% in "hot-spots" (median of 8%).

The immunohistochemical positivity for EMA, progesterone receptor, and SSTR2a antibodies demonstrated the meningothelial origin of the neoplasia (►**Fig. 4–A, B** and **C**). The negativity for STAT6 (►**Fig. 4 - C**) and the presence of immune-positivity for the vascular endothelial markers (CD34) limited to the vessel walls (►**Fig. 4**–F) ruled out the hypotheses hemangiopericytoma and of tumors of vascular origin. The diffuse cytoplasmic immunopositivity for anti-mitochondrial antibody determined the diagnosis of oncocytic meningioma (►**Fig. 4 - D**).

Discussion

A very limited number of cases of oncocytic meningiomas have been reported in the literature and little is known about the imaging and histological features of this variant. Previous studies have reported tumors with a broad dural base, homogeneous contrast enhancement, and with a tendency to hemorrhage.[6,9]

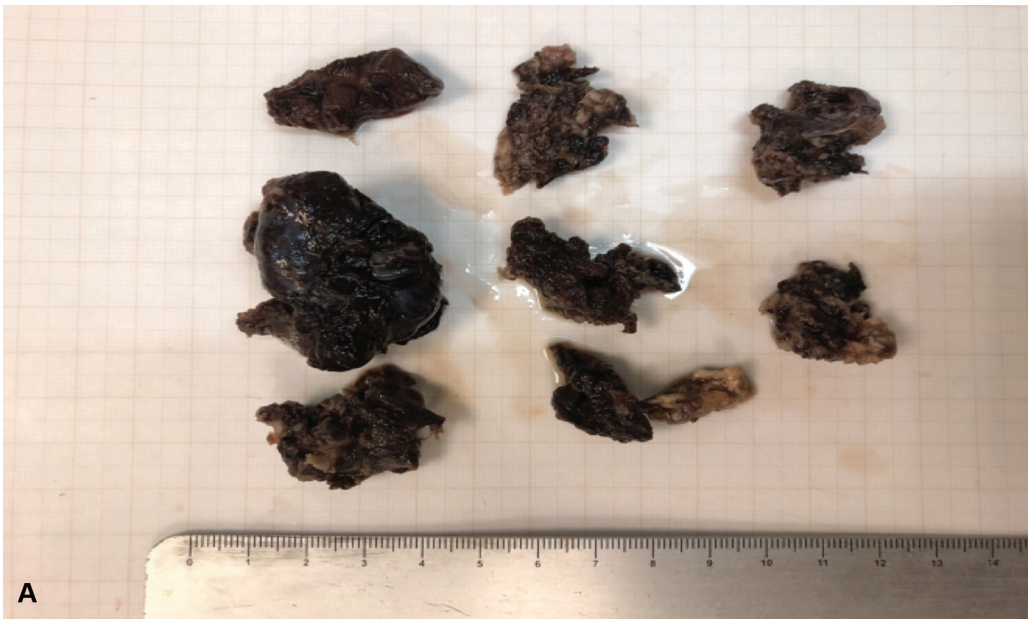

Fig. 2 (A) Macroscopic appearance of the tumor after fixation on 10% buffered formalin.

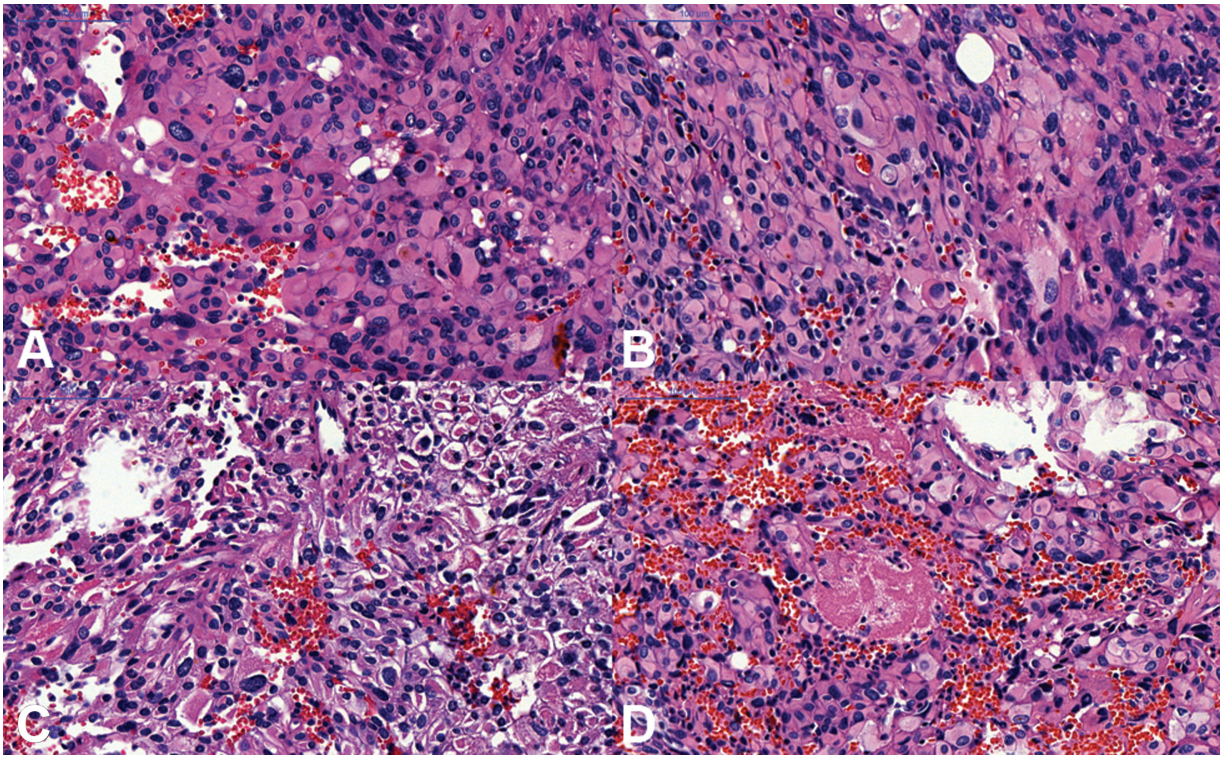

Fig. 3 (**A**) Hematoxylin & eosin stained slide highlighting intensely pleomorphic tumor cells with well-defined borders. (**B**) The tumor cells show frequent nuclear pseudoinclusions, eosinophilic and granular cytoplasm, and areas of hypercellularity. (**C**) Most tumor cells present pale and clearly granular cytoplasm. (**D**) Areas hemorrhage and focus of necrosis (center of the field) are frequent in this tumor.

In our case, although there was no doubt regarding the extra-axial origin of the tumor, some image characteristics such as the absence of a dural tail and exuberant vascularization with large caliber vessels intermingling the entire tumor were considered atypical characteristics[3] for meningothelial neoplasm.[10] In angiography, there was no pattern of vascularization commonly found in meningioma, characterized by large central vessels with multiple peripheral branches of fine caliber. All these findings led to the preoperative hypothesis of non-meningothelial mesenchymal neoplasms, mainly hemangiopericytoma.

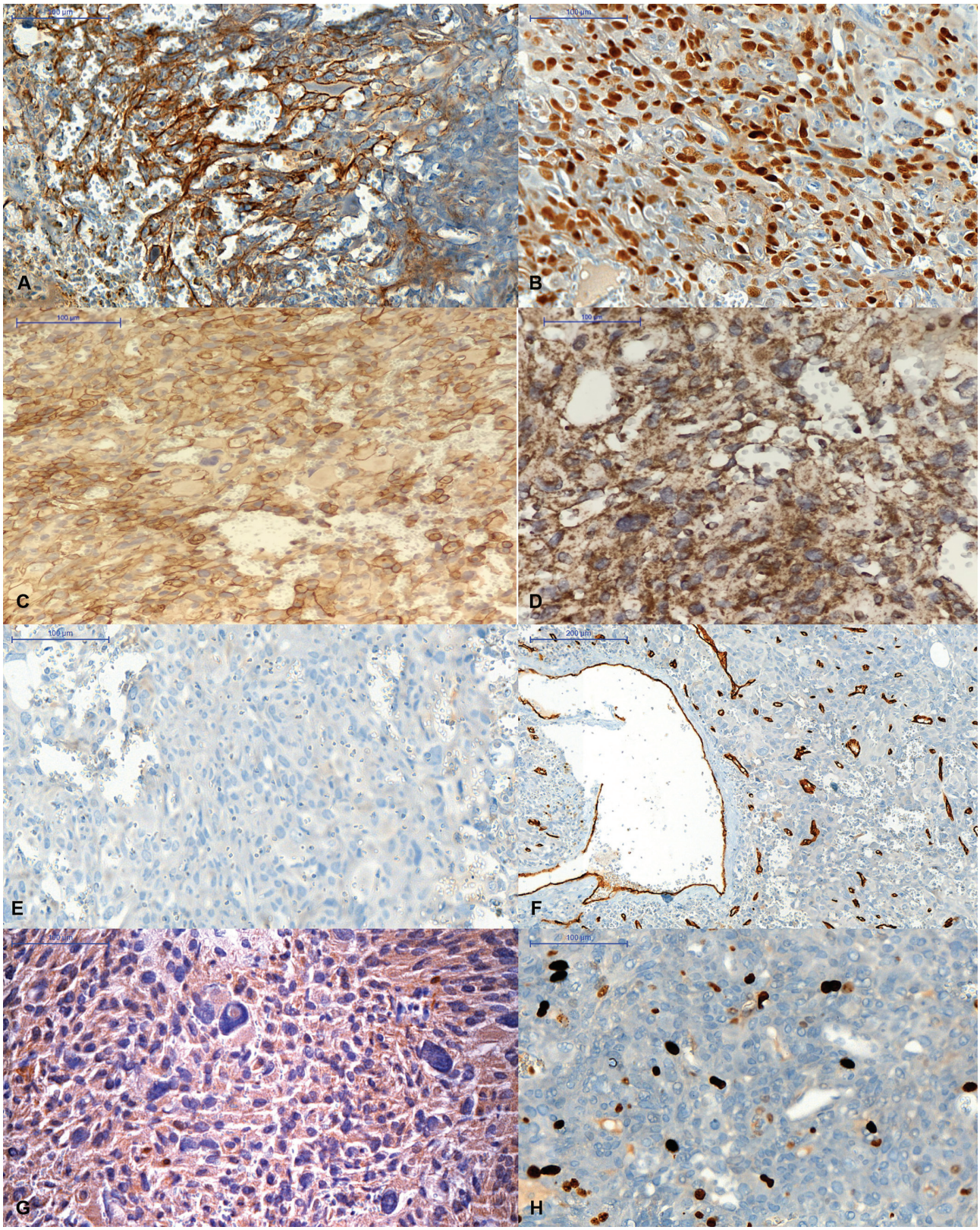

Fig. 4 (**A**) Focal membrane immunoreactivity to EMA in tumor cells. (**B**) Nuclear immunoreactivity to progesterone receptor. (**C**) Diffuse membrane immunoreactivity to anti-SSTR2A. (**D**) Strong granular cytoplasmatic immunoreactivity to antimitochondrial antibody in tumor cells. (**E**) Negative immunoreaction to GFAP. (**F**) Vascular endothelial immunoreactivity to CD34 highlighting intense vascularization of the tumor. (**G**) Negative immunoreaction to STAT6, ruling out the possibility of solitary fibrous tumor epithelioid variant. (**H**) Low to moderate immunoreactivity to Ki67 (8% in the neoplastic cells).

Upon evaluation by imaging exams, this neoplasm can be confused with other tumors.[11] The usual treatment for both hemangiopericytoma and meningiomas is surgical resection, with gross total resection when feasible. Following surgery, the histopathological examination, associated with immunohistochemical testing, is essential for the diagnosis. In oncocytic meningiomas, the morphological evidence of large cell tumor of granular cytoplasm and meningothelial lineage together with the confirmation of numerous mitochondria in the cytoplasm differentiate this entity from other neoplasms with granular appearance.[3]

In general, in tumors that have an oncocytic morphology, such as oncocytic thyroid tumors and oncocytic adrenal gland tumors, the increased number of intracytoplasmic mitochondria has been related to impairment of mitochondrial DNA encoding for mitochondrial proteins, which results in mitochondrial proliferation via stimulation of transcription factors encoded by the nucleus.[12] In oncocytic neoplasms, the histological appearance is thought to be caused by a disequilibrium between mitochondrial proliferation and mitochondrial destruction and/or cell division, resulting in an accumulation of mitochondria.[13] Furthermore, oncocytic thyroid tumors are also reported to have a higher prevalence of large deletions of mitochondrial DNA (mtDNA) and mutations of mtDNA genes that code for oxidative phosphorylation proteins, which could be related to energy production defects.[14] The mitochondrial abnormalities may contribute to this predisposition to necrosis instead of apoptosis[14] and is a possible explanation for the uncommon pattern of vascularization of this oncocytic meningioma and the reported tendency for bleeding and infarction, as has also been seen in this case.

The need for adjuvant treatment is evaluated according to complete or incomplete removal of the tumor and atypical findings, like brain invasion, increased mitotic activity, increased cellularity, small cell with high nuclear to cytoplasmic ratio, sheeting, and foci of spontaneous necrosis.[2,15]

The knowledge of this entity is important because, despite some worrying microscopic and imaging aspects, it generally behaves indolently, with surgical resection being the therapy of choice and no need for adjuvant treatment.

Conflict of interests

The authors have no conflict of interests to declare.

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New Technique Seeking Prophylaxis in the Displacement of Distal Ventriculoperitoneal Shunt Catheter – Case Report

Nova técnica buscando profilaxia no desacoplamento do cateter distal de derivação ventriculoperitoneal – Relato de caso

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Abstract

Idiopathic intracranial hypertension is a comorbidity treated in neurosurgical practice today with the ventriculoperitoneal derivation technique. However, despite its great safety and efficacy, this technique is susceptible to infrequent failures, such as displacement of the catheter leading to the need for reoperation. In the present article, we report a case involving a peritoneal catheter tip retropulsion for subcutaneous tissue in an obese patient with posterior correction using an extending connector to the distal catheter, without harming the drainage flow. In our case report, the patient went on without complications and without the occurrence of new displacement after 8 months of surgery. The results obtained by this technique supported the idea that this alternative construction minimizes the risk of displacement of the peritoneal tip catheter in obese patients and with high intra-abdominal pressure, helping to reduce the need for reoperations. In addition, the present case report supports the need for further studies and clinical trials on the subject.

Keywords

- ventriculoperitoneal shunt
- catheter displacement
- shunt complication

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Resumo

A hipertensão intracraniana idiopática é uma comorbidade tratada na prática neurocirúrgica usualmente com técnica de derivação ventriculoperitoneal. No entanto, apesar de sua grande segurança e eficácia, a técnica é sujeita a falhas, pouco frequentes, como o desacoplamento do cateter, levando à necessidade de reoperação. Relatamos, no presente artigo, um caso de correção cirúrgica a partir de prolongamento do cateter distal com a utilização de conector extensor sem prejuízo ao fluxo de drenagem em paciente obeso acometido por recidiva de migração da ponta do cateter peritoneal para o tecido subcutâneo. Em nosso relato de caso, o paciente seguiu sem complicações e sem a ocorrência de novos desacoplamentos após 8 meses do ato operatório. Os resultados obtidos pelo estudo corroboram a necessidade de maiores investigações buscando o conhecimento da eficácia e segurança da técnica empregada buscando minimizar os riscos de migração da ponta do cateter peritoneal em pacientes obesos e de elevada pressão intra-abdominal, ajudando a diminuir a necessidade de reoperações.

Palavras-chave

- derivação ventriculoperitoneal
- migração de cateter
- complicação da derivação

Introduction

The ventriculoperitoneal shunt method is commonly used in neurosurgical practice for the treatment of comorbidities related to the production or drainage of cerebrospinal fluid, being recognized since the appearance of the first valves removed for this purpose in 1950 by Holtes and Spitz.[1] It is commonly used for the treatment of idiopathic intracranial hypertension.[2] However, despite their considerable effectiveness, these devices are often plagued by mechanical and functional failures.

These complications, which commonly occur in the shunt distal catheter, are caused by mechanical failures, bacterial infections, and displacements with extrusion of the peritoneal connection to the subcutaneous tissue.[3]

In the present report, we present a recent case of an obese patient with migration of the tip of the distal catheter to the abdominal subcutaneous adipose tissue, requiring two sequential surgical reviews. After using and failing conventional practices of sutural repositioning and anchoring, we used the experimental technical application of coupling and extension of the distal catheter from the connector to a second catheter. The technique apparently proved to be efficient in the search for reducing the complications related to it is displacement without compromising the possibility of subsequent surgical revision of different needs.

Methodology for Literature Review

The information and references contained in the review of the present article were obtained through research on a search platform, using the SciELO, PubMed, and Up to Date databases looking for more recent data on the topic.

The keywords and search strategies, used to review the topic Pseudotumor cerebri and looking for historical precedents similar to the case presented, were: *pseudotumor* AND *cerebri*, *ventriculoperitoneal* AND *shunt* AND *obese*. It was also used to collect updated information a time limit for works produced in the past 5 years.

Case Report

Female patient, 52 years old, body mass index (BMI) = 45.88 (1.52 cm and 106 kg). Initially admitted with a clinical condition of holocranial headache, presenting the upper limit on the numerical rating scale (NRS), claiming to be the worst pain of her life, persistent, without symptomatic relief with the use of analgesics and progressive for 7 days, along with nausea and emesis. On clinical examination, the patient presented papilledema. In imaging studies, it did not show any significant radiological alterations or something that justified the current clinical alterations. For diagnostic confirmation, a tap test was performed with the use of a digital spinal manometer with an opening pressure of 15 mmHg and with symptomatic relief after removal of 30 ml of cerebrospinal fluid, leading to the diagnostic confirmation of idiopathic intracranial hypertension (IIH).

First, the patient follows the clinical management with acetazolamide, a carbonic anhydrase inhibitor commonly used in the treatment of IIH; however, after using the drug in the ideal dose, the patient did not show any clinical improvement; therefore, surgical intervention was chosen.

Ventriculoperitoneal shunt (VPS) was performed using the stereotaxic method, without complications of the surgical procedure, just with the presence of only $\sim$ 11 cm of the distal catheter in the intraperitoneal region. Along with the clinical improvement of the previous symptoms of the patient, it was observed relief in the immediate postoperative period, and she was discharged 2 days after the surgery.

Seven days after the surgery, the patient returned to medical care with abdominal pain. For the investigation, an ultrasound of the abdomen was performed, in which a liquid collection was found in the subcutaneous tissue with extrusion of the distal catheter from the intraperitoneal region – with its displacement to the subcutaneous region, causing dissection of the abdominal subcutaneous mesh and, therefore, pain.

The distal catheter was repositioned using anchoring techniques. However, after 5 days, the patient returned to

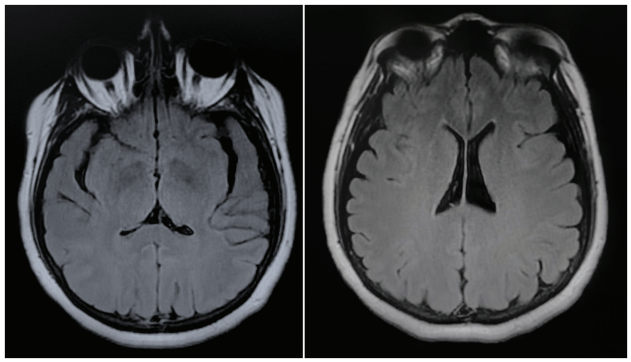

Fig. 1 FLAIR-weighted nuclear magnetic resonance imaging showing unaltered ventricular system and brain parenchyma evidencing the absence of hydrocephalus and indicating idiopathic intracranial hypertension.

Fig. 2 T-connector used to set and extend the distal tip of the ventricle peritoneal shunt system catheter to prevent displacement: (A) receives the first catheter from the shunt. (B) This end of the connector remains closed. (C) The tip that receives the peritoneal catheter.

medical care, presenting with recurrence of abdominal pain similar to the previous one.

Due to the persistence of the case, it was decided to order a second distal catheter from the VPS along with an appropriate connector for catheters. As operative technique, the connection of two distal catheters connected from the connector was chosen in order to obtain a greater length of the catheter in the intraperitoneal region. No changes were made to the proximal catheter.

Today, 8 months after the last surgery, the patient presents complete improvement of the signs and symptoms of both cephalic issues and abdominal pain.

Discussion

Peritoneal complications of VPS are previously known and widely exposed, being described in the literature with the need for surgical revision of the distal tip of the peritoneal catheter due to displacement in $\sim$ 50% of cases.[4] Obesity is considered an independent risk factor for migration of the distal catheter (odds ratio = 6.38, 95% confidence interval [CI] = 1.16–35.21; $p = 0.033$).[5]

However, this correlation is not yet fully physiopathologically elucidated, but it is believed that the increase of intra-abdominal pressure is one of the causes responsible for the susceptibility to displacement. It is important to highlight the direct linear relationship between the increase in BMI and the increase in intra-abdominal pressure ($r = 0.52$; $p = 0.018$) with a deviation of 0.31 ($p = 0.001$).[6] The sum of these relationships is notable when the epidemiological correlation between this complication and the incidence in obese patients is noticeable.[7] The interaction of the hydrophilic characteristics of the catheter, which, on one hand, helps to reduce scar fibrosis, but makes it more susceptible to uncoupling, is also significant.[8]

The results obtained with the process of extending the distal catheter through a connected connector are favorable to the belief that this technique is opportune in preventing migration of the tip of the peritoneal catheter in the case of obese patients, with great thickness of the subcutaneous adipose panicle and increased intra-abdominal pressure.

The technique is interesting because it does not require changes in the size of the standard incision, and it does not compromise the opportunity for subsequent surgical revision, a difficulty found in the subcutaneous anchoring techniques. However, despite the success achieved by the team, it is important to note that, the technique does not change the difficulties generated by the low coefficient of friction between the catheter and the adipose tissue, requiring more case studies to confirm its widespread efficacy.

In our research, we found two case reports also describing alternative techniques for the resolution of recurrence of displacement of the peritoneal catheter. However, none of the narrated techniques fully resembles the one used in the present case. Morrison et al reported a method performed on three patients using synthetic mesh for hernias to increase the friction of the catheter and prevent its retropulsion.[1] In 2017, Carnevale et al. detailed the procedure performed, successfully, with modification using the T connector[8]

Conclusions

The present study supports the use of the distal catheter extension technique with the use of a connector and complement of two continuous tubes aiming to prophylactically reduce the incidence of extrusion of the peritoneal tip for patients with high BMI. The results of the study support the need for further investigation seeking knowledge of the effectiveness and safety of the technique employed.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Book Chapter

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

Book

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

Theses and dissertations

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

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

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