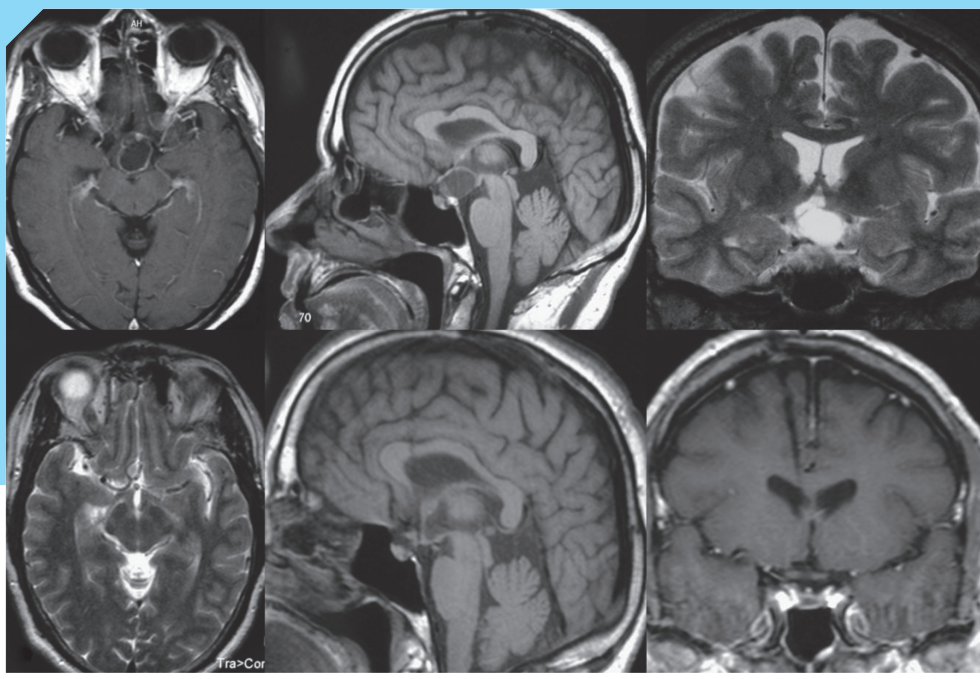
ISSN 0103-5355

Brazilian Neurosurgery

Arquivos Brasileiros de Neurocirurgia

Number 4 • Volume 42 • Pages 269–362 • December 2023



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ISSN 0103-5355

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Arquivos Brasileiros de Neurocirurgia

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Volume 42, Number 4/2023

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Original Articles

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(Fagundes W, Souza RA, Touzet G, Carpentier P, Dhellemmes P, Blond S. Stereotactic Intracavitary Irradiation for Cystic Craniopharyngiomas with Rhenium-186. Arq Bras Neurocir 2023;42(4):288–294)

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

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

ISSN 0103-5355

Intraoperative Ultrasonography in Neurosurgery: Experience of an Institution

Ultrassonografia intraoperatória em neurocirurgia: Experiência de uma instituição

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Arq Bras Neurocir 2023;42(4):e269–e276.

Abstract

Objective Intraoperative ultrasound (IOUS) is an imaging method that can be used in various neurosurgical procedures. It assists in the removal of brain tumors, hematomas, in the insertion of ventricular catheters, and in spinal and peripheral nerve surgeries. The original studies using IOUS were performed with devices that produced lower-quality images, generating little interest in their use. The introduction of ultrasound devices that yielded higher-quality images associated with a relative low cost and ease of use rendered IOUS attractive. Thus, we started using it in multiple neurosurgical procedures, studying its practicality, efficacy and limitations.

Materials and methods A retrospective case study on the use of IOUS in neurosurgery from August 2014 to December 2020 at a single institution, evaluating its practicality, efficacy and limitations.

Results A total of 127 IOUS scans were performed in 112 patients aged 19 to 83 (mean: 53.8) years: 106 scans of the brain, 4 of the spinal cord, and 2 of the peripheral nerves. Brain tumors were the majority, with 86 cases (67.8%). The IOUS was unsatisfactory in 9 cases (7.1%), and there were no cases of infection related to the IOUS.

Conclusion The IOUS is a dynamic, safe, and practical exam. It can be performed in a few minutes and repeated several times during the surgical procedure. It enables surgeons to observe the pulsation of tissues and vessels, the displacement of lumps in liquid collections, and to monitor the drainage of cysts and collections, in vivid, interactive and real-time images.

Keywords
- intraoperative ultrasound
- image-guided surgery
- brain tumor
- intramedullary tumor
- peripheral nerve tumor

received
January 19, 2021
accepted
June 16, 2021

DOI https://doi.org/10.1055/s-0042-1756209.
ISSN 0103-5355.

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

Resumo

Objetivo A ultrassonografia intraoperatória (USIO) é um método de imagem que pode ser utilizado em vários procedimentos neurocirúrgicos. Auxilia na remoção de tumores cerebrais, hematomas, no implante de cateteres ventriculares, e em cirurgias espinhais e de nervos periféricos. Os estudos iniciais com a USIO eram realizados com aparelhos que disponibilizavam imagens de baixa qualidade, o que gerava pouco interesse no seu uso. Com o desenvolvimento de aparelhos de ultrassom que produziam imagens de melhor qualidade, eram de fácil manuseio e tinham relativo baixo custo, reacendeu-se o interesse na USIO. Por este motivo, iniciamos a utilização da USIO em múltiplos procedimentos neurocirúrgicos, e estudamos sua praticidade, eficácia e limitações.

Materiais e métodos Estudo retrospectivo dos casos em que a USIO foi utilizada em neurocirurgia de agosto de 2014 a dezembro de 2020 em uma só instituição, com a avaliação de sua praticidade, eficácia e limitações.

Resultados Foram realizadas 127 USIOs em 112 pacientes com idades entre 19 e 83 (média: 53,8) anos, 106 no encéfalo, 4 em medula espinhal, e 2 em nervo periférico. Os tumores cerebrais foram a maioria, com 86 casos (67,8%). A USIO foi insatisfatória em 9 casos (7,1%), e não houve casos de infecção relacionada à USIO.

Conclusões A USIO é um exame dinâmico, seguro e prático. Pode ser feito em poucos minutos e repetido várias vezes durante o procedimento cirúrgico. É possível observar a pulsação dos tecidos e vasos, o deslocamento de grumos em coleções líquidas, e acompanhar a drenagem de cistos e coleções, em imagens vivas, interativas e em tempo real.

Palavras-chave

- ultrassom intraoperatório
- cirurgia guiada por imagem
- tumor cerebral
- tumor intramedular
- tumor de nervo periférico

Introduction

Intraoperative ultrasound (IOUS) is an imaging method used in neurosurgery to help locate brain tumors, guide the insertion of ventricular catheters and perform biopsies, identify anatomical structures, evaluate tissue vascularization, monitor the progress of surgery, and perform the final evaluation.[1,2] Initially, studies[3] with IOUS used devices with low image resolution that did not provide satisfactory spatial orientation. In addition, the transducers also had limitations: given that they were not intended for intracranial use, they did not fit perfectly in the surgical cavity, which generated many artifacts, reducing even further the quality of the image. Thus, many neurosurgeons lost interest in this modality of image-guided surgery. With the development of ultrasound devices that yield images with better contrast resolution, transducers that are better coupled in the surgical cavity, bringing them closer to the area of interest, reducing artifacts, the possibility of generating three-dimensional (3D) images, and the coupling to navigation systems, the interest in IOUS was rekindled.[4,5] Additionally, the IOUS devices are portable, easy to handle, and relatively inexpensive compared with other more expensive and laborious methods of image-guided surgery, such as intraoperative magnetic resonance imaging (MRI); thus IOUS has become a very interesting method, especially in our field. Therefore, we decided to use IOUS in various types of neurosurgical procedures and evaluate its practicality, efficacy and limitations.

Material and Methods

The present is a retrospective case study of the use of IOUS in neurosurgery from August 2014 to December 2020. All procedures were performed by the senior author of the present article. The ultrasound equipment used was MicroMaxx (SonoSite Inc., Bothell, WA, United States). Two types of transducers were used: a linear 6 MHz to 13 MHz and a 1 MHz to 5 MHz for deeper lesions or insertion of an intraventricular catheter. For the assembly of the equipment, the transducer was wrapped in a sterile plastic cover used in video-laparoscopy filled with ultrasound gel at the end next to the transducer and fixed with rubber bands. The equipment console was also covered in transparent sterile plastic to enable its handling during surgery.

For encephalic injuries, we followed this protocol: after bone flap removal, the intact dura mater was analyzed in two planes perpendicular to each other to map the lesion, and assess its location, characteristics, and relationship with adjacent structures, followed by color Doppler to study the vascularization of the lesion and identify the vessels in the region. The opening of the dura mater was planned according to the data obtained. In cases of subcortical injuries, new evaluations were performed after the opening of the dura to plan the best approach. In cases of brain tumors, the evaluations were repeated as many times as necessary to monitor the evolution of the resection and to detect possible iatrogenic lesions. The surgical cavity was filled with saline. After the dura mater was closed, a new study was performed to

assess the resection and detect bruises. Difficulties in performing the exam and problems encountered were noted.

In cases of spinal tumors, only the 6 MHz to 13 MHz linear transducer was used. The IOUS was performed after the removal of posterior bone elements, debris, and clots, and filling the cavity with saline. The scan was performed in the sagittal and axial planes before opening the dura. The location of the lesion, its characteristics, and changes in the structure of the spinal cord were evaluated followed by the use of color Doppler to map the vessels. The dura mater was opened according to the findings. The exams were repeated to follow the evolution of the resection. At the end of the procedure, with the dura mater closed, a new scan was performed for final evaluation and detection of hematomas.

For surgeries of peripheral nerve tumors, the 6 MHz to 13 MHz linear transducer was used in perpendicular planes to locate the tumor and plan the skin incision. The IOUS was then used to guide dissection and tumoral resection as well as to confirm complete resection and formation of hematomas at the end of surgery.

Results

A total of 127 IOUS scans were performed on 112 patients between August 2014 and December 2020. The age of the patients ranged from 19 to 83 (mean: 53.8) years, and the sample was composed of 52 male and 60 female patients. Of the 15 patients in which more than one procedure was performed, 9 had tumor recurrence (7 cases of high-grade glioma and 2 cases of meningiomas), and 6 had multiple lesions (5 cases of metastasis and 1 of meningioma). Brain lesions were the majority, with 106 cases, followed by spinal tumors in 4, and peripheral nerve tumors in 2 cases. ►**Table 1** shows a summary of the pathologies and the number of procedures.

Regarding the practicality of use, we observed that the ultrasound device takes up little space in the operating room, its assembly is quick, and it can be used both in elective and

Table 1 Pathologies and number of intraoperative ultrasound procedures performed

		Number of cases	Number of procedures
Brain			
	Glioma	19	25
	Meningioma	22	25
	Metastasis - Supratentorial - Infratentorial	 14 3	 18 5*
	Vestibular schwannoma	6	6
	Epidermoid/dermoid cyst - Supratentorial - Infratentorial	 3 1	 3 1
	Hypophyseal adenoma	2	2
	Frontal invasive spinocellular carcinoma	1	1
	Cavernoma	3	3
	Rathke cleft cyst	1	1
	Intracerebral hematoma	3	3
	Ischemic stroke/biopsy	1	1
	Arteriovenous malformation	7	7
	Aneurysm	19	19
	Neurocysticercosis	1	1
Spinal cord			
	Astrocytoma	1	1
	Ganglioglioma	1	1
	Meningioma	1	1
	Hemangioma	1	1
Peripheral nerve			
	Schwannoma	2	2
Total		112	127

Note: *Intraventricular catheter insertion guided by intraoperative ultrasound.

emergency surgeries. Few cases were necessary in order for us to become familiar with the operation of the device and the examination. The IOUS itself requires only a few minutes to be performed, and it can be repeated as many times as necessary without adding too much time to the surgical procedure.

Most brain injuries were brain tumors, which were all easily located, even those deep and small. We could identify cystic and necrotic areas, vessels, edema and ventricular displacements. It was particularly useful in monitoring resection and in the identification of residual tumors, especially in gliomas.

Intracerebral hematomas were also identified. In a particular case, IOUS was determinant to define the conduct in real time, as it identified a ruptured aneurysm inside an intracerebral hematoma. We had the opportunity to use IOUS in five giant aneurysms, four in the internal carotid artery (ICA) and 1 in the middle cerebral artery. The aneurysms were easily identified. Three giant ICA aneurysms were partially thrombosed, and IOUS clearly showed the aneurysmal sac wall and its relationship with adjacent structures, the intramural thrombus, and the swirling flow within the aneurysm through Doppler. After insertion of a clip, IOUS enabled the confirmation of the exclusion of the aneurysm from the circulation, which was corroborated by postoperative angiography. We used IOUS in seven surgeries to resect arteriovenous malformations (AVMs). It was useful to identify and define the AVM, and to locate drainage veins and nourishing arteries before opening the dura mater, thus avoiding unnecessary openings and accidents.

For the insertion of an intraventricular catheter, IOUS proved to be of great value because it accurately guided the ventricular puncture and the positioning of the catheter. Similarly, it was very useful to guide the resection of deep lesions aided by metal cannulas.

In spinal cord surgeries, we were able to identify the tumors in all cases and observe the sonographic characteristics of the normal spinal cord and its pathological changes. The IOUS was also useful in peripheral nerve surgeries to locate and guide tumor resection.

In the 127 procedures performed, IOUS was unsatisfactory in 9 (7,1%) cases, all of brain tumors. In three cases, IOUS was interrupted due to perforation and extravasation of gel through the plastic layer, without contaminating the surgical field. In five procedures (four cases of glioma and one case of metastasis), we did not obtain the proper coupling of the transducer in the surgical cavity, as it was not possible to completely fill the cavity with saline due to the position of the patient's head, which generated many artifacts and impaired the assessment of the progression of the resection. In one case of recurring meningioma, the evaluation was impaired due to calcification of the dura mater above the tumor, which compromised visualization. There were no infectious complications related to IOUS.

Illustrative Cases

Case 1

A 59-year-old male patient presented with headache, vomiting, reduced visual acuity, and left hemiparesis. An MRI scan showed a deep temporal lesion to the right. The IOUS clearly identified the lesion, its heterogeneous appearance, and the cystic area, which presented with similar aspect on the MRI, as well as the control after resection. A computed tomography (CT) scan in the immediate postoperative period confirmed gross total resection of the lesion, an anaplastic astrocytoma (►**Fig. 1**).

Case 2

A 27-year-old male patient with a history of generalized seizures and normal neurological examination. An MRI scan showed a 12-mm lesion located adjacent to the right ventricular atrium. The IOUS located the lesion and, aided by a metal probe, shown in the image with the typical reverberation sign, guided the resection of this cavernoma and evaluated the resection control. A CT scan in the immediate postoperative period confirmed complete resection (►**Fig. 2**).

Case 3

A 58-year-old female patient with a history of progressive paraparesis and dorsal back pain with 10 months of

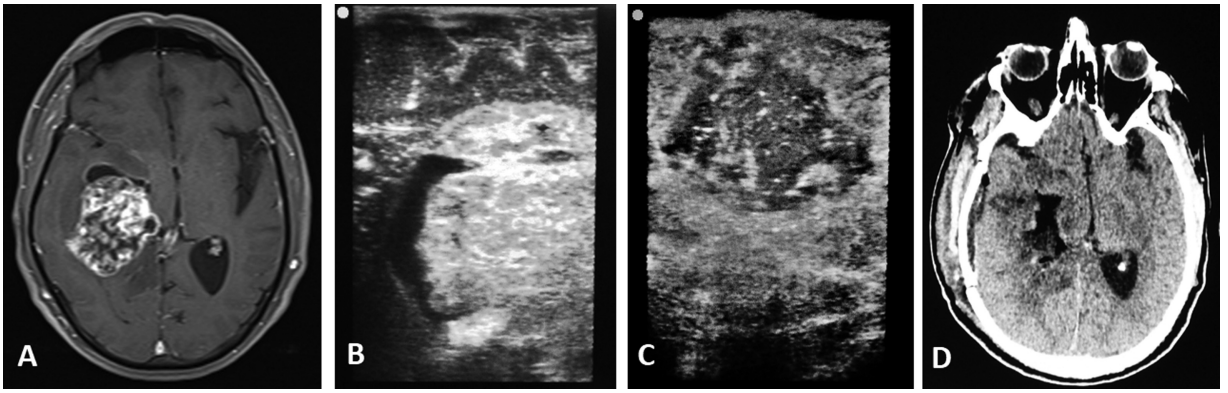

Fig. 1 (**A**) T1-weighted magnetic resonance imaging (MRI) scan with gadolinium in the preoperative period, showing a heterogeneous temporal tumor with a cystic area. (**B**) Intraoperative ultrasound (IOUS) scan showing the tumor with heterogeneous appearance and the cystic area, similar to the preoperative MRI. (**C**) The IOUS for final resection control showing gross total resection. (**D**) Immediate postoperative computed tomography (CT) scan confirming gross total resection.

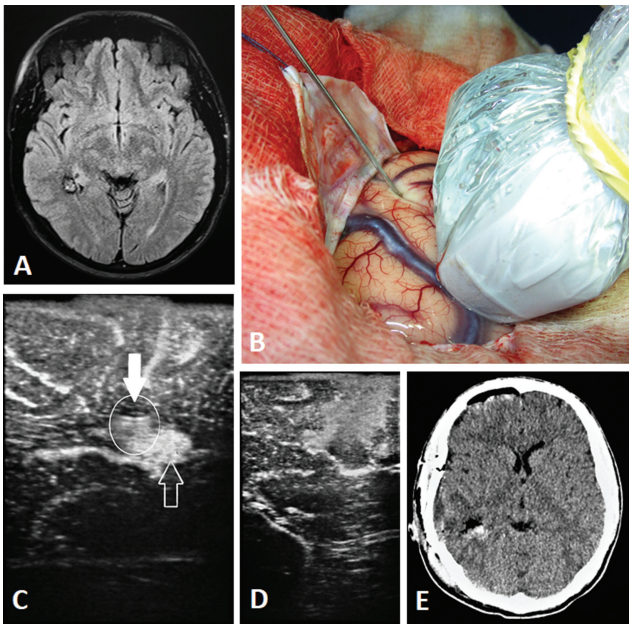

Fig. 2 (A) Preoperative T2-fluid-attenuated inversion recovery (FLAIR) MRI scan showing a lesion adjacent to the right ventricular atrium. (**B**) The IOUS guiding the metal probe to the lesion. (**C**) The IOUS demonstrating the reverberation caused by the metallic probe (full white arrow and circle) and the hyperechoic lesion (white hollow arrow). (**D**) Control IOUS showing complete resection. (**E**) Postoperative CT scan confirming complete resection.

evolution. An MRI scan showed an intramedullary tumor in the cervical-thoracic transition. Surgery enabled the visualization of the spinal cord enlargement without precise limits, whereas the IOUS defined the tumor precisely, with widening of the spinal cord, with a slightly more hyperechoic appearance than the normal spinal cord. We could clearly observe the loss of normal sonographic aspects of the spinal cord in the area of the tumor, which was a ganglioglioma (►**Fig. 3**).

Case 4

A 28-year-old male patient complaining of burning pain in the lateral compartment of the right thigh associated with loss of strength and atrophy of the right thigh after 12 months of evolution, which showed, on physical examination, hypotrophy of the right quadriceps and paresis for extension of the right leg. A thigh MRI scan revealed a tumor with 2 cm in diameter on the lateral and deep compartment of the right thigh, suggestive of schwannoma. Electroneuromyography showed involvement of the right femoral nerve. The IOUS identified the tumor easily in terms of location and depth, enabling a less aggressive surgery for this case of schwannoma of the femoral nerve (►**Fig. 4**).

Case 5

A 54-year-old female patient admitted to the emergency department with a history of sudden headache followed by decreased level of consciousness and a score of 6 on the Glasgow Coma Scale (GCS). A CT scan revealed a left temporal intracerebral hematoma associated with subarachnoid and intraventricular hemorrhage. It was not possible to perform

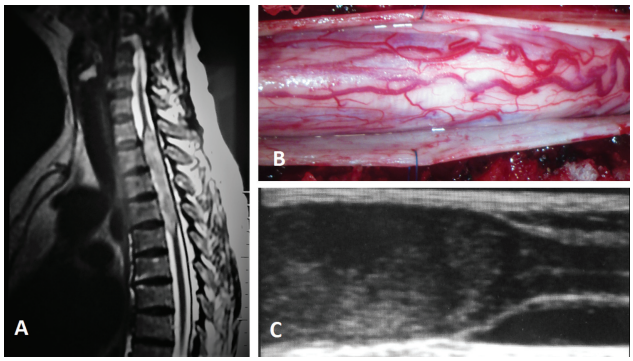

Fig. 3 (A) Preoperative T2-weighted MRI scan showing a cervicothoracic intramedullary tumor. (**B**) Surgical image showing spinal cord enlargement without precise limits. (**C**) The IOUS showing the tumor, slightly hyperechoic, widening the spinal cord. It is possible to distinguish the exact point in which the medulla loses its normal sonographic aspects (the high reflectivity of the medullary surface, the hypoechogenicity of the nervous tissue, and the central echo).

CT angiography (angio-CT) or angiography. Emergency surgery was performed. The IOUS identified the entire intracerebral hematoma and diagnosed an aneurysm of the left middle cerebral artery in the middle of the hematoma before dural opening, enabling the surgeon to change the approach strategy in real time (►**Fig. 5**).

Discussion

The IOUS is an auxiliary method of image-guided surgery capable of providing information in real time in the initial phase as well as during the surgery, compensating distortions caused by the brain shift.[6] Comparatively to other image-guided surgeries, IOUS is less costly, consumes less time, it is easily adaptable to the operating room, and does not expose the patient and health professionals to ionization radiation.[7]

The indications for the use of IOUS range from elective procedures to emergency surgeries due to its ease of use and portability. In pediatric neurosurgery, IOUS is used in peritoneal ventricular derivation in neonates, drainage of arachnoid cysts,[8] and control of resection of Chiari malformation type I.[9] In adults, IOUS is extremely versatile, and is used to insert catheters and electrodes,[10] drain cysts and abscesses, and identify and remove foreign bodies.[11,12,13]

In intracerebral hematoma drainage surgeries, IOUS can accurately identify the location of the clot, map the vessels, identify aneurysms or associated AVMs, and evaluate the final result of the surgery. We had the opportunity of using IOUS in an emergency surgery to drain an intracerebral hematoma suspected of having a ruptured aneurysm in which it was not possible to perform angio-TC or angiography to confirm the diagnosis in the preoperative period. The IOUS easily delimited the area of the hematoma and confirmed the diagnosis of a ruptured middle cerebral artery aneurysm prior to dural opening, completely changing the approach strategy in real time.

The IOUS also assists in the insertion of intraventricular catheters, and is of crucial importance in cases associated

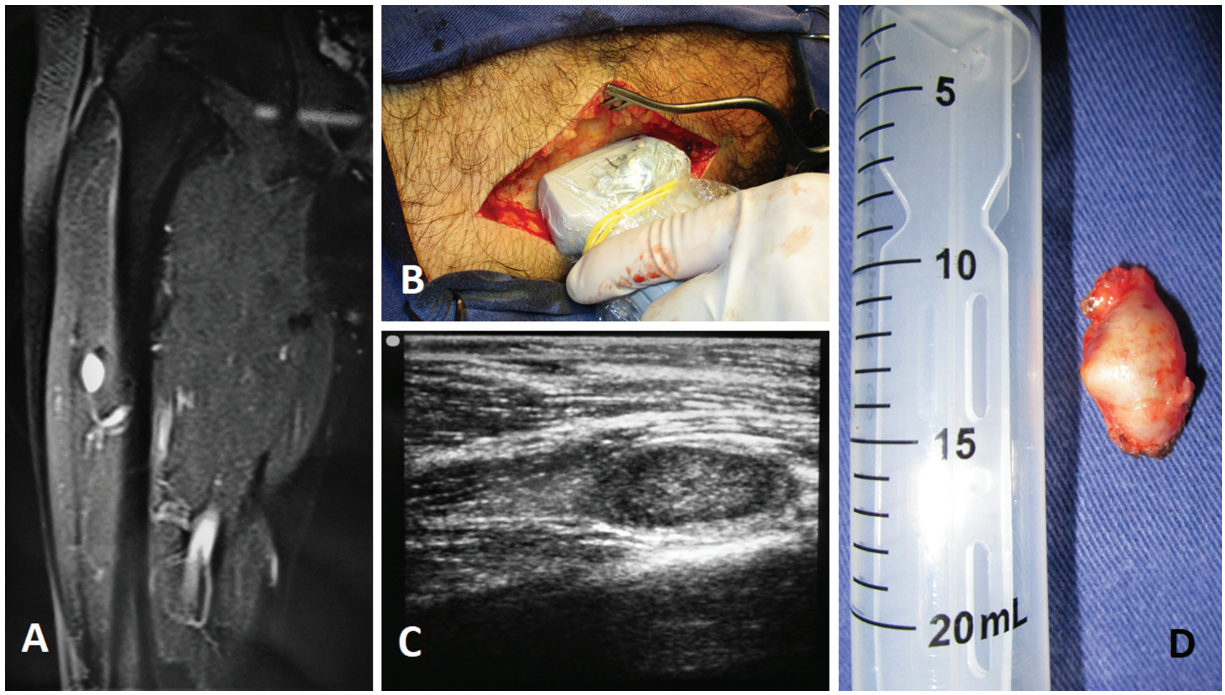

Fig. 4 (**A**) T1-weighted MRI scan with gadolinium showing a tumor in the depth of the right thigh. (**B**) A photograph of the IOUS guiding the surgery. (**C**) The IOUS demonstrating the tumor. (**D**) A photograph of the surgical specimen.

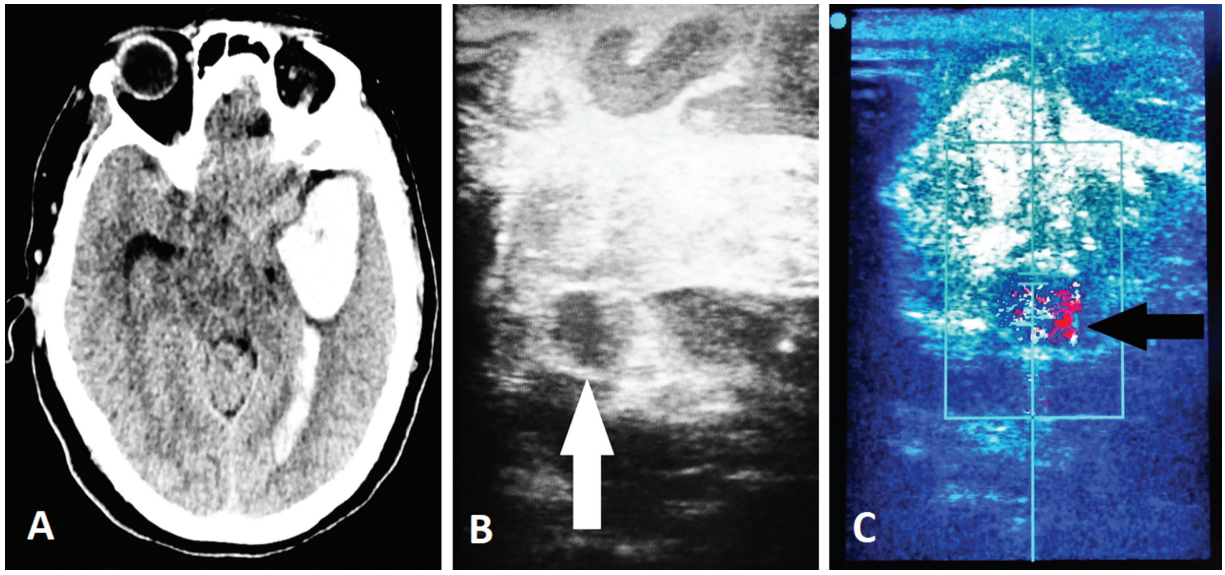

Fig. 5 (**A**) Preoperative CT scan showing left temporal intracerebral hematoma associated with subarachnoid hemorrhage and intraventricular hemorrhage suggesting aneurysmal rupture. (**B**) The IOUS showing the hyperechoic intracerebral hematoma associated with a circular image with a hyperechoic wall and hypoechoic content suggestive of aneurysm (white arrow). (**C**) The IOUS with color Doppler showing swirling flow inside the circular lesion, confirming the diagnosis of aneurysm (black arrow).

with compression and deviation of the ventricles. Wilson et al.[14] studied 249 cases of ventriculoperitoneal shunt and compared the accuracy of the insertion of the intraventricular catheter using IOUS, stereotaxic navigation, and the free hand, and concluded that there was greater precision in the insertion and reduction of the proximal obstruction of the catheter when guided by ultrasound and stereotaxic navigation.

In biopsies or surgeries involving small and deep lesions, IOUS is very useful because it enables surgeons to easily visualize and insert metal probes and silicone catheters into the chosen target with great precision.[15] Di Lorenzo et al.[16] compared biopsies guided by IOUS and stereotactic biopsies guided by CT and concluded that, for supratentorial lesions greater than 15 mm, the accuracy of the methods are similar, with IOUS having the advantages of being faster, simpler, and having a lower cost.

In brain tumor surgeries, IOUS is applied to map the lesion, and identify its limits, cystic and necrotic areas, and the relationship of the tumor with adjacent anatomical

structures such as vessels, ventricles and bony prominences, providing real-time information to assist in the surgeon's decision regarding the best approach strategy and minimize surgical aggression. It enables the evolutionary monitoring of the resection and the identification of residual lesions, maximizing the removal of the tumor.[17,18] In our experience, IOUS was able to identify all brain tumors studied, including low-grade gliomas, and clearly determine their limits, their relationships with large vessels, their cystic or necrotic portions, the associated hematomas, and the areas of edema when present.

In surgeries for spinal tumors, IOUS is a tool of great help to the surgeon because it enables the visualization of intraspinal abnormalities and monitoring of the progress of the resection and the result of the surgery. Quencer and Montalvo,[19] studying the sonographic characteristics of the spinal cord, observed regularity in three characteristics of the normal spinal cord: the high reflectivity of the medullary surface; the hypoechogenicity of the nervous tissue; and the central echo. In their experience,[19] the absence of these sonographic characteristics indicates the presence of neoplastic pathological processes affecting the spinal cord. Epstein et al.[20] analyzed 186 intramedullary tumors and observed that astrocytomas expand the spinal cord asymmetrically and are slightly more echogenic than normal tissue. Ependymomas expand the medulla symmetrically and are located in the central region. They are hyperechogenic, uniform, and with well-defined limits. Epstein et al.[20] easily identified rostrocaudal cysts: in 4 cases of spinal cord demyelinating disease, they observed sonographic characteristics different from those found in spinal tumors, such as minimal spinal cord expansion or normal spinal thickness, hypoechogenicity without associated hyperechogenicity, and visualization of the central canal. The central canal was not observed in any of the 182 cases of intramedullary tumors, confirming the findings by Quencer and Montalvo.[19] Therefore, IOUS, in addition to aiding in the location of the lesion, the characterization of the tumor, the identification of the cystic areas, and the monitoring of the tumor resection, may suggest its nature according to its sonographic characteristics, whether neoplastic or demyelinating disease, thus avoiding unnecessary resections. To increase the accuracy of IOUS in spinal tumor surgeries, studies[21] with 3D ultrasound coupled to navigation systems have been conducted, and they show encouraging results.

The IOUS is also beneficial for peripheral nerve tumor surgeries and resections of neuromas, especially those of small dimensions, located in deep regions; IOUS helps the surgeon perform procedures that are more precise and less traumatic to the patient.[22]

Critics[23,24,25] point out that IOUS yields poor image quality due to poor spatial and contrast resolution compared with other auxiliary modalities of image-guided surgery, such as intraoperative MRI and intraoperative CT. They also report that the quality of the IOUS image suffers a gradual deterioration during the surgical procedure due to the production of artifacts caused by blood, air, instruments, and poorly-coupled transducers in the surgical cavity. After the resection starts, the formed cavity introduces significant changes in the sound-attenuation factor. There is a need to fill with saline solution, which has a sound attenuation close to zero. The difference in attenuation of the saline solution with the brain tissue causes an artifact perceived as a shiny, hyperechoic area, which can be misinterpreted as a tumor remnant. The artifact can be observed in the images as an area of increased brightness below the bottom of the cavity filled with saline. This is the most common artifact found on IOUS in brain tumor surgeries.[26]

Nowadays, there are commercial ultrasound devices that provide high-quality images, which are equipped with transducers of various sizes and frequencies that can be introduced into the surgical cavity, bringing the transducer closer to the area of interest and reducing the formation of artifacts. They generate two-dimensional (2D) images and 3D reconstructions, and enable the fusion of images with magnetic resonance and coupling to neuronavigation systems.[4,5,6,21,27,28] To minimize the artifacts generated by surgical manipulation, researchers are studying the use of liquids with impedance similar to that of brain tissue to fill the surgical cavity to reduce the reverberations and noise caused by the change in sound transmissibility and maintain the image quality during the evolution of the procedure.[26] For the monitoring of the resection and identification of the tumor remains, optimizing resection, notably in high-grade gliomas, ultrasound contrast may be used.[29,30] Prada et al.[31] demonstrated that the use of contrast is extremely specific in the identification of residual tumors. The ability to distinguish the tumor, the artifacts and a normal brain is based on the ability to show the degree of vascularity and not the echogenicity of the tissues.

Conclusion

The IOUS is a dynamic, safe and practical examination that, despite showing a 2D image on screen, when scanning the studied area, enables a very accurate 3D perception of the location and dimensions of the lesion addressed and the anatomy of the region. Additionally, it can be performed in a few minutes and repeated several times during the surgical procedure. It enables the observation of the pulsation of tissues and vessels, the displacement of lumps in liquid collections, and the monitoring of the drainage of cysts and collections, in vivid, interactive and real-time images.

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

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Intracranial Pressure Monitoring in Patients with Severe Traumatic Brain Injury: A Cohort Study with Paired Analysis

Monitorização da pressão intracraniana em pacientes vítimas de traumatismo craniencefálico grave: Um estudo coorte com análise pareada

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Arq Bras Neurocir 2023;42(4):e277–e281.

Abstract

Introduction Intracranial hypertension continues to be the most frequent cause of death in patients with traumatic brain injury (TBI). Thus, invasive monitoring of intracranial pressure (ICP) is a very important tool in neurointensivism. However, there is controversy regarding ICP monitoring and prognosis.

Objectives To evaluate whether there is a difference in mortality between patients with severe TBI who underwent invasive ICP monitoring compared with those who did not undergo such procedure.

Methodology This is a unicentric study in the prospective cohort mode. A total of 316 patients with severe TBI were evaluated and, out of these 316 individuals, 35 were submitted to ICP monitoring. All clinical data were evaluated by the Tertiary Hospital Neurosurgery team in the city of São Paulo.

Results Of the total cohort, 35 (11%) patients underwent ICP monitoring, while 281 did not. Comparing the 2 groups, there was no difference in terms of early mortality between patients who were submitted to monitoring and those who were not (34.3 versus 14.3%; $p = 0.09$); there was also no difference in terms of hospital mortality (40 versus 28.5%; $p = 0.31$) or intensive care unit (ICU) length of stay (16.10 days, 95% confidence interval [CI]: 10.6–21.6; versus 20.60 days, 95%CI: 13.50–27.70; $p = 0.31$).

Conclusions In this cohort, we did not identify differences in mortality or in duration of hospitalization between patients with ICP monitoring and those exclusively with clinical-radiological evaluation. However, further national co-operative studies of services using ICP monitoring are needed to achieve results with greater generalization power.

Keywords
- intracranial pressure
- hospital mortality
- intracranial hypertension
- brain injuries
- traumatic

received
November 2, 2020
accepted
March 9, 2021

DOI https://doi.org/10.1055/s-0041-1731012.
ISSN 0103-5355.

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

Resumo

Introdução A hipertensão intracraniana continua a ser a causa mais frequente de morte em pacientes com traumatismo cranioencefálico (TCE). Assim, a monitoração invasiva da pressão intracraniana (PIC) é uma ferramenta de grande importância em neurointensivismo. No entanto, há controvérsias em relação à monitorização da PIC e sua relação com o prognóstico.

Objetivos Avaliar se há diferença de mortalidade entre pacientes com TCE grave submetidos à monitorização invasiva da PIC em comparação com aqueles não monitorizados.

Metodologia Trata-se de um estudo unicêntrico no modo de coorte prospectiva. Foram avaliados 316 pacientes com TCE grave e, desses 316 indivíduos, 35 foram submetidos à monitorização da PIC. Todos os dados clínicos foram avaliados pela equipe de Neurocirurgia de Hospital Terciário na cidade de São Paulo.

Resultados Da coorte total, 35 (11%) pacientes foram submetidos a monitorização da PIC, enquanto 281 não o foram. Comparando-se os 2 grupos, não houve diferença em termos de mortalidade precoce entre pacientes submetidos a monitorização e os que não foram submetidos (34,3 *versus* 14,3%; $p = 0,09$); não houve também diferença em termos de mortalidade hospitalar (40 *versus* 28,5%; $p = 0,31$) ou no tempo de internação na UTI (16,10 dias, intervalo de confiança [IC] 95%: 10,6–21,6 *versus* 20,60 dias, IC95%: 13,50–27,70; $p = 0,31$).

Conclusões Nesta coorte, não identificamos diferença de mortalidade ou de duração de tempo de internação entre pacientes com monitorização da PIC e aqueles com avaliação exclusivamente clínicorradiológica. Fazem-se, no entanto, necessários mais estudos cooperativos nacionais dos serviços que utilizam a monitorização da PIC para obtenção de resultados com maior poder de generalização.

Palavras-chave

- pressão intracraniana
- mortalidade hospitalar
- hipertensão intracraniana
- lesões encefálicas
- traumáticas

Introduction

Intracranial hypertension is the main cause of death in head trauma, due to changes in cerebral hemodynamics that generate catastrophic repercussions for the suffering brain. The normal values of intracranial pressure (ICP) in adults are between 3 and 15 mmHg, and values greater than this interval are normally filled with expansive intracranial processes, which in the context of polytrauma are mainly translated into subdural and epidural hematomas, traumatic subarachnoid hemorrhages, and diffuse injuries.

According to the Brain Trauma Foundation (BTF)[1] from the United States and to the European Brain Injury Consortium (EBIC), ICP monitoring is indicated in all patients with traumatic brain injury (TBI) with a score between 3 and 8 on the Glasgow Coma Scale (ECGl) and with abnormal skull computed tomography (CT).[2] In addition, it is also indicated in patients with normal skull tomography, but with at least two of the following criteria: arterial hypotension (SB$p < 90$ mmHg or DB$p < 60$ mmHg), age > 40 years old and decortication or decerebration posture. These indications are supported by the latest Brain Trauma Foundation guideline, where it is recommended to monitor the ICP to reduce in-hospital death within 2 weeks of the event.

Although these criteria are established in the literature, there are not enough studies to demonstrate whether there is a better prognosis in patients victims of TBI who are monitored compared with those evaluated only clinically. As an example, there is a study[3] performed by Bratton et al. in which he questioned the effectiveness of ICP monitoring, because when comparing patients with image monitoring with patients monitored by ICP monitor, they did not identify significant differences in the prognosis.

In our service, between 2011 and 2012 (Ferreira et al.),[4] a propensity score cohort analysis was performed, in which no difference was found in the outcomes hospital mortality, mortality in 14 days, and mortality in rehabilitation centers (after 14 days). Therefore, our objective is to assess whether there was a difference in terms of mortality in this more recent period of cohort analysis.

Material and Methods

This is a single-center study in the prospective cohort mode. The studied sample included individuals of both genders who were victims of severe cranioencephalic trauma (TBI) admitted consecutively to an intensive care unit (ICU) specialized in trauma at the Hospital das Clínicas of the Medical School of the Universidade de São Paulo (FMUSP, in the Portuguese acronym), São Paulo, state of São Paulo, Brazil, from March 2012 to January 2015. Patients > 14 years old with a clinical-radiological presentation of severe TBI admitted to the ICU and who needed a more substantial

assessment of ICP were included. Those with penetrating or open trauma, who had chronic subdural hematoma, or referred from external ICUs were excluded from the study. These patients were followed-up throughout the hospitalization period and their data were accounted for in a digital database to assess their mortality after 14 days, as well as to evaluate the length of hospital stay. The present study was approved by the Research Projects Analysis Commission (CAPPesq, in the Portuguese acronym) of the Hospital das Clínicas of the FMUSP under the protocol n° 00119/10.

The clinical predictors evaluated included:

- Pupillary reactivity (anisocoria, isocoria or fixed);
- International normalized ratio (INR)
- Activated partial thromboplastin time (APTT);
- Glasgow Coma Scale (GCS);
- Age;
- Male gender
- Simplified Acute Philosophy Score (SAPS) 3 score.

Possible confounding factors include:

- Time taken to transfer admitted patients to Intensive Care Unit from Emergency Department, categorized as < 24 h and > 24 h.
- Transfer mode, categorized as direct transport (transfer from the accident scene to the study hospital) or indirect transport (transfer after initial transport to less specialized hospitals).
- Kinetic energy involved in the trauma: high kinetic energy (running over, car accidents, falls from a high level) and low kinetic energy (physical aggression and falls from one's own level).

The GCS was evaluated in the extra-hospital and in-hospital environment; however, only the highest score was considered, due to the possibility of confounding factors such as sedation. Therefore, only individuals who scored < 9 on the scale were considered as having severe TBI.

Regarding the statistical analysis, the unpaired Student's *t*-test or the Mann-Whitney test for continuous variables were used to assess the association of the variables, and the chi-squared test or the Fisher exact test were used for the categorical variables. To assess the normality of continuous variables, the Shapiro-Wilk test was used. Categorical data are presented as absolute numbers (with percentages), parametric data as mean and standard deviation (SD), and nonparametric data as medians and interquartile range (IQR). Predictors that, in the univariate analysis, had $p < 0.10$ were selected for the multivariate analysis, which was done through logistic regression.

To determine the performance of the model, the discrimination was made by analyzing the area on the receiver operating characteristic (ROC) curves. The higher the area under the ROC curve (AUC), the better the prognostic discrimination. A model with an AUC of 0.50 has no discriminatory power, while an AUC of 1.0 reflects perfect discrimination. Calibration was assessed using the Hosmer-Lemeshow goodness of fit test, which assesses the ability of the model to correctly predict clinical outcomes. The internal validity was done with bootstraping procedures. This form of validation optimizes the prediction of clinical outcomes for similar populations. The data were analyzed using the STATA 11.0 software (StataCorp, College Station, TX, USA). Then, a "propensity score" type pairing was performed to enable the correlation between clinical outcomes and the use or not of monitoring, aiming, in this way, to reduce the heterogeneity of the compared groups.

Results

In total, 316 patients were included in the present study, of which 273 (86%) were male and 43 (14%) were female. The average age of the studied group was 38 ± 16 years old, and the main trauma mechanisms were falls (30.1%), followed by pedestrian accidents (26.1%) and motorcycle accidents (19.5%). Only 35 patients underwent ICP monitoring, in whom a paired propensity score analysis was performed. The most common associated extracranial injuries were facial trauma ($n = 165/32\%$), followed by orthopedic and thoracic trauma ($n = 143/25.9\%$, both), and spine trauma ($n = 80/15$, 4%). The 14-day mortality rate was 26.6% and the in-hospital mortality rate was 36.4% when the 316 patients were evaluated.

As noted in ►**Table 1**, the average age of the patients who underwent ICP monitoring was 43.94 ± 21.3 old, while the age of the clinically monitored patients was 37.62 ± 18.4 years old, which shows that the group clinically monitored was younger, although this age difference was not statistically significant ($p = 0.18$). In addition, 27 males were subjected to invasive monitoring, while those who were not totaled 32, which, even with this difference, allowed both compared groups to be homogeneous in this respect ($p = 0.188$). In all other clinical variables evaluated, such as GCS, SAPS3, APTT, INR, and pupils, there was no significant difference between the samples, allowing for a later comparison of the most reliable prognosis.

As described in ►**Table 2**, there was no significant difference between patients with ICP monitoring and those not monitored in terms of early mortality (34 versus 14%), hospital mortality (40 versus 28%), average length of stay in the ICU (20.82 versus 16.14 days), and mean length of hospital stay (28 versus 34.82 days). It is important to note that there were no adverse events (infection or intracranial hemorrhages) in the patients who underwent ICP monitoring.

Discussion

The present article exposed, as demonstrated above, a prospective analysis between groups of patients with TBI. Two groups of 35 individuals, 1 with invasively monitored patients and the other with patients submitted to clinical radiological evaluation, were obtained from a prospective cohort of 316 patients. Intracranial pressure monitoring is considered a fundamental pillar in the intensive monitoring of patients with severe TBI, whose basic principle is to

Table 1 Multivariate Analysis Type Propensity score

Variables	Patients followed up with an ICP monitor	Clinically monitored patients	*p-value*
Age	43.94 ± 21.3	37.62 ± 18.4	0.1899
Male	27	32	0.188
Glasgow Coma Scale (Median. p25-p75)	6 (4–8)	6 (3–8)	0.9241
SAPS, Simplified Acute Physiology Score 3	51.91 (95%CI: 47.6–56.1)	49.31 (95%CI: 44.1–54.4)	0.4335
APTT	1.18 (95%CI: 1.06–1.30)	1.20 (95%CI: 1.01–1.39)	0.8627
INR	1.40 (95%CI: 1.3–1.5)	1.56 (95%CI: 1.22–1.9)	0.3598
Pupil	3 Mid-position fixed 7 anisocoric 24 isochoric	2 Mid-position fixed 4 anisocoric 24 isochoric	0.756

Abbreviations: APTT, activated partial thromboplastin time; CI, confidence interval; ICP, intracranial pressure; INR, international normalized ratio.

Table 2 Assessment of prognostic variables

Variable	Patients followed up with an ICP monitor	Clinically monitored patients	*p-value*
Early mortality (before 14 days)	12 (34%)	5 (14%)	0.093
Hospital mortality	14 (40%)	10 (28%)	0.45
Length of stay in ICU	20.82 days (95%CI: 13.55–27.70)	16.14 days (95%CI: 10.62–21.65)	0.3132
Length of hospital stay	28 days (95%CI: 18.96–37.03)	34.82 days (95%CI: 20.55–49.15)	0.4155

Abbreviation: ICU, intensive care unit.

maintain an ICP < 22 mmHg.[1] However, based on the exposed data, no significant difference was demonstrated between the two groups regarding the studied variables. There are discrepancies in results obtained in the literature, and other studies have obtained similar results, such as those by Ferreira et a.l[5] and Biselli et al.,[4] in addition to the metanalysis performed by Yuan et al.[6] in 2015, which also did not found clinical evidence to indicate that ICP monitoring is superior to no ICP monitoring, although with the caveat that some studies included in this methanalysis indicated a reduction in the mortality. Although with the caveat, for the latter, that some studies indicate that there was a reduction in the mortality of patients submitted to invasive ICP monitoring. Yuan et al.,[7] McLaughlin et al.,[8] Dawes et al.,[9] and Agrawal et al.[10] obtained opposite results, demonstrating a benefit in the use of ICP monitoring.

As can be seen, this is a very controversial topic in the scientific community and there is still no clear consensus on the real benefits of using this form of monitoring. What we can see from the present study is that, most likely, the highest mortality rates in the invasive monitoring group do not result from the procedure itself, but from the fact that the individuals selected for this have more severe conditions than the other group due to the perception of the neurosurgery team that chose to monitor them. We can also exclude infections of the central nervous system, since no such case was reported in the monitored patients. Another disturbing factor is the possibility that there are other variables that were not considered during the propensity score pairing and that, in fact, may impair the final analysis of the data obtained.

The fact that the study was performed in a Brazilian public tertiary hospital may impair the external validation of the data, since the lack of resources and the often precarious pre-hospital care can be confusing bias. Only a few patients were monitored, which inevitably can lead to selection bias. A very controversial study[10] that caused repercussions in the scientific community was performed with 324 patients who were victims of severe TBI by a medical team in Bolivia, which showed similar results to ours.[11] However, several methodological errors were evident throughout its design, such as the inexperience of the Bolivian team in the approach of the patients, the nonconsideration of multisystemic trauma and length of stay, and, finally, the different approach for each group, in which unmonitored patients received more days of treatment. These listed factors make this study unfeasible to, separately, determine a change in the selection criteria in patients with post-traumatic intracranial hypertension. In the latest Brain Trauma Foundation (BTF) guidelines, the recommendation generated from this study was that the use of ICP monitoring determines lower mortality in 14 days (grade of recommendation IIb), since they had found a trend towards reduced mortality in the first 14 days in the group that was monitored with ICP. Regarding the previous study performed in our service, there was no difference in outcomes, showing that additional measures must be taken to improve the prognosis of these patients.

Conclusion

This cohort demonstrated, after adjustment by the propensity score method to minimize the possible biases inherent to

the study, there was no statistically significant difference between patients submitted to invasive ICP monitoring and those submitted only to clinical-radiological evaluation. Nevertheless, it is important to emphasize that, although some studies ratify such results, the theme is still not well-established and further studies with a larger number of individuals involved and with an analysis of multiple variables are necessary to, in fact, be able to establish the best role of ICP invasive monitoring in the management of patients with severe TBI.

Note

The present study was performed at the Hospital das Clínicas of the Medical School of the Universidade de São Paulo.

Conflict of Interests

The authors have no conflict of interests to declare.

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Protocol of a Nerve Neurotmesis Sciatic Repair using Polyvinyl Alcohol Biofilm in Wistar Rats

Protocolo de reparação de uma neurotmese do nervo ciático utilizando o biofilme de álcool polivinílico em ratos Wistar

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Arq Bras Neurocir 2023;42(4):e282–e287.

Abstract

Background Animal models are commonly used to assess the efficacy of new materials to be employed in the surgical repair of a nerve injury. However, there is no published surgical repair protocol for sciatic nerve neurotmesis in rats.

Objective To produce and evaluate a protocol for the tubing technique using a polyvinyl alcohol biofilm after sciatic nerve neurotmesis.

Methods Eighteen rats were randomized into 3 groups ($n = 6$ per group): control group - CG, neurotmesis group - NG, and neurotmesis biofilm group - NBG. The NG and NBG animals were submitted to neurotmesis of the sciatic nerve at 60 days of life, followed by suture of the nerve stumps; in the NBG, the animals had the suture involved by polyvinyl alcohol biofilm. A descriptive evaluation of the surgical technique was performed after the experimental period. The Shapiro-Wilk normality test was used for body weight, and analysis of variance (ANOVA) with Bonferroni posthoc ($p < 0.05$) was applied.

Results All groups showed good repair of the skin and muscle sutures; however, 33.30% of the CG presented disruption of skin points. Furthermore, 16.70% of the stumps were not structurally aligned and 33.30% had neuromas in the NG, while in the NBG, all stumps were aligned and none of them had neuroma .

Keywords
- biofilm
- neurosurgical procedure
- peripheral nerve injuries
- rats
- sciatic nerve

received
May 27, 2021
accepted
October 13, 2021

DOI https://doi.org/10.1055/s-0042-1742297.
ISSN 0103-5355.

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

Conclusions The present study was able to produce a protocol with high reproducibility in view of the mechanical stability, targeting of the nerve stumps, muscle healing, the low frequency of skin breakage and the low complexity level of the technique, and it can be used in future studies that aim to evaluate other biomaterials for nerve repair in rats.

Resumo

Introdução Modelos animais são comumente utilizados para avaliar a eficácia de novos materiais a ser empregados no reparo cirúrgico de lesões nervosas. No entanto, não há protocolo de reparo cirúrgico publicado para neurotmese do nervo ciático em ratos.

Objetivo Produzir e avaliar um protocolo para a técnica de tubulização usando um biofilme de álcool polivinílico após uma neurotmese do nervo ciático.

Métodos Dezoito ratos foram randomizados em três grupos ($n = 6$ por grupo): grupo controle - GC, grupo neurotmese - GN e grupo neurotmese biofilme - GNB. Os animais do GN e do GNB foram submetidos à neurotmese do nervo ciático aos 60 dias de vida, seguida de sutura dos cotos do nervo; no GNB, os animais tiveram a sutura envolvida por biofilme de álcool polivinílico. Após o período experimental, foi realizada avaliação descritiva da técnica cirúrgica. Para o peso corporal, foi utilizado o teste de normalidade Shapiro-Wilk e aplicada a análise de variância (ANOVA) com posthoc de Bonferroni ($p < 0,05$).

Resultados Todos os grupos apresentaram bom reparo de suturas de pele e musculares; porém, 33,30% do GC apresentou rompimento dos pontos da pele. Além disso, 16,70% dos cotos não estavam estruturalmente alinhados e 33,30% apresentavam neuromas no GN, enquanto todos os cotos estavam alinhados e nenhum apresentava neuroma no GNB.

Conclusões O presente estudo foi capaz de produzir um protocolo com alta reprodutibilidade tendo em vista a estabilidade mecânica, direcionamento dos cotos nervosos, cicatrização muscular, a baixa frequência de rompimento da pele e o baixo nível de complexidade da técnica, podendo ser utilizado em estudos futuros que avaliem outros biomateriais para reparo de nervo em ratos.

Palavras-chave
- biofilme
- procedimento neurocirúrgico
- lesões nervosas periféricas
- ratos
- nervo ciático

Introduction

The gold standard in repairing neurotmesis has been the autogenous free nerve graft. However, the surgical tubing technique, which consists of suturing the neural stumps inside the guide tube, has been studied since 1980,[1] bringing some benefits such as the prevention of neuromas, adequate guidance for aligning the stumps, inhibition of fibroblast infiltration, and, consequently, reduced scar tissue formation in the injured site.[2] This ultimately promotes the formation of a new extracellular matrix and, therefore, successful nerve regeneration.[3]

Several materials are made to serve as guide tubes for the nerve regeneration process, among which those of biological origin (muscles, blood vessels, tendons) and those of natural and synthetic origin stand out.[4,5] Materials of synthetic origin can have their mechanical, chemical, and structural properties modified to increase the nerve regeneration through incorporating substances in its structure or its production in the form of mesh, sponge, and solid or porous tubes. The nervous conduit must be non-toxic with sufficient strength and flexibility, but without pressing the nerve, minimally immunogenic and simple to manufacture. In addition, it must guide the direction of the regenerative nerve, isolate the regenerated axon from the scar tissue, and protect the regenerated nerve against surrounding compression.[6] Synthetic conduits in the literature can be classified into non-biodegradable and biodegradable materials.[7]

Although models for crush injury (neuropraxia) already exist and have been described in the literature,[8] and there is wide availability of artificial conduits,[9] which are initially tested on animals (mostly rats) to be later applied in clinic,[10] there are no standardized protocols which evaluate the behavior of these materials in experimental nerve repair models of a neurotmesis using the tubing technique.

Therefore, the present study aims to establish a surgical protocol for nerve repair of a neurotmesis using the sciatic nerve tubing technique in Wistar rats, using a polyvinyl alcohol conduit and a water-soluble, non-biodegradable polymer as a model. This model is well-accepted in the biomedical environment and has already been described in the literature for other therapeutic purposes.[11,12]

Material and Methods

The study was performed at the neuromuscular plasticity laboratory of the anatomy department and the nanostructured biodevices laboratory (BIONANO) of the biochemistry department at Universidade Federal de Pernambuco (UFPE). The sample consisted of 18 Wistar rats, maintained at a temperature of 23 ± 1°C, subjected to inverted light/dark cycles (12 hours) with commercial diet (Purina, St. Louis, MO, USA) and water ad libitum. The animals were randomized using the Random Allocation version 2.0 software) at 40 days of age into 3 groups: a) the control group (CG, $n = 6$), rats that which did not undergo neurotmesis; b) neurotmesis group (NG, $n = 6$), rats which underwent a complete lesion in the midpoint of the sciatic nerve with subsequent suture; c) neurotmesis and biofilm group (NBG, $n = 6$), rats that underwent injury and had the suture covered with biofilm. The sciatic nerves were then analyzed in the 6th postoperative week.

Manufacturing and Obtaining Polyvinyl Alcohol Biofilm

Polyvinyl alcohol biofilms were produced by Bionano laboratory using 16% PVA and 2% alginate solutions in a 3:1 concentration.

The solutions were placed in syringes and subjected to electrospinning for 8 and 5 hours, respectively. The biofilms were subsequently submitted to the cross-linking process for 24 hours, and then were immersed in a solution of 98.9% methanol, 1% glutaraldehyde and hydrochloric acid. Next, they went through 5 deionized water baths, were placed to dry at 8°C for 3 to 7 days, cut into 10 mm × 10 mm squares, and then sterilized under ultraviolet light for 30 minutes.

Surgical Procedure for Sciatic Nerve Injury

All animals were intraperitoneally anesthetized at the age of 60 days with a 0.05 mL and 0.1 mL xylazine hydrochloride (Anasedan) (20 mg Kg^{-1}) and ketamine hydrochloride solution (Dopalen) (100 mg Kg^{-1}) for each 100 g of the animal's body weight, which had been previously measured. Trichotomy was then performed after sedation on the right gluteal region, and then the area was cleaned with chlorhexidine antiseptic. The animal was sent to the sterile location, placed in the anatomical position, and the surgical procedure was started. A longitudinal incision was made in the skin of the posterosuperior region of the right paw, starting one centimeter below the greater trochanter of the femur in a diagonal direction and ending near the popliteal fossa at the level of the hamstring muscles. The sciatic nerve was exposed after disjoining the superficial gluteal and biceps femoris muscles. The sciatic nerve was visualized using a LEICA Zoom 2,000 Stereo Microscope, 10.5–45x (Leica Camera AG, Wetzlar, Germany), and a tentacle was placed under the nerve for its isolation with the adjacent tissues. AU: Please, note that if this is the name of a company, you must provide its complete name and location (city, state, and country) between parentheses.

Neurotmesis was performed in the animals of the injury groups with surgical scissors, 5 mm proximal to the division of the 3 main branches of the sciatic nerve (tibial, common fibular, and sural), followed by direct coaptation of the nerve extremities with fascicular alignment and monofilament suture 7–0 CATGUT (Ethicon Inc., Raritan, NJ, USA) in about 3 points of the epineurium.[13] In addition, the suture was covered with polyvinyl alcohol biofilm in the NBG. The animals in the CG only suffered a longitudinal skin incision, disjunction of the muscles described above, and visualization of the sciatic nerve. Then, muscle and skin suture with 4–0 nylon monofilament (Somerville) was performed to promote the same surgical stress as in the other groups (►**Fig. 1**).

Surgical Care

After applying the anesthetics, the analgesic tramadol hydrochloride (5% -100 mg/kg of animal weight, diluted in 0.9% saline - 1:1) was applied subcutaneously, being reapplied every 12 hours for 3 days. Topical antibiotic therapy (rifamycin SV sodium - 10 mg/ml; neomycin sulfate + bacitracin - 5 mg/g + 250 IU/g) was performed at the end of the surgery, enrofloxacin antibiotic (10% - 5 mg/Kg of animal weight) was then administered for 4 days every 24 hours, and the meloxican antiinflammatory (0.2% - 0.1 mL/Kg of animal weight) was applied subcutaneously for 2 days every 24 hours. All surgical instruments used in the procedure were previously sterilized.

Macroscopic Analysis of the Surgical Technique and Euthanasia of Animals

The animals had their body weight measured in the 6th postoperative week, and then were anesthetized again with a 0.05 ml and 0.1 ml xylazine (Anasedan) (20 mg.Kg^{-1}) and ketamine hydrochloride solution (Dopalen) (100 mg.Kg^{-1}) for each 100 g of animal weight. The right sciatic nerve was visualized to have an evaluation of the performed surgical technique, and a macroscopic analysis was subsequently performed. The evaluation was performed after the experimental period, according to the questionnaire developed (►**Table 1**). The animals received an intracardiac dosage of 1 mL of potassium chloride (KCl) while still under the effect of anesthetics for their euthanasia.

Statistical Analysis

A database was built in Microsoft Excel, 2016 version, (Microsoft Corp., Redmond, WA, USA) using the obtained data, and later analyzed using the IBM SPSS Statistics software, Version 20.0 (IMB Corp., Armonk, NY, USA). The data were expressed in frequency for the qualitative evaluation obtained through the sciatic nerve macroscopy evaluation questionnaire, and then they were expressed as mean and standard deviation, and the Shapiro-Wilk normality test was performed to evaluate body weight. The analysis of variance (ANOVA) was subsequently used followed by the Bonferroni test, as the data were normal. A significance level of 5% was adopted ($p < 0.05$).

Results

►**Table 2** represents the sample characterization before the surgical intervention, in which a similarity was observed between the groups at the beginning of the study.

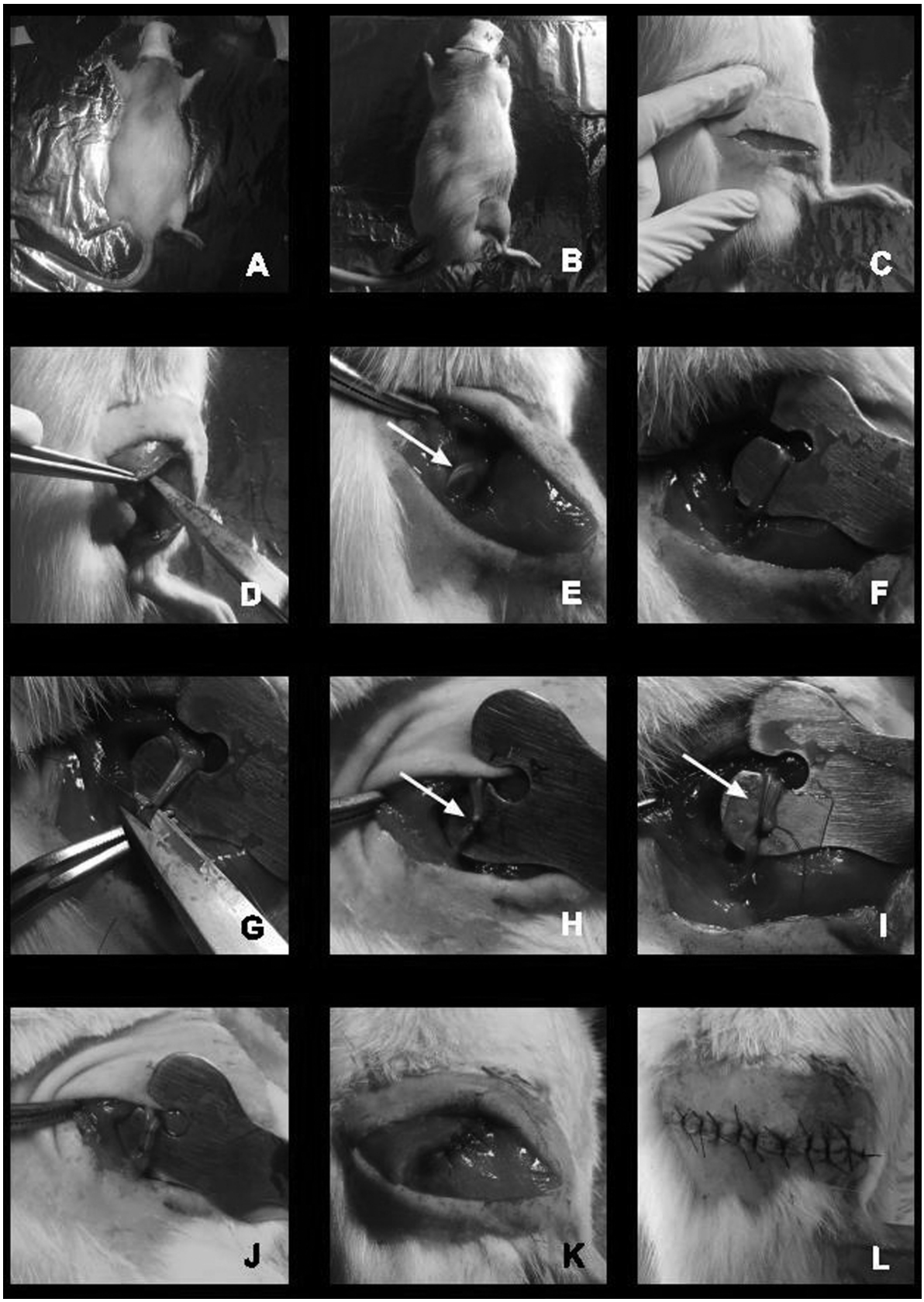

Fig. 1 Surgical procedure: (**A**) Animal in the anatomical position; (**B**) trichotomy; (**C**) skin incision; (**D**) disjunction of the superficial gluteal muscles and biceps femoris; (**E**) visualization of the sciatic nerve (arrow); (**F**) isolation of the nerve; (**G**) neurotmesis; (**H**) neurorrhaphy (arrow); (**I**) biofilm positioned (arrow); (**J**) biofilm involving the nerve and sutured; (**K**) muscular suture; (**L**) skin suture.

Table 1 Questionnaire for macroscopic evaluation of surgical repair

1. Was the skin suture well repaired?	() Yes	() No	() Not applicable
2. Have the skin spots broken?	() Yes	() No	() Not applicable
2.1. If yes, a new suture was performed	() Yes	() No	() Not applicable
3. Was the muscle suture well repaired?	() Yes	() No	() Not applicable
4. Was the suture of the muscle absorbed?	() Yes	() No	() Not applicable
5. Are the stumps aligned structurally?	() Yes	() No	() Not applicable
6. Was the biofilm absorbed?	() Yes	() No	() Not applicable
6.1. If not, was the biofilm in place?	() Yes	() No	() Not applicable
7. Are there neuromas?	() Yes	() No	() Not applicable

Table 2 Characterization of the sample before neurotmesis

	CG ($n = 6$)	NG ($n = 6$)	NBG ($n = 6$)	p
Preoperative weight (g)	267.00 ± 25.13	265.00 ± 12.44	265.00 ± 25.38	0.983

Abbreviations: CG, control group; GN, neurotmesis group; GNB, neurotmesis biofilm group.
ANOVA was used, followed by the Bonferroni test. The level of significance was 5%.

Table 3 Frequency of responses to the descriptive evaluation questionnaire 6 weeks after surgical repair of a neurotmesis in Wistar rats

Questions	GC			GN			GNB		
	Y	N	NA	Y	N	NA	Y	N	NA
1. Was the skin suture well repaired?	100%	0%	0%	100%	0%	0%	100%	0%	0%
2. Have the skin spots broken?	33.30%	66.70%	0%	0%	100%	0%	0%	100%	0%
2.1. If yes, a new suture was performed	33.30%	0%	66.70%	0%	0%	100%	0%	0%	100%
3. Was the muscle suture well repaired?	100%	0%	0%	100%	0%	0%	100%	0%	0%
4. Was the suture of the muscle absorbed?	0%	100%	0%	0%	100%	0%	0%	100%	0%
5. Are the stumps aligned structurally?	100%	0%	0%	83.30%	16.70%	0%	100%	0%	0%
6. Was the biofilm absorbed?	0%	0%	100%	0%	0%	100%	0%	100%	0%
6.1. If not, was the biofilm in place?	0%	0%	100%	0%	0%	100%	100%	0%	0%
7. Are these neuromas?	0%	100%	0%	33.30%	66.70%	0%	0%	100%	0%

Abbreviations: CG, control group; GN, neurotmesis group; GNB, neurotmesis biofilm group; N, No; NA, not applicable; Y, yes.

►**Table 3** shows the percentage of responses related to the questionnaire for the descriptive evaluation of surgical repair. The animals of all groups had their skin and muscle sutures well repaired; however, skin stitches were broken in two animals in the CG (33.30%), and a new suture was performed after surgery. There was no absorption of the muscle suture in any of the groups.

Although the biofilm was not absorbed in the NBG, all the stumps were structurally aligned 6 weeks after surgery, and there were no neuromas. However, 16.70% of the animals in the NG had misalignment of the stumps, and 33.30% had neuromas.

Discussion

As neurotmesis is the most severe traumatic injury that can affect the peripheral nervous system and requires surgical treatment,[14] the present study experimentally evaluated the repair and surgical recovery of a neurotmesis submitted to the application of a PVA biofilm.

The skin suture rupture in two animals in the CG may have been a consequence of the animals moving freely, increasing the tissue reaction induced by the suture itself with softening of the surrounding tissues, delaying the onset of fibroplasia.[15] Despite this, the surgical technique was effective, since perfect asepsis and respect for the force lines of the tissue are necessary in order for the suture to effectively heal with natural approach of the edges and without exaggerated tension; this prevented infection, ischemia, or scarring necrosis,[16] and all animals in the study had good suture repair of both the skin and the muscle.

However, the muscle suture thread was not absorbed in all animals, as nylon monofilament (Somerville) is a non-absorbable synthetic and inorganic thread which loses 30%

of its original tensile strength in 2 years. It was chosen for this for being a non-reactive tissue and for its ability to stretch even with its permanence in the body, reducing the risk of infection and tissue stiffness.[15]

Due to the results observed in the structural alignment of the nerve stumps, the biofilms used promoted nerve stability after injury, while there was no alignment in 16.70% of the animals in the NG. This corroborates a recent study which stated that the suture technique by itself does not guarantee mechanical stability, requiring additional strategies for better repair, such as biofilm or those already used in research of suture associated with glue or fibrin conduit.[17]

On the other hand, the biofilms were not absorbed after 6 weeks of surgery to repair neurotmesis. This is similar to previous findings with the use of a nervous conduit composed of PVA in the injury of the sciatic nerve, demonstrating the presence of the material 12 weeks after injury, being surrounded by fibrin capsule and connective tissue, the result of its biodegradation.[18]

The presence of neuromas in NG is possibly related to a disorganized or incomplete regeneration of a nerve after its injury, due to the deposition of scar tissue by fibroblasts.[19,20] On the other hand, the absence of this structure in NBG reiterates some of the main benefits of the tubulization technique in nerve repair, which are the proper orientation of the axonal stumps toward the distal stump or target tissues, prevention of neuromas, diffusion of neurotrophic factors released by the damaged nerve, accumulation of extracellular matrix components, and inhibition of fibroblast infiltration, reducing the formation of scar tissue at the injury site.[2]

Conclusion

The present study was able to establish a surgical protocol for nerve repair of a neurotmesis using the sciatic nerve tubing technique in Wistar rats, using a polyvinyl alcohol conduit and a water-soluble, non-biodegradable polymer as a model. Allied to this, as the structural alignment and the absence of neuroma are parameters considered for faster nerve repair,[21] it is believed that the tubing technique tested in the present study proved to be effective in the sciatic nerve repair process from a macroscopic point of view.

Therefore, following the guidelines of this protocol, we propose that new studies are carried out to assess the histological and functional repair of the sciatic nerve; these studies should also include a group that has a distance between the stumps in order to evaluate axonal growth within the biofilm.

Ethical Declaration

The procedures used for handling and caring for animals are in accordance with international standards established by the National Institute of Health Guide for Care and Use of Animal, and the project was approved by the Ethics Committee on the Use of Laboratory Animals (CEUA, in the Portuguese acronym) of the Biological Sciences Center - Universidade Federal de Pernambuco under protocol number 23076.052306/2017–10.

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Stereotactic Intracavitary Irradiation for Cystic Craniopharyngiomas with Rhenium-186

Irradiação estereotáxica intracavitária para craniofaringiomas císticos com Rênio 186

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Arq Bras Neurocir 2023;42(4):e288–e294.

Abstract

Objective The intracavitary irradiation of cystic tumors has been used as a therapeutic alternative modality in the management of cystic craniopharyngiomas. In the present study, we review our experience, considering the technical issues, outcomes, and complications associated with the use of stereotactic intracavitary irradiation (SICI) with colloidal rhenium-186 (^{186}Re) for cystic craniopharyngioma.

Material and Methods The records of 33 patients with cystic craniopharyngiomas treated by SICI with colloidal ^{186}Re were retrospectively reviewed. The median radiation dose to the cyst wall was of 408 Gy (range: 175 Gy to 500 Gy). All tumors were composed of a large cyst cavity, and 9 (27.3%) also had a solid component. The mean follow-up period was of 3.7 years.

Results After SICI, 31 (93.9%) patients showed radiological evidence of cyst regression, and, in 2 (6.1%), no response was observed. An improvement in the visual deficits was observed in 8 cases (24.2%), and an improvement in endocrinogical disturbances, in 2 cases (6.1%). We observed complications in 3 patients (9.1%): diabetes insupidus in 1 case (3%), aggravation of visual acuity in 1 case (3%), and severe headache after infusion of the colloid in 1 case (3%); and 1 patient (3%) died after meningitis.

Conclusion Stereotactic intracavitary irradiation with colloidal ^{186}Re is a safe procedure, with satisfactory results in the present series, and should be considered, in the management of cystic craniopharyngiomas, the first-intention therapy or as an adjuvant to other therapeutical modalities, with acceptable morbidity and mortality rates.

Keywords
- craniopharyngioma
- rhenium
- stereotactic techniques
- stereotactic radiation therapy

received
June 10, 2020
accepted
March 9, 2021

DOI https://doi.org/10.1055/s-0041-1733864.
ISSN 0103-5355.

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

Resumo

Objetivo A irradiação intracavitária tem sido empregada como modalidade terapêutica alternativa no manejo dos craniofaringiomas císticos. No presente estudo, revisamos nossa experiência, considerando parâmetros técnicos, resultados e complicações associadas ao uso da irradiação estereotáxica intracavitária (IEIC) com rênio-186 (^{186}Re) coloidal em pacientes com craniofaringiomas císticos.

Material e Métodos Os prontuários de 33 pacientes com craniofaringiomas císticos tratados por IEIC com ^{186}Re coloidal foram revisados retrospectivamente. A dose média de radiação na parede do cisto foi de 408 Gy (variação: 175 Gy a 500 Gy). Todos os tumores eram compostos por uma grande porção cística, e, em 9 casos (27,3%) havia também um componente sólido. O período médio de seguimento foi de 3,7 anos.

Resultados Após a IEIC, 31 (93,9%) pacientes apresentaram evidência radiológica de regressão do cisto, e em 2 (6,1%) não foi observada resposta. Melhora do déficit visual foi observada em 8 casos (24,2%), e dos distúrbios endocrinológicos, em 2 casos (6,1%). Complicações ocorreram em 3 pacientes (9,1%): diabetes insipidus em 1 caso (3%), piora da acuidade visual em 1 caso (3%), e cefaleia intensa após a infusão do coloide em 1 caso (3%); e 1 paciente (3%) faleceu após meningite.

Conclusão A IEIC com ^{186}Re coloidal é um procedimento seguro, com resultados satisfatórios nesta série, e deve ser considerada no manejo de craniofaringiomas císticos, seja como intervenção primária, seja como adjuvante a outras modalidades terapêuticas, com taxas de morbidade e mortalidade aceitáveis.

Palavras-chave

- craniofaringioma
- rênio
- técnicas estereotáxicas
- radiocirurgia estereotáxica

Introduction

Craniopharyngiomas are benign neoplasms (grade I according to the classification of the World Health Organiozatoion [WHO]) of epithelial origin that arise from the remnants of the Rathke pouch in the sellar region. They account for 4.5% of all brain tumors[1] with a bimodal incidence, presenting peaks between 5 and 15 and 45 and 60 years of age,[2] and contributing to 1.2% to 4% of all intracranial tumors in children. Despite the benign histology, these tumors should be considered low-grade malignancies because of their location and progression without treatment, which generally results in a reduction in life expectancy and a 5-year overall survival rate of 80%.[3]

In large series, 54% to 94,4% of the patients have tumors with a significant cystic portion.[4] Total surgical removal is the best option, but it may be associated with significant postoperative morbidity. Ophthalmological deterioration (13% to 15%), hypothalamic obesity (26% to 52%), and an endocrinological decline (> 90%) are the complications described.[5] Moreover, high rates of recurrence are known, from 13% to 30% in cases of gross total resection (GTR), from 71% to 90% in cases of subtotal resection (STR), and of 21% in STR associated with external beam irradiation (EBI).[6]

In this context, adjuvant therapies have been considered, such as radiotherapy, radiosurgery, stereotactic drainage and intracavitary injection of radioactive colloidal solutions, or chemotherapeutic agents.[7]

Intracavitary contact irradiation was introduced by Leksell and standardized by Backlund, and intracavitary irradiation with rhenium-186 (^{186}Re), by Szikla.[8–10]

In the present study, we review our experience, considering the technical issues, outcomes, and complications associated with the use of stereotactic intracavitary irradiation (SICI) with colloidal ^{186}Re for cystic craniopharyngiomas.

Material and Methods

Patient Population

Between October 1986 and November 2001, 45 patients were considered to be treated by SICI using colloidal ^{186}Re for cystic craniopharyngiomas. In total, 33 patients were considered fit for this retrospective analysis. The other 12 cases were excluded because of insufficient follow-up data for evaluation in 2 cases, leakage during the gamma camera test in 4 cases, technical problems with the injection of ^{186}Re in 2 cases, poor clinical status in 1 case, and other reasons in 3 cases. Patients with tumors of other origin treated by SICI at our institution were excluded from the study.

All patients were submitted to neurological, ophthalmologic, endocrinological, and neuroradiological examinations, including computed tomography (CT) scans and magnetic resonance image (MRI) scans.

Insertion of Intracavitary Catheter

Insertion of the cyst catheter was performed under stereotactic conditions, using a Talairach stereotactic frame under general anesthesia. The precise location of the cyst was determined, the target point (the center of the cyst) and best trajectory were defined, avoiding vascular structures, as well as the ventricular system, if possible. After perforation of the cyst wall, the contents of the cyst were aspirated,

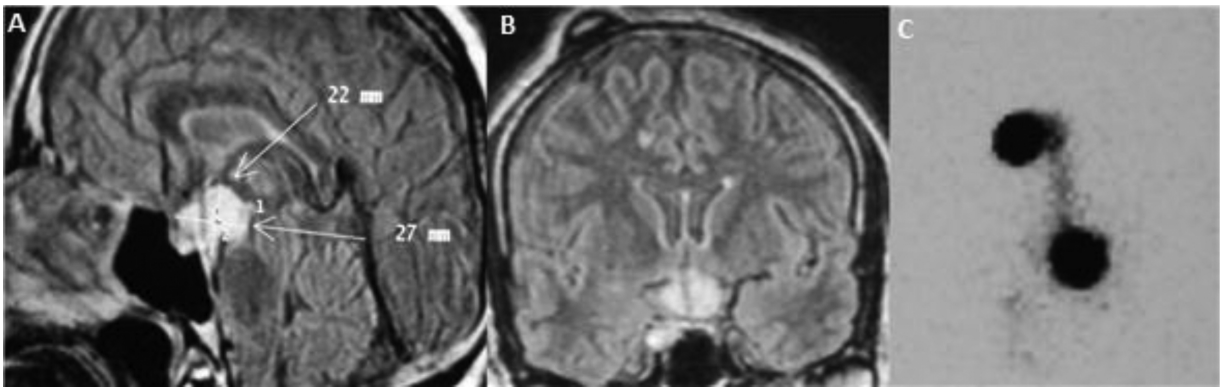

Fig. 1 Sagittal (**A**) and coronal (**B**) views of an MRI scan showing the satisfactory position of the intracystic catheter,. And a gamma-camera control image without leakage of the radioisotope (**C**).

enabling partial decompression, and sent for a pathological examination. Finally, the catheter was attached to a subcutaneous Ommaya reservoir placed posteriorly to the incision (►**Fig. 1**).

A postoperative MRI scan was obtained to assess the position of the catheter and the decompression of the cyst.

Control Examination Before Irradiation

The integrity of the cyst wall was controlled postoperatively by gamma camera using a reduced dose of colloidal ^{186}Re (500 µCi) (►**Fig. 1**). This test aimed to detect an eventual leakage of the radioisotope. In case of a leak to the subarachnoid space, intracavitary irradiation was not performed until a new test confirming the absence of a leak.

Another MRI scan was performed to confirm the position of the catheter and to evaluate the volume of the cyst after the gamma camera control, and immediately before the SICI, considering to control.

Rhenium-186 and Dosimetry

Dosimetry was based on the volume of the cyst as determined by the gamma camera. The dosage used ranged from 2 mCi to 20 mCi (mean: 9.0 mCi). The mean cumulative dose delivered to the cyst wall was of 408.4 Gy (range: 175 Gy to 500 Gy). The dose was calculated based on the formula proposed by Backlund.[9]

The optimal dose should destroy the epithelium of the cyst with minimal side effects to the surrounding structures. According to Vanhauwaert et al.,[11] doses lower than 100 Gy were related with frequent early cyst recurrence, while doses higher than 1,000 Gy were associated with a high risk of complications; therefore, they suggested that doses between 200 Gy and 250 Gy could present a lower complication rate, with minimal recurrence.

Postirradiation Care

Brain and hepato-splenic scintilography were performed immediately and daily following the injection of colloidal ^{186}Re. An examination of the urine to find traces of the radioisotope was also performed to confirm the absence of leakage. During the treatment, the patient was confined to an isolated bedroom because of gamma emissions.

Radioisotope evacuation of the cyst was performed between four and five days after the therapeutic injection. If a leakage of cerebrospinal fluid (CSF) was detected, a complete evacuation and washing of the cavity was immediately performed.

The CT scan was performed routinely before hospital discharge.

The follow-up period ranged from 3 months to 10 years (mean: 3.7 years). The survival time was calculated from the date of the intracavitary irradiation.

The volume of the cyst was reassessed by a postoperative MRI and compared with previous exams. Volume changes were labeled, according to the proportion of decrease, as $\geq$ 90%, 90% to 25%, and $<$ 25% regression, or no regression (►**Table 1**).

The follow-up included ophthalmologic, endocrinologic, neurological and radiological evaluations (including MRI) to assess the clinical conditions and cyst volume after irradiation, and they were obtained at three and six months after the treatment, and at six-month intervals.

Statistical Analysis

The Pearson Chi-squared (χ^2) test was used for the parametric values, and the Student *t*-test for the non-parametric values. The Fisher exact and Bonferroni correction were used when the values were inferior to five. The Epi-Info 2000 (version 1.1.2, Centers for Disease Control and Prevention, Atlanta, GA, US) software, version 1.1.2, was used.

Table 1 Reduction in cystic volume regarding craniopharyngiomas treated by SICI using colloidal ^{186}Re

Reduction in cystic volume (%)	Number of cases (%)
$\geq$ 90%	15 (45.45%)
90%–25%	05 (15.15%)
$<$ 25%	11 (33.33%)
0%	02 (6.06%)
Total	**33 (100%)**

Abbreviations: ^{186}Re, rhenium-186; SICI, stereotactic intracavitary irradiation;

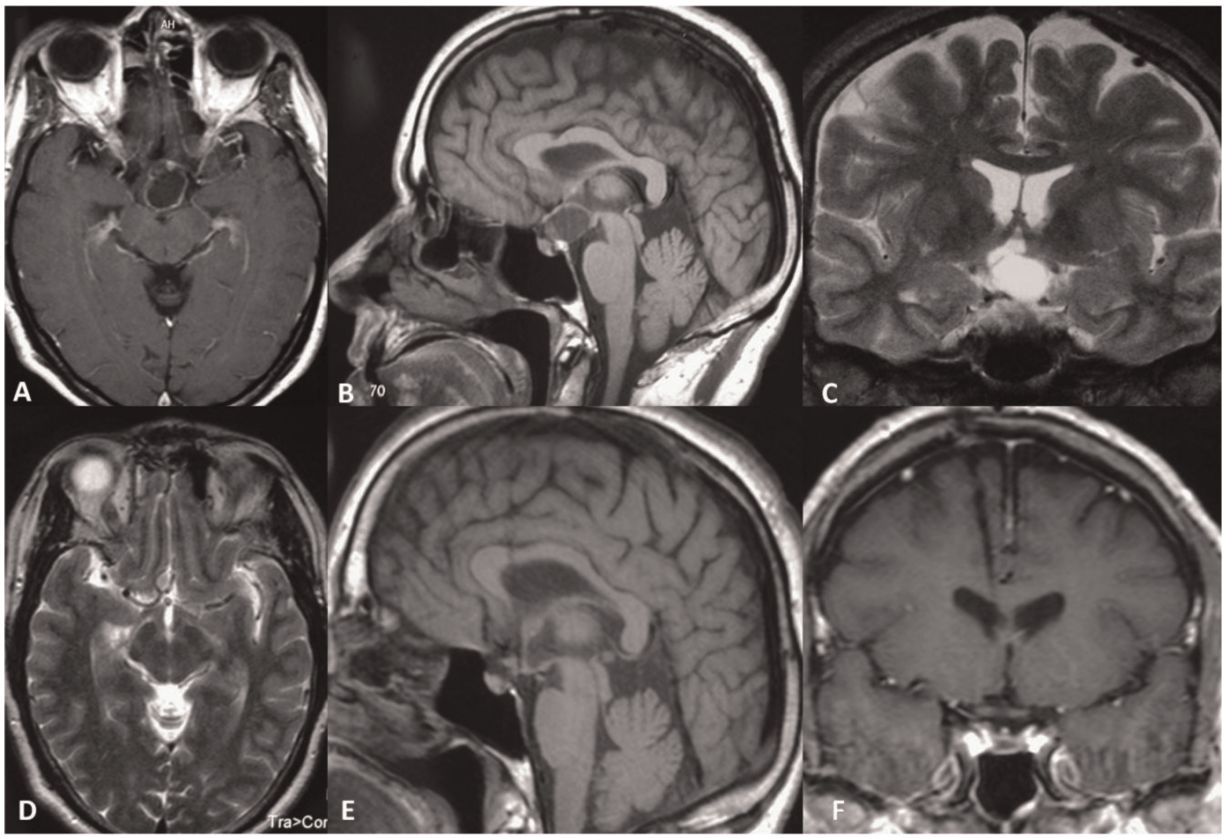

Fig. 2 Case 1. An MRI scan showing the cystic craniopharyngioma before treatment: (**A**) axial T1-weighted image; (**B**) sagittal T1-weighted image; and (**C**) coronal T2-weighted image. control MRI 30 months after the treatment: (**D**) axial T2-weighted image; (**E**) sagittal T1-weighted image; and (**F**) coronal T1-weighted image showing complete obliteration of the cyst after stereotactic intracavitary irradiation with colloidal ^{186}Re.

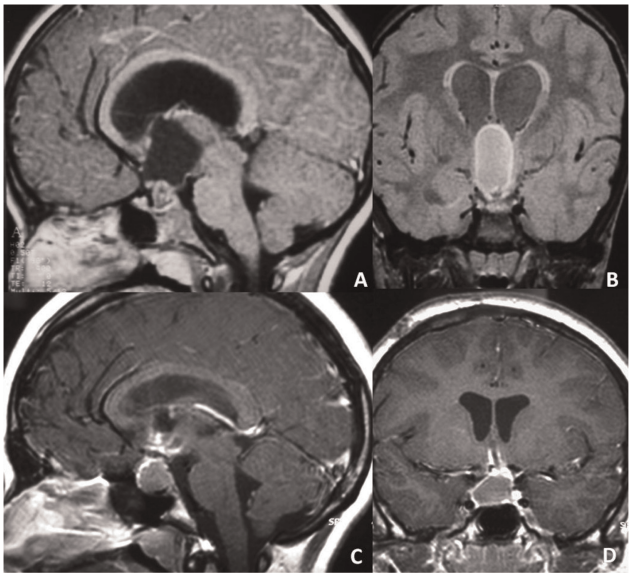

Fig. 3 Case 2. An MRI scan showing the cystic craniopharyngioma: (**A**) sagittal T1-weighted image; and (**B**) coronal fluid-attenuated inversion recovery (FLAIR) before treatment. Control MRI 48 months after the treatment: (**C**) sagittal T1-weighted image; and (**D**) coronal T1-weighted image showing complete obliteration of the cystic portion of the tumor after stereotactic intracavitary irradiation with colloidal ^{186}Re.

Ethical Issue

The present study was approved by the Committee of Ethics in Research of the Health Sciences Center at Universidade Federal do Espírito Santo (Vitória, state of Espírito Santo, Brazil), in accordance with Brazilian law and the regulations governing research involving human beings, instituted by resolution No.466/2012 of the Brazilian National Health Council, under CAAE number 85930818.7.0000.5060, advice number 2.631.734.

Results

The results of the SICI in the 33 patients in the sample are summarized in ►**Table 1**.

There were 20 male (60.6%) and 13 female (39.4%) patients, with a mean age of 41.8 years (range: 5 to 86 years). In total, 10 patients (30.3%) were under 15 years of age.

In 9 cases (27.2%), the craniopharyngioma was purely cystic, and, in 24 cases (72.7%), there was a solid portion associated. A total of 18 patients (54.5%) had previously undergone additional treatments, and surgery was performed in 7 (38,8%) of them, and intralesional chemotherapy and/or radiosurgery were performed in 11 (61,2%). A combination of radiosurgery for the solid component of the tumor

and ^{186}Re intracavitary irradiation was performed in 1 patient (3.0%) with satisfactory results.

In 31 patients (93.9%), there was radiological evidence of a decrease in cyst volume after the instillation of ^{186}Re. The ►**Fig. 2** and **3** presents two cases of wide cyst regression with the treatment. It was labeled, according to the proportion of the decrease in volume, as $\geq$ 90%, 90% to 25%, and $<$ 25% regression (►**Table 1**).

In 12 patients (36.4%), a radioisotope leak was observed in the first test before irradiation. These patients underwent a second test, which indicated that 9 (27.2%) of them presented spontaneous resolution, enabling the irradiation. In the remaining 3 (9.1%), the leak persisted, requiring surgical repositioning of the catheter before the irradiation. A total of 4 patients (12.1%) underwent a second session of irradiation, 2 (9%) presented cyst recurrence, 2 (9%) developed a new cyst, and another 2 (9%) had a leak after the radioisotope instillation, followed by complete aspiration, without clinical repercussion.

We observed complications in 3 patients (9.1%): diabetes insipidus in 1 case (3%), aggravation of visual acuity in 1 case (3%), and severe headache after infusion of the colloid in 1 case (3%).

During the follow up period, there were four deaths in the present series, but only one of them was directly related to the SICI therapy, because of meningitis followed by septicemia.

Curiously, we observed one case in which, after catheter implantation followed by aspiration of the contents of the cyst and the gamma camera test, a leak was observed, and the instillation of ^{186}Re was not possible. Nevertheless, complete obliteration of the cyst was observed during the four years of follow-up.

Discussion

Stereotactic intracavitary irradiation has been used mostly for the treatment of cystic craniopharyngiomas, with satisfactory results.[3]

Comparing the results of patients treated with stereotactic endocavitary irradiation for craniopharyngiomas, using yttrium-90 (^{90}Y) and ^{186}Re, Netzeband et al.[12] observed better results with ^{90}Y, although the number of patients treated with ^{186}Re was too small to obtain statistical significance.

Intracavitary irradiation was introduced by Leksell and Liden,[8] and standardized by Backlund,[9] employing radioactive chromic phosphate. The subsequent application of this technique using a variety of different beta and gamma radiation-emitting isotopes has been reported.[10,12,13] (►**Table 2**)

The use of colloidal ^{186}Re was introduced by Szikla et al.[10] in 1984, for the treatment of cystic craniopharyngiomas, and, later, for cystic gliomas. Those authors considered the advantageous physical properties of ^{186}Re in comparison to those of other radioisotopes (►**Table 2**): the relatively low-energy beta radiation (358 KeV), which enables a restricted penetration of soft tissue and limits the depth of the necrosis of the cyst wall to 1 mm instead of 3 mm using ^{90}Y. This property might reduce the risk of damage in the adjacent structures, posed by the late effect of radiation, as seen in patients treated with 90Y, that tend to present radiation-induced edema in peripheral areas.

The phosphorus-32 (^{32}P) and ^{90}Y isotopes are pure beta emitters, while gold-198 (^{198}Au) and ^{186}Re are also gamma emitters. The gamma emission of ^{186}Re (137 KeV) enables an excellent scintigraphic control of a possible leakage of radioactivity to CFS spaces before and during SICI.

Intracavitary irradiation aims to destroy the epithelium of the cyst without damaging the surrounding structures, and an adequate dose of the radionuclide must be employed and no radioisotope leaks must be present.

Szikla et al.[10] suggested that the injected radiocolloid progressively migrates to the cyst wall during the treatment. Szeifert et al.[14–16] demonstrated by histologic studies that, regarding the cyst wall of craniopharyngiomas following intracavitary irradiation with ^{90}Y, the lining of the layer of epithelial cells was damaged and the cyst wall shrank, with thickening of the capillary walls and proliferation of endothelial cells and subendothelial connective tissue with focal calcification and narrowed lumens of small vessels with a large amount of thick collagen bundles showing hyaline degeneration.

Netzeband et al.[12] compared the results of SICI for craniopharyngiomas using ^{90}Y and ^{186}Re; they observed more CSF leaks using ^{186}Re, and considered that the higher tendency of this complication could be due to the chemical properties of ^{186}Re, which is a sulfide and tends to convert to a water-soluble perrhenate. Berenger et al.[17] considered this observation the result of a better resolution of scintigraphic images using the ^{186}Re, which enables a precise determination of even small leaks, which is usually not possible with

Table 2 Properties of the radioisotopes used in the stereotactic intracavitary irradiation of cystic tumors[10]

Feature	^{186}Re	^{198}Au	^{90}Y	^{32}P
Physical half-life (days)	3.8	2.7	2.7	14.3
Maximum beta energy (KeV)	1076	966	2284	1710
Mean beta energy (KeV)	358	322	761	695
Maximum range in the soft tissue (mm)	4.5	4	10.9	7.9
Half-value depth in the soft tissue (mm)	1	0.9	2.9	0.8
Maximum gamma energy (Kev)	137	412	–	–

Abbreviations: ^{32}P, phosphorus-32; ^{90}Y, yttrium-90; ^{186}Re, rhenium-186; ^{198}Au, gold-198.

^{90}Y or ^{32}P. Those authors pointed out that the lower granulometry of ^{186}Re may have some implication in its tendency to leak, because sometimes, although the cyst wall is intact, it is permeable to colloidal isotopes of low granulometry. On the other hand, this feature enables a homogeneous distribution inside the cyst, and, even in case of an undesirable leak to the subaracnoid space, it is possibly less toxic.

The mean desired dose to the cyst wall is 400 Gy, ranging from 200 Gy to 600 Gy according to different criteria, including histology, volume, and location of the tumors. Sometimes it is difficult to calculate the exact dose due to factors such as the irregular shape of the cyst or multiple cavities, which complicate the estimation of the volume.[10]

Stereotactic intracavitary irradiation has been used mostly for the treatment of cystic craniopharyngiomas, with satisfactory results,[10,18–20] but reports of its use in cases of cystic gliomas are very limited in the literature.

Szikla et al.[10] treated 29 cystic gliomas by intracavitary irradiation with colloidal ^{186}Re with a mean wall dosage of 580 Gy. In total, 17 patients presented low-grade tumors, and 8 patients had high-grade gliomas. They observed a decrease or stabilization of the volume of the cyst in all patients with low-grade gliomas, with white matter edema in two cases. regarding the high-grade gliomas, in six patients the volume of the cyst decreased or stabilized, without major complications. In one patient, although the cyst had decreased, tumor progression compensated rapidly the clinical improvement due to inactivation of the cyst. The mean survival time in this last group was of five months.

Our results are similar to those reported in the literature. In the present study, it was not possible to define the isolated significance of SICI with ^{186}Re, considering that only one patient did not undergo additional therapy, and a multivariate analysis was no possible because of the small sample and the absence of mortality in the group with pilocytic astrocytomas.

It is important to point out that this technique it is indicated for the cystic portion of the tumor, although in two cases we have observed a decrease, and in one case, stabilization of the solid portion of the tumor. Stereotactic intracavitary irradiation can be repeated if no response is initially obtained, or even in the case of recurrence of the cyst, as we have performed successfully in two patients, as well as Pollack et al.[13] The response of the intracavitary irradiation or the cystic shrinkage may take some months, and becomes stable after one year, and unfortunately cannot be previously preview.[18,19]

The possible complications of this technique can be related to the stereotactic procedure itself (what is uncommon) or to the radioisotope injection, and they include intracerebral hematoma after cyst puncture,[21] meningitis,[18,19] and necrotic hemorrhage. All of these complications have been observed in the treatement of craniopharyngiomas using ^{90}Y. In the study by Berenger et al.,[17] there was one death related to a leak in the treatment for craniopharyngioma using ^{86}Re.

Palsy of the third nerve was observed in one case in the present series. It was probably related to temporary damage to the nerve caused by the radiation, as was also observed by other authors.[5] Brain edema was observed in one patient, and it was probably related to unsatisfactory aspiration of the radioisotope after the irradiation because of technical difficulties.

Removal of the cyst must be considered, but this may be hazardous depending on its location. The cyst may be treated with aspiration alone, but it usually recollects. The subsequent blockage of the catheter is a potential problem, considering the protein content. In some cases, SICI may be considered as a primary therapy, although the best indication is for patients with persistent symptoms due to cystic lesions following surgery, radiotherapy or even radiosurgery, which keep reaccumulating despite repeated aspiration.

Young children under 5 years of age are not candidates for SICI; but, in specific situations, implantation of an intracavitary catheter followed by intermittent aspiration and subsequent and timely irradiation is not contraindicated.

An alternative approach to intracavitary irradiation is bleomycin, an antineoplastic agent, which has been proposed by several authors,[22–24] with satisfactory results. However, the risk of a toxic effect from a leak may be more severe with bleomycin than with ^{186}Re.

Stereotactic intracavitary irradiation using the radioisotopes is an alternative therapeutic modality for cystic tumors, including craniopharyngiomas, gliomas, and even other tumors composed of a considerable cyst cavity. However, to date, this technique has not been used much, for different reasons, particularly because of the need to have a multidisciplinary team and special conditions to manipulate the radioisotopes, and specially because there are no studies with class-I level of evidence showing the real benefits of this kind of therapy, and the samples of the series in the literature are very limited.[25–27]

Nowadays with the development of radiosurgery, SICI can play an important role in the treatment of mixed tumors with a cystic portion. Combined therapy, using radiosurgery for the solid portion, and intracavitary ^{186}Re for the cystic component, can be performed, as we did in one case, with an excellent result.[28–30]

Conclusion

Stereotactic intracavitary irradiation with colloidal ^{186}Re seems to be a safe procedure, with satisfactory results in the present series, and it should be considered in patients with cystic craniopharyngiomas, alone or combined with other treatment modalities, considering clinical and tumoral features, aiming to provide the best outcomes to the patients.

Conflict of Interests

The authors have no conflict of interests to declare.

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Interventional Neuroradiology: Why Don't Brazilian Female Physicians Like It?

Neurorradiologia intervencionista: Por que as médicas brasileiras não gostam?

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Arq Bras Neurocir 2023;42(4):e295–e301.

Abstract

Objective Much has been discussed about gender diversity in all professional fields, particularly in medicine. Recent studies showing that there are fewer than ten female professionals in interventional neuroradiology (INR) in a continental country like Brazil, and less than thirty in all of Latin America, have prompted an investigation into the causes of the low numbers of women choosing to follow this medical specialty. This project intended to reveal the reasons through an anonymous form applied to women in the final year of the three medical residencies considered prerequisites for INR in Brazil: neurology, radiology and neurosurgery.

Materials and Methods The questionnaire addressed to each of the three fields contemplated the professionals' preference to follow their respective subspecialties, in addition to common considerations that could be deemed barriers to INR.

Results Surprisingly, the weak link in the chain was demonstrated to be radiology, which is the exclusive prerequisite residency for training in INR in many countries. However, in Brazil, most doctors who graduate in INR come from Neurosurgery and, secondly, from neurology. These two specialties together account for less than half of the female residents compared to radiology alone.

Conclusion All of the following items were already expected: difficulty in reconciling a double shift; employment opportunity; long training time; the lack of female leaders inspiring new generations of doctors; issues involving radiation and motherhood; and still the barriers of misogyny and machismo. But specific studies need to be conducted to find out why very few radiology residents follow INR training in Brazil.

Keywords
- interventional radiology
- gender inequality
- neurosurgery
- professional practice
- neurology
- radiology

received
August 22, 2022
accepted
January 24, 2023

DOI https://doi.org/10.1055/s-0043-1776268.
ISSN 0103-5355.

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

Resumo

Objetivos Muito se tem discutido sobre a diversidade de gênero em todas as áreas profissionais, particularmente na medicina. Estudos recentes que mostram que há menos de dez profissionais do sexo feminino em neurorradiologia intervencionista (NRI) em um país continental como o Brasil, e menos de trinta em toda a América Latina, levaram a uma investigação sobre as causas do baixo contingente de mulheres que opta pelo seguimento dessa especialidade médica. Este projeto pretende revelar os motivos, por meio de um formulário anônimo aplicado às mulheres que cursavam o último ano das três residências médicas consideradas pré-requisito para a NRI no Brasil: neurologia, radiologia e neurocirurgia.

Materiais e Métodos O questionário dirigido a cada um dos 3 ramos contemplou a preferência das profissionais em seguir suas respectivas subespecialidades, além de considerações comuns que poderiam ser tidas como barreiras à NRI.

Resultados Surpreendentemente, demonstrou-se que o elo fraco da corrente é a radiologia, que é o pré-requisito exclusivo de residência para treinamento em NRI em muitos países. No entanto, no Brasil, a maioria dos médicos formados em NRI é proveniente da neurocirurgia e, em segundo lugar, da neurologia. Essas duas especialidades juntas contam com menos da metade das residentes do sexo feminino em comparação com a radiologia sozinha.

Conclusão Todos os seguintes aspectos já eram esperados: dificuldade em conciliar dupla jornada; oportunidade de emprego; longo tempo de treinamento; a falta de lideranças femininas que inspirem as novas gerações de médicas; questões que envolvem radiação e maternidade; e, ainda, as barreiras da misoginia e do machismo. Mas estudos específicos precisam ser feitos para descobrir os motivos pelos quais pouquíssimas residentes de radiologia seguem o treinamento de NRI no Brasil.

Palavras-chave

- radiologia intervencionista
- iniquidade de gênero
- neurocirurgia
- prática profissional
- neurologia
- radiologia

Introduction

Despite the technological evolution combined with the high efficiency of the interventional treatments for cerebrovascular diseases, the progressivism of interventional neuroradiology (INR) does not extend to modern concepts of gender equality.[1–5] The female workforce specializing in INR is notoriously the minority of professionals.[6–8] This causes the field to be considered very advanced from a technical point of view, but this advance remains on the fringes of current feminist advances.[9,10]

With the growing prominence of themes related to inclusion and diversity, a discussion arises about the main reasons behind the prevalence of male professionals in INR and the low rate of female participation.[1,4,7,8] This scenario is not reflected in the training of professionals in medicine and in other health-related professions.[11–15] The female gender, since 2019, is numerically superior to the male gender among health professionals.[16]

In Brazil, three specialties are prerequisites for the subspecialization in INR: neurosurgery, neurology and radiology. Currently, there are 9 female interventional radiologists in Brazil, out of a total of 149 professionals (6.04%). There are 22 INR training centers, which offer a total of 30 vacancies per year. Among these, only 6 (20%) are occupied by women in training/fellowship (4 in the first year of training, 2 in the second year), which may indicate a small and initial change in this scenario.[17]

The factors behind the low numbers of women in INR are still nebulous. One can infer the issue about motherhood and exposure to ionic radiation – which, in addition to being oncogenic, is teratogenic – and the professionals who can opt for this field are generally in the years of fertility and offspring planning.[1,2] Moreover, psychosocial factors are added due to challenges brought about by the choice of a subspecialty with highly complex cases and great demand for urgent procedures.[4,6,8]

Considering that women are moving towards representing the largest percentage of the medical workforce in Brazil,[18] as well as the growing demand of the population for the diagnosis and treatment of cerebrovascular diseases, we intend to identify possible factors of disinterest in the subspecialization in INR among female residents of the last year of neurosurgery, neurology and radiology. Furthermore, we intended to raise possible cases of misogyny experienced by these residents during their formative years, which could further discourage them from following a predominantly male field.

Materials and Methods

The present is a prospective cross-sectional study conducted through a questionnaire applied to all female residents who are currently in the last year of residency in neurosurgery

(fifth year of residency or R5), neurology (third year of residency or R3), and radiology (R3) in the Brazilian territory.

It was a voluntary and anonymous questionnaire sent via email and social media, and hosted by the virtual program Microsoft Forms. Contacts were provided by national organizations, namely: the Brazilian Society of Neurosurgery, the Brazilian College of Radiology, and the Brazilian Academy of Neurology.

Data collection was performed through 18 questions in specific questionnaires for each of the 3 major specialties, divided into 3 sections. The first one, consisting only of the informed consent form, was presented to all participants as the first mandatory question necessary to continue participating in the research. The second section consisted of nine questions related to the reasons why these women chose to follow INR, another subspecialty, or no subspecialty. The third one had three questions regarding gender inequality during medical residency.

The results of the quantitative variables were expressed as means, medians, minimum and maximum values, and standard deviations. The qualitative variables were expressed as frequencies and percentages.

All questions were formulated by the main author, and they are subjective and in multiple-choice format, with specific ramifications capable of directing participants to the next appropriate questions and related to previous answers. Just one of the questions is descriptive and discursive.

Results

The questionnaire was sent to 312 Brazilian residents in their last year of training. Of these, we obtained responses from all 23 R5s in neurosurgery, 82 of the 222 R3s in radiology, and 21 of the 67 R3s in neurology, totaling 126 physicians. We did not describe the women's sociodemographic data to preserve the anonymity of the study.

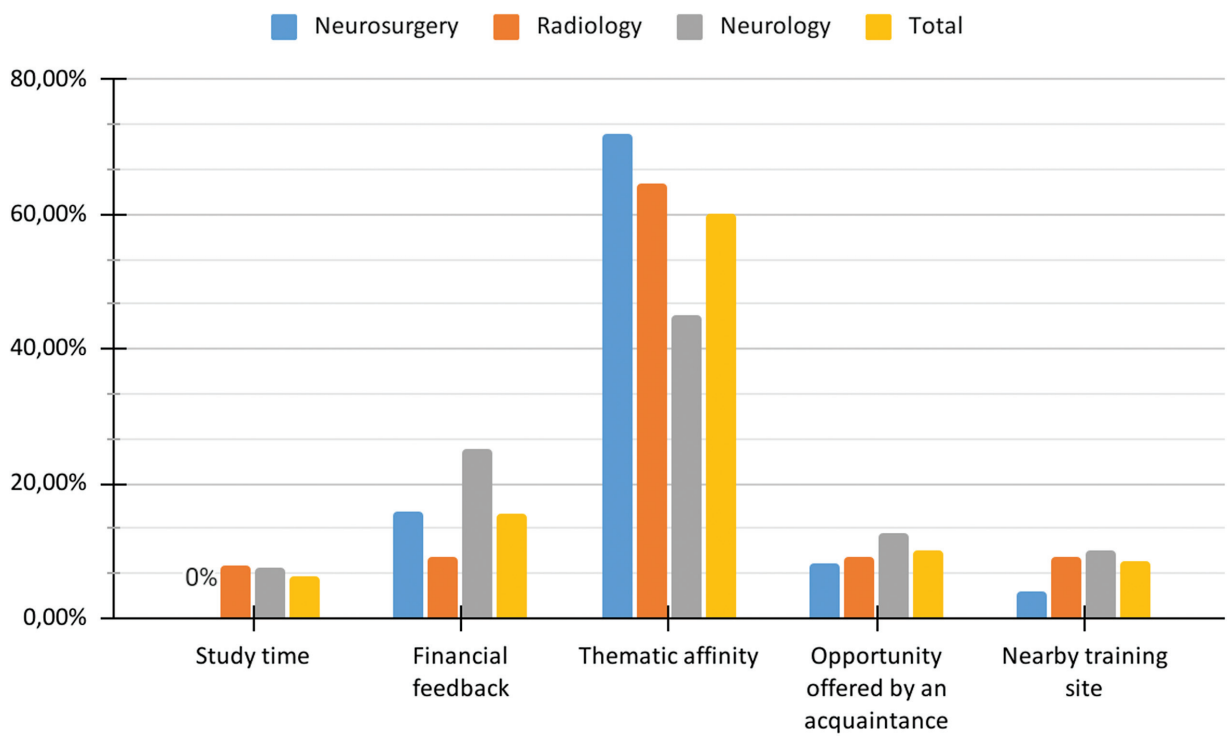
Currently, in Brazil, 156 physicians are R5s in neurosurgery, 23 of whom are women (14.74%); half of the R3s in radiology are women (322/643); and there are 67 women among the 329 R3s in neurology (20.3%). Therefore, of the 1,128 physicians eligible to follow the INR training, 412 (36.52%) are women. An average of 92% of all respondents intend to continue their studies after completing their medical residency, either with some subspecialty, fellowship, or postgraduate modality.

As for the reasons for choosing the subspecialty, we received 25 responses from neurosurgery, 65 from radiology and 40 from neurology residents due to the possibility of choosing more than 1 alternative among those provided. ►**Graph 1** shows the total percentage of responses to each question by specialty. Affinity with the subject was the most chosen among all. The subspecialties chosen by the 116 participants who intend to proceed the studies are shown in ►**Tables 1**, **2** and **3**.

Among the residents of neurosurgery, radiology and neurology, 13 (56.52%), 13 (15.85%), and 11 (52.38%) respectively considered at any moment subspecializing in INR. Of these, only 4 (30.76%) neurosurgery residents will actually remain working in the field.

Regarding the professionals who considered subspecializing in INR but will not, ►**Table 4** exemplifies the main reasons for this choice by the total number of responses recorded (68).

In total, 10 (43.47%) neurosurgery, 68 (84.14%) radiology, and 10 (47.61%) neurology female residents never consid-



Graph 1

Table 1 Subspecialties chosen by Neurosurgery residents

Subspecialty	Number of residents
Pediatrics	5
Endovascular neurosurgery (interventional neuroradiology)	**3**
Spinal neurosurgery	3
Functional neurosurgery	3
Neurosurgical treatment of epilepsy	2
Peripheral nerves	1
Oncological neurosurgery	1
Vascular	1
Neurotraumatology	0
Neurointensivism	0
Urgent/Emergency care	0
Hydrodynamics and neuroendoscopy	0
Fetal neurosurgery	0
Base of the skull	0

Table 2 Subspecialties chosen by Radiology residents

Subspecialty	Number of residents
Breast	8
General advanced radiology	7
Abdominal	6
Diagnostic neuroradiology	6
Other	6
Thorax	5
Internal medicine	5
Non-vascular intervention	1
Interventional radiology (peripheral endovascular interventional)	1
Head and neck	1
Pediatrics	1
Oncology imaging	0
Interventional neuroradiology	**0**
Cardiac imaging	0

Table 3 Subspecialties chosen by Neurology residents

Subpecialty	Number of residents
Neuropediatrics	5
Neurophysiology – electroneuromyography and neuromuscular diseases	4
Neurophysiology – electroencephalography and epilepsy	3
Movement disorders	2
Cerebrovascular	1
Pain	1
Cognition and behavior	1
Neuroimmunology	1
Neuro-oncology	1
Sleep	0
Neurogenetics	0
Interventional neuroradiology	**0**
Neuroinfectology	0
Neurovestibular	0
Hansenology	0
Somatoform disorders	0
Other	0

ered INR. ►**Table 5** shows the main reasons for this by the total number of responses recorded (230).

As for the cases of misogyny experienced by these residents during their training, most claimed to have suffered situations of abuse: 100% of the neurosurgery, 54.88% of the radiology, and 61.91% of the neurology residents.

As for the types of abuse reported, the participants were able to select the options: psychological, moral, physical, sexual, all types of abuse, cannot say, and did not suffer any abuse. Most of the participants reported cases of abuse, mainly psychological. More details are shown in ►**Table 6**.

►**Graph 2** shows the percentages of participants who experienced difficulties during residency just because they were women.

Discussion

We found studies[2–4,8,16,18] that assess the male predominance in INR and the obstacles faced by women in this fields. But the present study is the first to assess female interest in the field of INR and the misogynistic experiences reported by female residents in the final year of the three specialties that are prerequisites for INR in Brazil.

More than 92% of the residents intend to do a subspecialty, but only 32.17% have considered training in INR at any moment of their formation. Of these, only 16.2% actually decided on the field, all of them from neurosurgery.

The main reasons reported by residents for dropping out of the subspecialty were: radiation (25%); exhaustive work pace (23.53%), and long training time (22.06%). Similar responses were reported by Wah and Belli:[4] 32% of the participants agreed that interventional radiology (IR) is less attractive to women due to concerns about the balance between working shifts and family life, the risks of radiation exposure, the effect of pregnancy on training and practice, and the male-dominated work environment.

A systematic meta-analysis[3] published in 2021 clarifies that, in the academic environment, women have lower H-

Table 4 Reasons reported by residents who considered subspecializing in interventional neuroradiology BUT WILL NOT

	Neurosurgery	Radiology	Neurology	Total
Long training time	18.18%	33.33%	8.33%	22.06%
Glimpse of difficulty in the job market	0%	18.18%	20.83%	16.18%
Unfeasible remuneration	0%	3.03%	0%	1.47%
Exhausting work pace, with emergencies at night and on weekends	9.09%	27.27%	25%	23.53%
Overly complex clinical cases	0%	0.00%	0%	0%
Radiation (teratogenic and oncogenic risk)	45.45%	9.09%	37.5%	25%
Work for hemodynamics machine owners (due to the high cost of the machines)	0%	6.06%	8.33%	5.88%
Other	27.27%	3.03%	0%	5.88%

Table 5 Reasons reported by residents for NEVER considering subspecializing in interventional neuroradiology

	Neurosurgery	Radiology	Neurology	Total
Preference for another field	40%	19.35%	29.17%	22.17%
Lack of interest/affinity for the field	15%	18.28%	16.67%	17.83%
Long training time	5%	11.83%	12.5%	11.3%
Forethought of difficulty in the job market	5%	7.53%	12.5%	7.83%
Unfeasible remuneration	0%	1.08%	0%	0.87%
Exhausting work pace, with emergencies at night and on weekends	0%	23.12%	16.67%	20.43%
Overly complex clinical cases	0%	5.38%	0%	4.35%
Radiation (teratogenic and oncogenic risk)	20%	10.75%	8.33%	11.3%
Work for hemodynamics machine owners (due to the high cost of the machines)	15%	2.69%	4.17%	3.91%
Other	0%	0%	0%	0%

Table 6 Types of harassment suffered by female residents by specialty

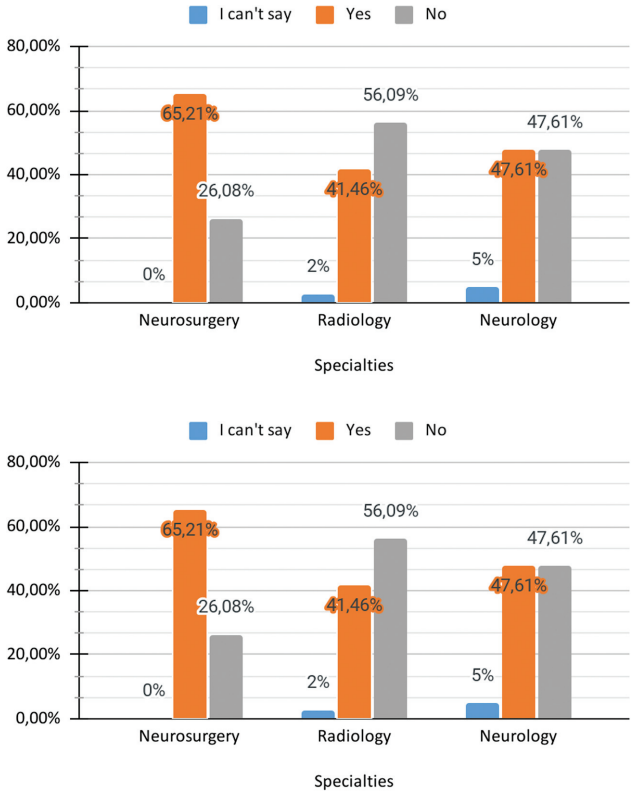
	Yes, psychological	Yes, moral	Yes, physical	Yes, sexual	Yes, all options	I cannot say	No
Neurosurgery	69.56%	56.52%	4.34%	4.34%	13.04%	8.69%	0%
Radiology	45.12%	37.8%	2.43%	3.65%	1.21%	3.65%	45.12%
Neurology	52.38%	8.53%	4.76%	9.52%	0%	0%	38.09%
Total	51.2%	40.8%	3.2%	4.8%	3.2%	4%	36%

indexes (calculated by counting publications and their citations in documents available on the internet) and fewer publications, in addition to being less frequently relevant in rankings, which causes a causality dilemma: are women less successful because they have fewer opportunities or do they have fewer opportunities of being successful because they are not as good as men?

As for working time and exhaustive on-call routine and family/personal life, the same meta-analysis[3] showed that the rate of part-time employment ranged from 11% to 50% for women and from 1% to 22% for men.[3] According to a review of 707 studies on radiology,[19] male professors reported the possibility of working more hours than female physicians data corroborated by Lewis et al.,[16] demonstrating that it is more complex for women to reconcile the pace of work and personal life. Overwork is required even more, when notoriously women in the same positions are paid worse than their male counterparts in underdeveloped countries.[18]

Regarding radiation versus maternity, it becomes contradictory when there is a trend towards feminization in radiology and diagnostic imaging: in 2020, 38% of physicians specializing in this field in Brazil were women. In 2021, more than 50% of the residents in the final year of radiology were also women.[17] However, this feminization is not reflected in INR.[18,20–22]

When questioned about the possibility of working with INR, only 16% (13) of radiology residents said they had



Graph 2

considered the possibility, and none actually intends to subspecialize in INR. In neurosurgery and neurology, more than 50% (24) of the residents considered subspecializing in INR at least at some point in their training. This scenario was surprising, since, in Europe, radiology is the exclusive prerequisite for INR, and it is not possible for neurosurgeons and neurologists to subspecialize in this field. Of the 412 women theoretically able to attend INR as of 2022 in Brazil, more than 78% (321) are graduating in radiology, and this is precisely the group that is least interested in continuing in the field. Of the 82 radiology residents who answered the questionnaire, 84% never even considered INR as a subspecialty. The most frequent reasons mentioned by those who considered INR but abandoned the idea were the long training time and the exhausting pace of work. This may lead to the conclusion that there is a cultural difference between physicians who graduate in radiology in Brazil and in other countries. Here it must be the largest focus of attention for future projects.

In Brazil, only 6.04% of INR specialists are women, and a female minority is observed in other countries as well. An exacerbated and unjustified concern with the health of the developing fetus due radiation is the main cause of the gross underrepresentation of women in the area.[18,22]

To better understand this issue, preconception fetal risks are related to genetic mutations culminating in hereditary anomalies (increase of 0.41% to 0.46% per 1 Gy of exposure). A woman can also become sterile due to radiation (variation of dose limit: 12 Gy before puberty to 2 Gy in premenopause). In practice, the gonadal radiation dose in common IR procedures is lower than 1 mrem (0.01 mGy), leading to a need for 20 years of maximum exposure to occupational radiation levels to reach a dose of 1 Gy.[20]

Thus, to run any of these risks, a woman would need to be exposed directly to the beam of radiation for a continuous period of time, without the use of any personal protective equipment. In the case of pregnant interventionists, exposure is to scattered radiation only (following safe threshold doses), with most of the radiation attenuated by a 0.5-mm lead apron.[20,21]

Efforts should be made to inform aspiring interventional neuroradiologists that the radiation effects of IR procedures are not deleterious when safety standards are followed. However, information about the safety of IR alone is not enough to encourage residents to pursue this subspecialty.

As for misogyny, difficulties related to gender, and various types of abuse, the present study revealed data similar to those found in a study with Brazilian neurosurgeons published in 2021,[21] in which 100% of the women interviewed claimed to have suffered psychological, moral, physical, and/or sexual abuse; in the present research, this was also true regarding neurology (61.91%) and, to a lesser extent, radiology (54.88%), corroborating what was raised by the authors of this study regarding the feminization of radiology, in contrast to the low number of women in neurosurgery.[18,22]

Conclusion

Obstacles already established are still responsible for keeping women away from training in INR in Brazil. They include the difficulty in finding a balance in the double journey that involves domestic life and a profession of such complexity. Women end up standing out less; thus, there are few successful female role models to inspire new professionals.

An exacerbated and unjustified concern with the issue of radiation versus motherhood is still taboo, since radioprotection provides adequate safety for the health of the pregnant interventionist and the fetus.

Among the obstacles imposed by misogyny and gender inequality, those who had the most history of experiences of moral abuse during their training were the physicians of the group in which there is a greater male predominance: neurosurgery.

However, what was revealed in the present paper in a more surprising and dramatic way was the great negative weight that the radiology residency contributes to the training of women INR. Despite representing 78% of the 412 women able to follow this subspecialty as of 2022 in Brazil, none will actually follow it, and 84% have never even considered this possibility. Affinity for other subspecialties was the most reported factor; however, it is necessary to better understand the factors that involve this issue, if the future objective is to numerically engage more women in this profession in Brazil.

Authors' Contributions

LMG: conceptualized and designed the study, collected, interpreted, and analyzed data, and reviewed the manuscript.

MAM: conceptualized and designed study, collected, interpreted, and analyzed data, and drafted the manuscript.

ESL: collected, interpreted, and analyzed data, and drafted the manuscripts.

Conflict of Interests

The authors have no conflict of interests to declare.

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Microsurgical Treatment of Anterior Communicating Artery Aneurysms: An Analysis of 74 Consecutive Cases. Approach Side Choice and Outcome Considerations

Tratamento microcirúrgico de aneurismas da artéria comunicante anterior: Uma análise de 74 casos consecutivos. Escolha da abordagem e considerações sobre resultados

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Arq Bras Neurocir 2023;42(4):e302–e308.

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Abstract

Introduction Anterior communicating artery aneurysms (ACoAAs) are intracranial aneurysms whose treatment is still considered a challenging task.

Materials and Methods Altogether, 74 patients were included in this study. The variables included age, sex, comorbidities, incidence of subarachnoid hemorrhage (SAH), the Fisher, Hunt-Hess, and WFNS scores, approach side, length of hospital stay, and mortality. We also investigate A1/A2 dimensions, association with approach side choice and the influence of surgeon's experience on the outcome.

Results There were 61 patients (82.2%) admitted with SAH and 13 were treated for unruptured aneurysms. The A1 and A2 branches were larger ipsilaterally to the selected approach side ($p < 0{,}001$). No deaths occurred in the unruptured aneurysm group. In the SAH group, mortality was strongly correlated with the Hunt-Hess score ($p < 0.001$), Fisher grade ($p < 0.001$), and WFNS score ($p < 0.001$). No significant difference was found in mortality between the right-side and the left-side approaches ($p = 0.253$). A significant survival difference was identified on the group operated by the senior surgeon versus the non-senior group ($p = 0.048$).

Keywords
- vascular neurosurgery
- anterior communicating artery aneurysm
- subarachnoid hemorrhage
- microsurgery

received
August 22, 2022
accepted
January 24, 2023

DOI https://doi.org/10.1055/s-0043-1776269.
ISSN 0103-5355.

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

Discussion and Conclusion A1 dominance was identified as a factor associated to the approach side for SAH cases at our center. Understanding the factors involved in brain aneurysm surgery remains a relevant and underexplored subject. Further studies involving larger case series and multicenter collaborations are necessary to elucidate these factors and to determine the external validity of our findings.

Resumo

Introdução Os aneurismas da artéria comunicante anterior (ACoAA) são aneurismas intracranianos cujo tratamento ainda é considerado uma tarefa desafiadora.

Materiais e Métodos Ao todo, 74 pacientes foram incluídos neste estudo. As variáveis incluíram idade, sexo, comorbidades, incidência de hemorragia subaracnóidea (HAS), escala de Fisher, Hunt-Hess e WFNS, lado de abordagem, tempo de internação e mortalidade. Também investigamos as dimensões A1/A2, a associação com a escolha do lado de abordagem e a influência da experiência do cirurgião no resultado.

Resultados Foram admitidos 61 pacientes (82,2%) com HAS e 13 foram tratados por aneurismas não rotos. Os ramos A1 e A2 foram maiores ipsilateralmente ao lado de abordagem selecionada ($p < 0{,}001$). Nenhuma morte ocorreu no grupo de aneurismas não rotos. No grupo HAS, a mortalidade esteve fortemente correlacionada com a escala de Hunt-Hess ($p < 0{,}001$), pontuação de Fisher ($p < 0{,}001$) e pontuação WFNS ($p < 0{,}001$). Não foi encontrada diferença significativa na mortalidade entre as abordagens direita e esquerda ($p = 0{,}253$). Foi identificada diferença significativa de sobrevida no grupo operado pelo cirurgião sênior versus o grupo não sênior ($p = 0{,}048$).

Discussão e Conclusão A dominância A1 foi identificada como fator associado ao lado de abordagem dos casos de HAS em nosso centro. A compreensão dos fatores envolvidos na cirurgia de aneurisma cerebral permanece um assunto relevante e pouco explorado. Mais estudos envolvendo séries de casos maiores e colaborações multicêntricas são necessários para elucidar esses fatores e para determinar a validade externa de nossas descobertas.

Palavras-chave
- neurocirurgia vascular
- aneurisma da artéria comunicante anterior
- hemorragia subaracnoídea
- microcirurgia

Introduction

Anterior communicating artery aneurysms (ACoAAs) are among the most frequent intracranial aneurysms in several case series, and their treatment is still considered a challenging task.[1,2] Even for non-ruptured aneurysms, technical difficulties may be associated with morbidity. In cases presenting with subarachnoid hemorrhage (SAH), the degree of bleeding and clinical status of the patient are frequently associated, and both have implications for the outcome.[3]

Another variable for the treatment of ACoAAs is selecting the approach side. Some authors have recommended the systematic use of right-side approaches, as most surgeons are right-handed and the left hemisphere is dominant in most individuals.[3,4] However, many other factors should be considered while selecting the approach side optimally. Aneurysm size, A1 dominance, A2 orientation, aneurysm dome direction, presence of anatomical variations, aneurysm neck accessibility, presence of gyrus rectus hematoma, previous surgeries, presence of other aneurysms, and personal preference have been described as additional relevant variables.[1,5,6] The surgeon's experience has also been considered a predictor of good outcomes.[7,8] On the other hand, there are centers who perform side choice on a case by case analysis. Previous studies have successfully predicted A1 dominance via analysis of computed tomography angiography (CTA) images, enabling faster decision-making regarding approach side in ACoAAs microsurgery.[9]

In this study, we present a retrospective analysis of a case series involving treatment of ACoAAs and discuss several aspects relevant to the selection of the approach side and factors related to the outcome.

Material and Methods

We reviewed the ACoAA cases treated microsurgically at a tertiary university hospital between April 2013 and December 2019. The data collection did not expose the patients to any additional intervention and the study was approved by the university's ethical committee. The study was performed at a tertiary university hospital, which is reference for neurosurgical cases to a population of approximately 1 million people.

Altogether, 116 patients with ACoAA were referred to our hospital. The treatment modality was decided based on the experience of the attending neurosurgeon. There were 41 patients who received endovascular treatment and were excluded from this analysis. As such, 75 patients underwent

microsurgical treatment. Only one patient was excluded because of incomplete records. Thus, 74 patients were considered eligible for inclusion in this study. Among these, 61 presented with SAH due to ACoAA rupture. The patients were treated by five attending neurosurgeons and neurosurgery residents. All attending neurosurgeons were right-handed.

Descriptive clinical data were obtained from the patients' medical records. The analyzed variables included age, sex, comorbidities, incidence of SAH, Fisher grade, Hunt-Hess score, World Federation of Neurosurgical Societies (WFNS) score, approach side, length of hospital stay, and mortality. Imaging studies were performed to measure the aneurysm size, direction, presence of gyrus rectus hematoma, neck size, and vessel dimensions on computed tomography (CT) scans. The anterior communicating complex vessels had diameters measuring approximately 0.5 cm from the anterior cerebral artery (ACA) insertion, and the larger A1/A2 was assumed to be dominant (►**Fig. 1**).

The computed tomography (CT) scans were obtained using Toshiba Activision 16 (Canon Medical System Corporation, Otawara, Japan) and GE Optima CT 660 (GE Healthcare, Chicago, IL, USA). Artis Zee (Siemens Medical Solutions, Inc., Malvern, PA, USA) was employed as the digital subtraction arteriography (DSA) suite. The diagnostic suite Arya (PACS Aurora 3.9.1; Pixeon, Florianopolis, SC, Brazil) was used to perform image analysis and measurements.

The DSA exam was performed in selected cases for better understanding of the anatomy and filling patterns of aneurysms that were considered more complex. A larger A1 was considered dominant for approach side indication in cases without DSA data. All patients were evaluated at 15 and 90 days after discharge, and a modified Rankin scale (mRS) score was assigned. The outcome was also analyzed based on the surgeon's experience. The mortality rate was compared between patients operated on by the senior surgeon of the group (M.A.Z.) and those operated on by the other four surgeons.

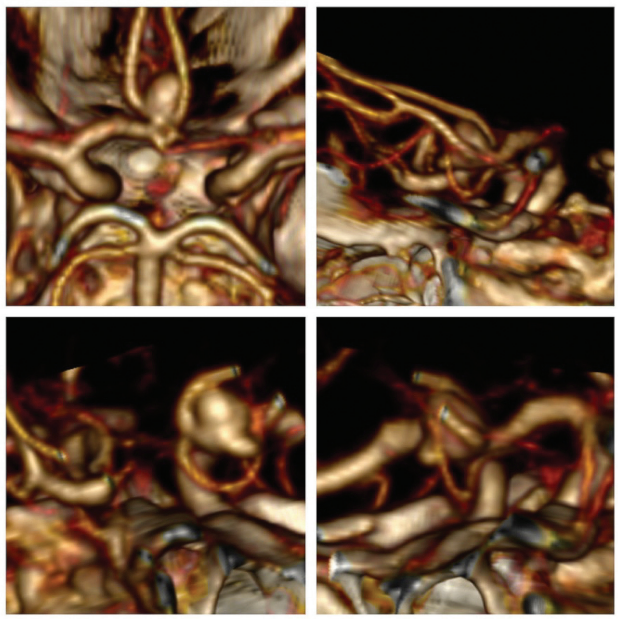

Fig. 1 Example of a case of subarachnoid hemorrhage. Direct measurements were made for A1, A2, aneurysm neck, and dome-neck size. Upper left figure shows the superior view of the Willis polygon, with an evident difference between the left and the right A1, which was a determining factor for selecting the approach side. Upper right figure shows the lateral view of the aneurysm, which was considered an anteriorly projected aneurysm during the analysis. The lower right figure represents the anterior right view of the lesion, while the lower left figure represents the anterior left view.

The Statistical Package Social Sciences (SPSS, IBM Corp., Armonk, NY, USA) software, version 19, was used for the statistical analysis. The quantitative data were examined for normality using the Shapiro–Wilk test. The normality hypothesis was rejected at $p < 0.05$. To evaluate the differences between the groups, quantitative data with normal distribution were tested with a two-sample *t*-test, while the non-normal variables were analyzed using the Mann–Whitney U test. Normal data were presented as means and non-normal data were presented as medians. Categorical variables were compared using the chi-squared test. A multivariate logistic regression was performed to further investigate the correlation between SAH-related mortality and the Hunt-Hess, Fisher, and WFNS scores. Survival results were compared between the senior neurosurgeon and the others using Cox regression.

Results

We studied 74 patients with a mean age of 56 years. Most of the patients were women (62.2%). There were 61 patients (82.2%) admitted with SAH and 13 were treated for unruptured intracranial aneurysms.

Altogether, 52% of the patients from our sample were smokers and 77% were hypertensive individuals. The median number of days until operation after the SAH episode was 3 and the longest delay for treatment was 27 days.

Most of the patients (51.4%) were treated using the right-side approach and 48.6% were treated using the left-side approach. Ages, comorbidities, and previous mRS scores did not differ between the approach sides for ruptured or unruptured aneurysms. In the unruptured aneurysm group, 61.5% were treated using the right-side approach, while 49.1% were treated using the right-side approach in the SAH group ($p = 0.545$).

The mean A1 diameters were 1.71 mm (standard deviation [SD] = 0.74) on the right and 1.81 mm (SD = 0.57) on the left side. The mean A2 diameters were 1.23 mm (SD = 0.41) on the right and 1.28 mm (SD = 0.38) on the left side. No significant differences were observed in vessel dimensions between the ruptured and unruptured aneurysms, or between the right and left-side approaches.

An association was identified between vessel side dominance and the selected approach side. For SAH patients, A1 dominance was associated with the approach side bilaterally ($p < 0.001$), while the association was weaker in patients with unruptured aneurysm. No significant association was observed between right-side dominance and the right-side approach for unruptured aneurysms ($p = 0.07$). However, the association between left-side dominance and the ipsilateral approach was significant ($p = 0.021$).

Table 1 Descriptive statistics, tables with means for normal and with medians for non-normal variables

	Total	Approach side		p-value
		Left	Right	
Age (years)	56.3	57.69	55.05	0.346
Delay for surgery (days)	3	2.5	3.00	0.540
In-hospital stay (days)	12	15	11	0.103
Days until mortality	17	17	18	0.332
Aneurysm dome-neck size (mm)	4.3	3.95	4.8	0.324
Aneurysm neck (mm)	2.64	2.59	2.69	0.603
Right A1 diameter (mm)	1.71	1.33	2.06	0.000
Right A2 diameter (mm)	1.23	1.11	1.33	0.021
Left A1 diameter (mm)	1.81	2.08	1.55	0.000
Left A2 diameter (mm)	1.28	1.42	1.15	0.002

There were 57 patients (77%) who did not present with gyrus rectus hematoma. The remaining 17 patients were distributed among right, left, and bilateral hematoma groups. No association was identified between gyrus rectus hematoma and the approach side ($p = 0.37$).

Approach and Side Comparison

Both the righ- and left-side approach groups were similar in terms of descriptive variables. There were 38 patients treated using the right-side approach and 36 using the left-side approach. The data are presented in ►**Tables 1** and **2**. Significant differences were observed between the groups in terms of hypertensive status ($p = 0.039$), with a greater number of hypertensive patients in the right-side approach group. A significant difference was observed between dimensions of the ACA branches depending on the approach side. The A1 and A2 branches were larger ipsilateral to the selected approach side. The mRS scores were similar between the groups.

The most common cranial approach was pterional craniotomy (67 cases, 90.5%). Among these cases, there were small custom-made variations of the classic pterional craniotomy. Orbitozygomatic (OZ) craniotomy was performed in five cases (6.7%). Among these, 4 patients had a superiorly projected aneurysm and one patient presented with a concomitant pericallosal artery aneurysm. Altogether, 22 superiorly projected aneurysms were treated. Among these, 18 were treated using the pterional approach. The patient who presented with a concomitant pericallosal aneurysm was treated using a bicoronal approach and one severely ill patient was treated with decompressive craniotomy.

There were 28 patients (37.8%) with at least one additional unruptured aneurysm. Among these, only three were not treated during the same surgery used to treat ACoAA. In 13 cases, surgical access was gained contralaterally to the dominant A1 side. Four of these cases had documented arteriographic filling from the smaller A1, while six cases had other contralateral brain aneurysms that were treated using the same procedure (5 middle cerebral artery aneurysms and 1 ophthalmic artery aneurysm). The remaining three cases had A1 size differences of 0.2 mm or less, which allowed for more freedom while selecting the approach side (all were operated from the right side).

Clinical Outcomes

None of the patients who underwent surgery for unruptured aneurysms experienced major complications and the mRS scores of this subgroup remained unchanged in all but one patient who exhibited an increase from a score of 1 preoperatively to a score of 2 after 3 months of follow-up. ►**Fig. 2** illustrates the prognostic distribution (distribution of mRS scores) within the whole group, the SAH group, and the unruptured aneurysm group.

Altogether, 21 patients died from SAH-related complications, with a mortality rate of 34.4% in this subgroup. All SAH patients, except one, were previously healthy and functional (mRS score of 2 or less). Among the survivors after a 3-month follow-up, 32 (52.4%) exhibited an mRS score of 2 or less and were still enrolled in rehabilitation programs.

Mortality was strongly correlated with the Hunt-Hess score ($r = 0.512$, $p < 0.001$), Fisher grade ($r = 0.46$, $p < 0.001$), and WFNS score ($r = 0.639$, $p < 0.001$), according to the Spearman correlation. No significant difference was found in mortality between the right and left-side approaches ($p = 0.253$, ►**Table 2**).

We performed a logistic regression analysis to further investigate the correlation between mortality and clinical scores. The WFNS scores independently predicted mortality ($p = 0.008$, odds ratio [OR] = 5.75, confidence interval [CI] = 1.584–20.903). The Fisher grades ($p = 0.137$, OR = 2.42, CI = 0.755–7.757) and Hunt-Hess scores ($p = 0.363$, OR = 0.53, CI = 0.141–2.049) were not independently associated with mortality.

The survival rate was significantly greater among patients operated on by the senior surgeon in the group (85 vs 61%, $p = 0.048$). All other examined variables were similar between the senior and non-senior groups. Survival curves for SAH patients who were operated on by the senior surgeon and for those who were operated on by other surgeons are depicted in ►**Fig. 3**. A Cox regression model developed to compare the senior and the non-senior groups identified a statistically significant difference ($p = 0.024$, ►**Fig. 3**).

Discussion

We have presented a retrospective case series of microsurgically treated ACoAAs. We performed descriptive analysis of the data obtained from 74 patients, including

Table 2 Qualitative variables and comparison between the right-side and left-side approaches

		N = 74 (%)	Approach side		*p*-value
			Left	Right	
Sex	Female	46 (62.2)	22	24	0.856
	Male	28 (37.8)	14	14	
Smoker	No	35 (47.2)	17	18	0.990
	Yes	39 (52.8)	19	20	
Hypertension	No	17 (23)	12	5	0.039
	Yes	57 (77)	24	33	
Diabetes	No	65 (87.8)	31	34	0.658
	Yes	9 (12.2)	5	4	
SAH	0	13 (17.5)	5	8	0.418
	1	61 (82.5)	31	30	
Hunt-Hess score	1	14 (23)	7	7	0.734
	2	14 (23)	6	8	
	3	11 (18)	5	6	
	4	19 (31)	12	7	
	5	4 (5)	1	2	
Fisher grade	1	6 (10)	3	3	0.671
	2	7 (11)	4	3	
	3	30 (50)	17	13	
	4	18 (30)	7	11	
WFNS score	1	19 (31)	9	10	0.549
	2	11 (18)	4	7	
	3	13 (21.3)	9	4	
	4	13 (21.3)	7	6	
	5	5 (8.4)	2	3	
Hydrocephalus	No	44 (59.5)	22	22	0.778
	Yes	30 (40.5)	14	16	
Decompressive craniotomy	No	67 (90.5)	32	35	0.637
	Yes	7 (9.5)	4	3	
Vasospasm	No	32 (43.2)	14	18	0.462
	Yes	42 (56.8)	22	20	
Direction	Anterior	24 (32.4)	14	10	0.059
	Upward	22 (29.7)	13	9	
	Downward	23 (31)	9	14	
	Posterior	5 (6.9)	0	5	
Mortality	No	53 (71.6)	28	25	0.253
	Yes	21 (28.4)	8	13	

Abbreviations: SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies.

38 treated using the right-side approach and 36 treated using the left-side approach. Both the groups were comparable, with significant differences only in the hypertensive status and in the A1-A2 vessel dimensions (►**Tables 1–2**). The SAH and unruptured aneurysm groups were also compared, revealing no significant differences in the previous descriptive data, but greatly different outcomes.

Patients treated for unruptured ACoAAs exhibited no worsening of the mRS scores after 3 months. In contrast, a general mortality rate of 34.4% was observed in the SAH group. Previous studies have reported mortality rates ranging from 10 to 26%.[10–13] A mortality rate of 20% was observed among SAH patients operated on by the senior surgeon, which was significantly different from that among those operated on by junior neurosurgeons ($p = 0.048$). Several studies have discussed the impact of vascular neurosurgery experience on surgical outcomes.[7,8,14,15] Since other relevant variables were statistically similar between the senior and the junior surgeon groups, we attribute the difference in the outcomes to the experience factor. In a previous study, Lawton and Du[16] described the influence of surgeons' experience on brain aneurysm surgery. The mortality rate declined, and the rate of favorable outcomes improved over time with surgical volume exposure.

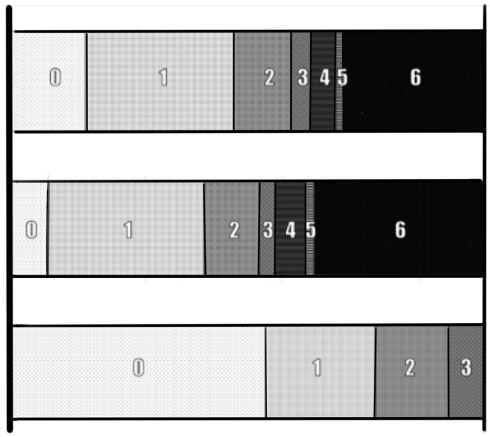

Fig. 2 Graph demonstrating the distribution of modified Rankin scale (mRS) scores after 3 months of follow-up. The first bar represents the distribution of the mRS scores within the whole group, the second bar represents the distribution within the SAH group, and the third bar represents the distribution within the unruptured aneurysm group.

As stated previously, higher Hunt-Hess scores, Fisher grades, and WFNS scores were strongly correlated with poorer outcomes. Mortality was also significantly correlated with hydrocephalus ($p = 0.03$), decompressive craniotomy ($p = 0.002$), and vasospasm ($p < 0.001$). After a 3-month follow-up, 32 patients in the SAH group (52.4%) exhibited an mRS score of 2 or less (►**Fig. 2**).

Classic pterional craniotomy accounted for 90.5% of the approaches used in this series. Other studies have reported the benefits of orbitopterional (OP) and OZ approaches.[17–19] High-riding, giant, and thrombosed ACoAAs may require upward-looking approaches.[19,20] In our series, five such cases demanded the OZ approach to reduce brain retraction. The remaining superiorly projected aneurysms were operated using the OP approach without any specific trend for complications. Brain relaxing maneuvers such as fissure splitting, liquor drainage, and dynamic retraction enabled successful treatment of these patients.

A marginal correlation between hypertension and the right-side approach was identified in our analysis ($p = 0.04$). Hypertension is a known risk factor for the development and rupture of brain aneurysms.[21] However, this association appears to be incidental.

Notably, A1 dominance was established through arteriography in 20 cases, resulting in 8 (40%) right-side dominant and 12 (60%) left-side dominant cases. The dominant A1 determined by arteriography was the same on the CT in 16 cases (80%). In four cases (20%), aneurysm filling originated from the smaller A1 on CT. A previous study predicted A1 dominance based on vessel size with an accuracy of 92.2%.[9] It is worth noting that even though DSA is the gold standard for aneurysm studies, it also results in additional radiation exposure and procedure-related risks.[9] Therefore, it was applied only to the aneurysms perceived to have a more complex structure in our case series.

The approach side has been the focus of discussion in many previous studies.[4] Our study demonstrated a spontaneous preference for the approach side based on the dimensions of the A1-A2 complex. The approach side was strongly correlated with the dominance of A1 and A2 observed on CTA. The presence of other treatable aneurysms also shifted the approach preference to an alternative that could treat more lesions. In four cases, the preference of approach side based on the CTA findings was changed due to the aneurysm filling pattern identified on DSA. Previous studies have reported a correlation between A1 dominance and the development of an ACoAA.[22,23] A recent study has also reported a correlation between dominant A2 and the

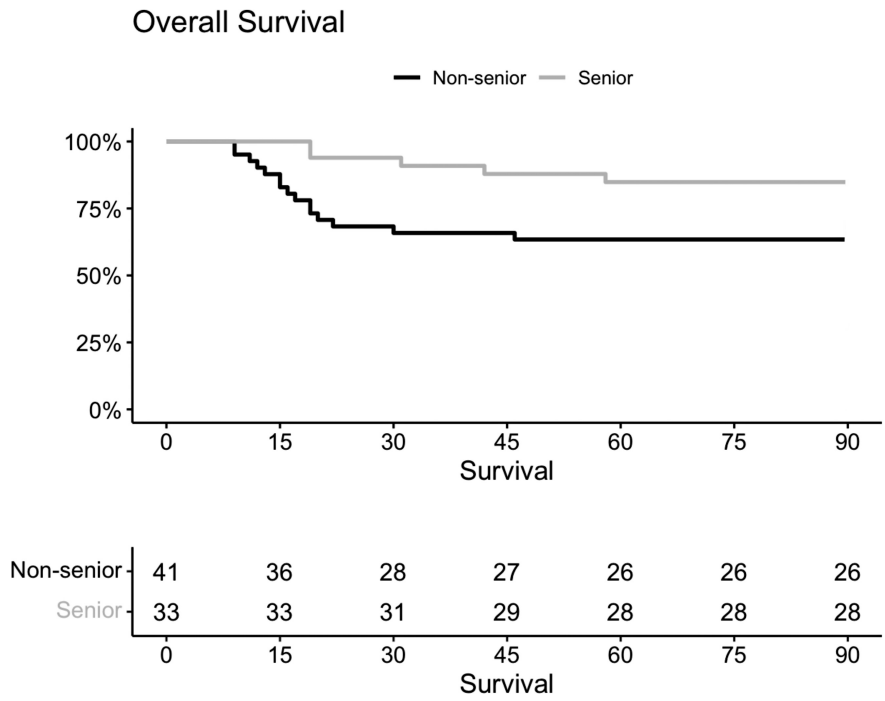

Fig. 3 Survival curves comparing the survival history between senior and non-senior surgeons revealed statistically significant difference ($p = 0.024$).

development and rupture of an ACoAA.[24] In our group, no difference in dominance was observed between the ruptured and unruptured aneurysms ($p = 0.578$).

It is worth mentioning that the present study has limitations that are inherent to retrospective studies. Additionally, it is a tendency of tertiary centers to receive patients with relatively more severe illnesses, which might have increased the mortality rate in this series. Another important limitation is that the results represent the experience of a single center. Multicenter studies are warranted to determine the external reproducibility of our findings.

Conclusions

At our center, A1 dominance was identified as a determining factor in selecting the approach side for SAH cases. A weaker association was observed between A1 dominance and the approach side for unruptured aneurysms. The existence of other unruptured aneurysms also influenced the selection of the approach side. We also demonstrated the effect of surgeons' experience on the outcomes in SAH patients, with a significant reduction in mortality among patients operated on by a more experienced surgeon. Understanding the factors involved in a ACoAA surgery remains a relevant and underexplored subject. Further studies involving larger case series and multicenter collaborations are necessary to elucidate these factors and to determine the external validity of our findings.

Funding
None.

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

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Influence of Serum Ferritin and B12 Levels in the Functional Outcomes of Patients with Ruptured and Unruptured Intracranial Aneurysms

Influência dos níveis séricos de ferritina e B12 nos desfechos funcionais de pacientes com aneurismas intracranianos rotos e não rotos

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Arq Bras Neurocir 2023;42(4):e309–e315.

Abstract

Introduction Pathological processes in the arterial wall that result in vessel dilation are the cause of intracranial aneurysms (IAs), and the risk factors for their formation and progression are not well established. Ferritin is associated with inflammation and angiogenesis; it has protective antioxidative activity, and controls cell differentiation. Vitamin B12 is related to neurological and hematological disorders; it can be used as differential diagnosis tool, and acts in the control of homocysteinemia, a predictor of worse prognosis. The present article aims to assess the correlation between serum ferritin and B12 levels and the patient's functional outcome.

Materials and Methods In the present cohort study, we assessed the serum levels of ferritin and B12, as well as the scores on the modified Rankin and Glasgow Outcome Scales at 6 months, of 2 groups, one with 19 and the other with 49 individuals, out of 401 patients treated for IA at Universidade de São Paulo from 2018 to 2019. We performed a statistical analysis, using logistic regression, to determine the aforementioned correlation.

Results In the univariable analysis, the serum levels of ferritin showed no significant impact on the functional outcome (odds ratio [OR]: 0.96 for every 100 pg/mL increase; 95% confidence interval [95%CI]: 0.761–1.210; $p = 0.732$); neither did the serum levels

Keywords
- brain aneurysm
- ruptured intracranial aneurysm
- unruptured intracranial aneurysm
- subarachnoid hemorrhage
- serum ferritin
- serum B12

received
January 10, 2022
accepted
March 7, 2023

DOI https://doi.org/10.1055/s-0043-1774745.
ISSN 0103-5355.

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

of B12 (OR: 0.998 for every 100 pg/mL increase; 95%CI: 0.826–1.206; $p = 0.987$). Moreover, no significant impact on the functional outcome was observed in the multivariable analysis regarding the serum levels of B12, age, hypertension, and aneurysm rupture (OR: 1.086 for every 100 pg/mL increase; 95%CI: 0.847–1.392; $p = 0.513$).

Conclusion We were not able to confirm a statistical correlation regarding the serum levels of ferritin and B12, and functional outcome of IA patients. These variables might be linked to other determinants of the pathophysiology of IAs, like inflammation and homocysteinemia.

Resumo

Introdução Processos patológicos na parede arterial, que resultam em dilatação dos vasos, são a causa dos aneurismas intracranianos (AIs), e os fatores de risco para a sua formação e evolução não estão bem estabelecidos. A ferritina está associada a inflamação e angiogênese, tem atividade antioxidante, e controla diferenciação celular. A vitamina B12 está relacionada a distúrbios neurológicos e hematológicos, é utilizada como ferramenta de diagnóstico, e atua no controle da homocisteinemia. Este artigo visa avaliar a correlação entre os níveis séricos de ferritina e B12 e o desfecho funcional do paciente.

Materiais e Métodos Neste estudo de coorte, analisamos os níveis séricos de ferritina e B12, assim como as pontuações nas escalas de desfechos de Rankin modificada e Glasgow aos 6 meses de 2 grupos, um com 19 e o outro com 49 indivíduos, dos 401 pacientes com AI tratados na Universidade de São Paulo de 2018 a 2019. Para determinar a já mencionada correlação, realizamos análise estatística usando regressão logística.

Resultados Na análise univariada, a ferritina sérica não resultou em impacto significativo sobre o desfecho funcional (razão de possibilidades [RP]: 0,96 para cada aumento de 100 pg/mL; intervalo de confiança de 95% [IC95%]: 0,761–1,210; $p = 0,732$), nem a B12 sérica (RP: 0,998 para cada aumento de 100 pg/mL; IC95%: 0,826–1,206; $p = 0,987$). Tampouco observou-se impacto significativo sobre o desfecho na análise multivariada usando B12 sérica, idade, hipertensão e ruptura de aneurisma (RP: 1,086 para cada aumento de 100 pg/mL; IC95%: 0,847–1,392; $p = 0,513$).

Conclusão Não foi confirmada a correlação estatística entre os níveis séricos de ferritina e de B12 e o desfecho funcional de pacientes com AI. Essas variáveis podem estar ligadas a outros determinantes da fisiopatologia do AI, como inflamação e homocisteinemia.

Palavras-chave
- aneurisma cerebral
- aneurisma intracraniano rompidoaneurisma intracraniano não rompidohemorragia subaracnóidea
- ferritina sérica
- B12 sérica

Introduction

Cerebral arteries can undergo pathological processes that involve dilation, which results in the formation of intracranial aneurysms (IAs). These conditions can progress until the arterial wall ruptures, causing intracranial bleeding, that is, aneurysmatic subarachnoid hemorrhage (aSAH).[1,2] Although most unruptured aneurysms are asymptomatic, their clinical complications, such as aSAH, result in a high mortality rate, which ranges from 40% to 50%. The existing treatment tools are microsurgery and endovascular procedures, but they also present risks, including death. The risk factors for the development of IAs are still unknown, with most affected individuals not presenting any known factors; therefore, their identification is necessary.[3–5]

Ferritin is the major iron-storage protein, and it is involved in a variety of pathophysiological processes in the human body. Elevated serum levels are related to coronary artery disease, malignancy, and poor transplantation outcomes.[6] Ferritin has an iron core in its structure; it presents ferroxidase activity and has an antioxidant function. It regulates cellular iron homeostasis, through biosynthesis and secretion, as part of a dynamic cycle of iron recycling.[7]

Ferritin may be used to monitor various diseases, because it is involved in several processes, such as: iron delivery, angiogenesis, inflammation, immunity, signaling, and cancer. It is a

proinflammatory signaling molecule/mediator; it inhibits lymphocyte and myeloid cell function, since iron is required for cell proliferation and differentiation; it also plays an important role in signal transduction and migration mediated by chemokine receptors, and it inhibits the inflammatory response by producing interleukin 10 (IL-10), which inhibits interleukin 2 (IL-2), lowering lymphocyte proliferation. In addition, ferritin is recognized as a reactant and marker of acute and chronic inflammation, and it promotes angiogenesis by binding high molecular weight kininogen (HK)/activated HK (HKa), which are cofactors of the intrinsic coagulation cascade.[8]

The possible relationship with IA formation is based on the evidence that ferritin is associated with inflammation and angiogenesis, which are processes present in the aneurysm formation cascade; it is linked to aSAH, which is one of the major consequences of ruptured aneurysms, and it is related to Kawasaki disease, a syndrome reported to be associated with coronary artery aneurysms.[9–11]

Vitamin B12 is an essential nutrient, meaning it must be ingested, since it cannot be produced by the body. It plays an important role in DNA synthesis and neurological function. Low serum levels of B12 are associated with coronary diseases, demyelination of nervous system structures, ineffective erythropoiesis, megaloblastic anemia, hyperhomocysteinemia, and hemolysis. On the other hand, high serum levels of B12 are associated with poor outcome in critically-ill patients, high levels of C-reactive protein (CRP), which is an inflammatory biomarker, chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, primary hypereosinophilic syndrome, as well as myelodysplastic syndromes and acute leukemias. Therefore, serum B12 levels may be used in the differential diagnosis or as a diagnostic hypothesis for various pathologies. Oral supplementation may be an effective treatment option, and B12 deficiency is linked to senility, increasing with age progression.[12–14] Homocysteine is associated with endothelial injury and has thrombogenic properties; thus, it is correlated with cardiovascular diseases. However t no correlations have been found with IA formation.[15]

The objective of the present study was to evaluate the influence of the serum levels of ferritin and B12 in the functional outcomes of patients with ruptured and unruptured IA.

Materials and Methods

Study Design

The present is a prospective cohort study, in which social and demographic data were collected from patient charts in the database of the Division of Neurosurgery of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) who were admitted due to SAH between January 2018 and November 2019. We also collected the serum levels of ferritin and B12 and IA rupture status upon admission. The analysis of the outcomes was performed prospectively using the modified Rankin Scale (mRS) and Glasgow Outcome Scale (GOS) at 6 months.

Population Data

Data from 401 patients were analyzed: 19 individuals were included in the serum ferritin analysis (►**Fig. 1**), and 49, in the serum B12 analysis (►**Fig. 2**). The subjects were evaluated regarding the serum levels of ferritin or B12, and

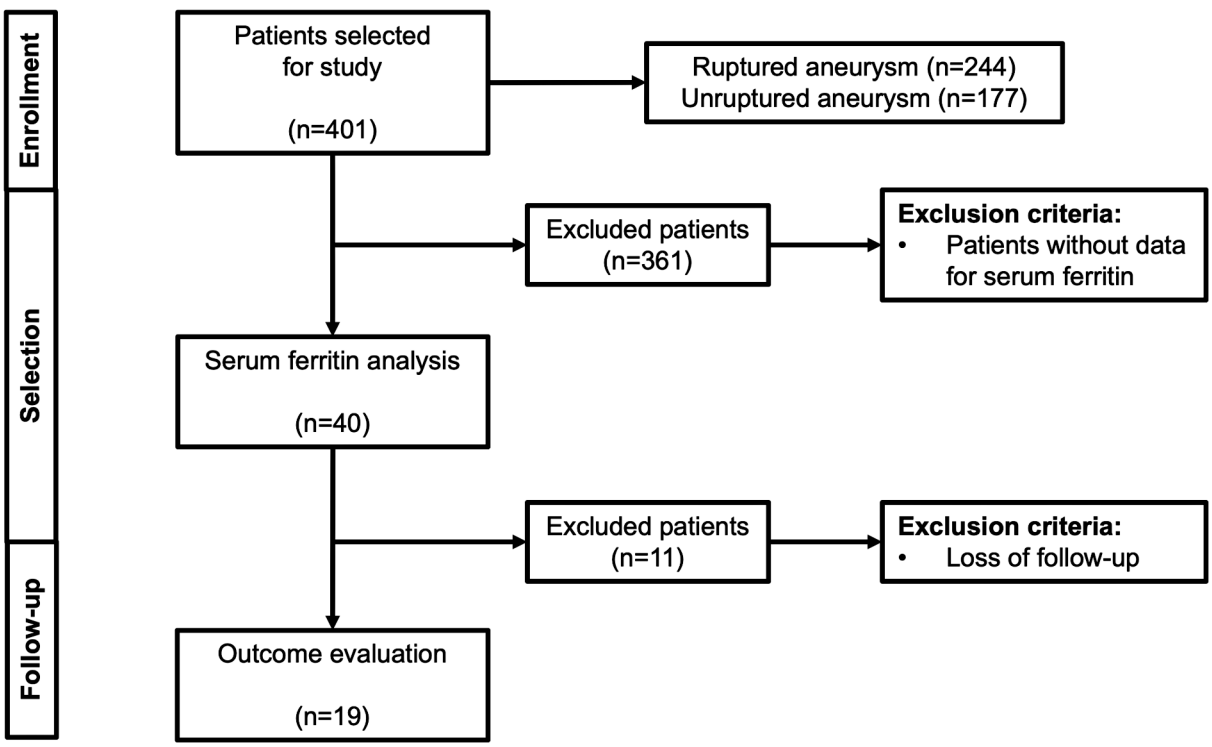

Fig. 1 Patient selection and inclusion and exclusion criteria for the ferritin analysis.

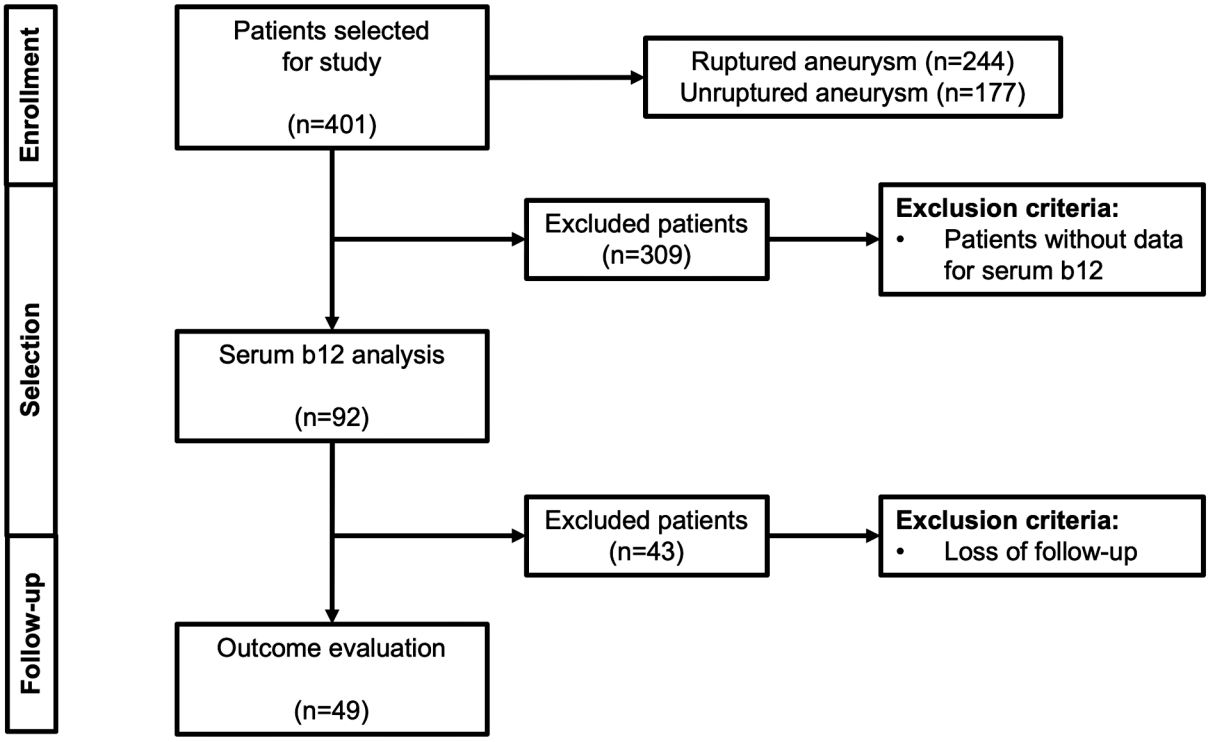

Fig. 2 Patient selection and inclusion and exclusion criteria for the B12 analysis.

the mRS and GOS scores at 6 months. Each group was subdivided into 2 groups based on their laboratory results: normal serum level or elevated serum level. For the ferritin analysis, the cut-off was a serum level of 500 ng/mL,[16] while for the B12 analysis, the cut-off was a serum level of 878 pg/mL.[17]

Exclusion Criteria

We excluded patients or whom there was no data on the serum levels of ferritin or B12 upon admission, as well as those lost to follow up in less than 6 months.

Inclusion Criteria

We included patients of both sexes and ages, with ruptured and unruptured brain aneurysms who were admitted at HCFMUSP between January 2018 and November 2019.

Statistical Analysis

We used logistic regression considering the serum levels of ferritin and B12 as independent, continuous, and binary variables. The outcomes were assessed through the scores on the mRS and GOS at 6 months. Univariate analyses for the serum levels of B12 and ferritin were performed. Moreover, a multivariate analysis including age and the presence of hypertension in the model was performed for the B12 cohort. The level of significance was established as 0.05.

Results

Serum Ferritin

The 19 patients in the ferritin group were divided into 2 subgroups based on their serum levels (normal or elevated). After stablishing a cut-off point of 500 ng/mL,[16] 17 patients were allocated in the normal ferritin level subgroup and 2 patients, in the elevated ferritin level subgroup.

Regarding the whole population analyzed, most patients were female, non-hypertensive, non-diabetic, non-smokers, with no history of hydrocephalus nor aSAH. Upon hospital admission, the median score on the Glasgow Coma Scale (GCS) was of 15, the Hunt and Hess grade was 2, and the score on the World Federation of Neurosurgical Societies (WFNS) scale was of 1. On average, at 6 months, the GOS score was of 3.6 ± 1.9, and the mRS score, of 2.9 ± 2.5. More detailed information can be found in ►**Table 1**.

Regarding the two ferritin subgroups, the major difference was that the mean WFNS score on admission was lower in the elevated subgroup (4.5) compared with the normal subgroup (2.1) ($p = 0.035$).

As shown in ►**Table 1**, the epidemiological characteristics of both groups were very similar regarding all parameters ($p > 0.05$), except for serum ferritin. We performed separate analyses for each outcome considering the impact of serum ferritin on the mRS and GOS scores at 6 months. The influence of serum ferritin on the mRS score at six months was analyzed through univariate logistic regression for the prediction of unfavorable outcomes six months after the IA. Higher serum levels of ferritin did not have an impact on the outcome (odds ratio [OR]: 0.96 for every 100 pg/mL increase; 95% confidence interval [95%CI]: 0.7611.210; $p = 0.732$) (►**Table 2**).

Serum B12

The 49 patients in the B12 group were divided into 2 subgroups based on their serum B12 levels (normal or elevated). After establishing a cut-off point of 878 pg/mL,[17,18] 43 patients were

Table 1 Characteristics and variables associated with the outcomes of patients with normal and elevated serum levels of ferritin

Variable	Normal	Elevated	*p*-value
Number of patients	17	2	
Age in years	59.1 ± 10.4	63.0 ± 1.4	0.1857
Female sex	87.5%	50%	0.3137
Aneurysm rupture	41.2%	100%	0.2105
Hypertension	41.7%	50%	1.0
Diabetes mellitus	16.7%	50%	0.3956
Smoker	25%	50%	0.5055
Hydrocephalus	7.7%	100%	0.1429
Previous subarachnoid hemorrhage	0	0	–
Score on the Glasgow Coma Scale on admission	12.5 ± 3.8	9.5 ± 3.5	0.4123
Hunt and Hess grade on admission	2.4 ± 1.3	2.0 ± 1.4	0.7486
Score on the World Federation of Neurosurgical Societies scale on admission	2.1 ± 1.6	4.5 ± 0.7	0.7486
Score on the Glasgow Outcome Scale at 6 months	3.4 ± 1.8	4.0 ± 1.4	0.6921
Score on the modified Rankin Scale at 6 months	3.0 ± 2.2	3.0 ± 2.8	1.0

Note: Data are presented as numbers or percentages, except for age and the scores on the scales and the Hunt and Hess grade, which are presented as mean ± standard deviation values.

Table 3 Characteristics and variables associated with the outcomes of patients with normal and elevated serum levels of vitamin B12

Variable	Normal	Elevated	*p*-value
Number of patients	43	6	
Age in years	59.0 ± 11.2	57.0 ± 12.4	0.718
Female sex	80.5%	83.3%	0.718
Hypertension	58.8%	66.6%	1.0
Diabetes mellitus	17.6%	16.7%	1.0
Smoker	19.4%	33.3%	1.0
Hydrocephalus	24.2%	20.0%	1.0
Previous subarachnoid hemorrhage	5.9%	0%	1.0
Score on the Glasgow Coma Scale on admission	13.3 ± 2.6	14.3 ± 1.0	0.222
Hunt and Hess grade on admission	2.2 ± 1.1	2.0 ± 1.2	0.816
Score on the World Federation of Neurosurgical Societies scale on admission	1.9 ± 1.3	1.8 ± 1.0	0.766
Score on the Glasgow Outcome Scale at 6 months	3.0 ± 1.6	4.5 ± 0.9	0.187
Score on the modified Rankin Scale at 6 months	2.5 ± 2.1	1.8 ± 1.3	0.325

Note: Data are presented as numbers or percentages, except for age and the scores on the scales and the Hunt and Hess grade, which are presented as mean ± standard deviation values.

Table 2 Univariate logistic regression for the prediction of unfavorable outcomes at 6 months after intracranial aneurysm with serum ferritin as an independent variable

Coefficients	Estimate	*p*-value
Intercept	−0.009	–
Serum ferritin (for every 100 pg/mL)	−0.040	0.732

allocated in the normal B12 level subgroup, and 6 patients, in the elevated B12 level subgroup.

Regarding the whole population analyzed, most patients were female, hypertensive, non-diabetic, non-smokers, with no history of hydrocephalus nor SAH. Upon hospital admission, the median GCS score was of 14, the Hunt and Hess grade was 2, and the WFNS score was of 2. At 6 months, the average GOS score was of was of 4.0 and the average mRS score was of 2.4.

The normal and elevated serum B12 level subgroups were similar to each other. More detailed information can be found in ►**Table 3**.

As shown in ►**Table 3**, the groups were very similar regarding all parameters, with no statistically significant values ($p > 0.05$) other than the serum level of B12. The (univariate) analysis was performed considering the impact of the serum level o B12 on the mRS score at 6 months.

We analyzed the influence of serum B12 on the mRs score at six months for the entire B12 group (►**Table 4**–model 1). The OR for every 100 pg/mL increase was of 0.998 (95%CI: 0.826–1.206; $p = 0.987$).

The multivariate analysis regarding the mRs score at 6 months, serum B12 levels, age (considering a 60-year cut), hypertension, and aneurysm rupture in the model (►**Table 4**–model 2) was also evaluated. There were no statistically significant findings ($p > 0.05$). Hypertension was the closest to significancy (OR = 7.23; 95%CI: 0.741–70.684; $p = 0.088$). The OR for every 100 pg/mL increase in the serum level of B12 was of 1.086 (95%CI: 0.847–1.392; $p = 0.513$).

Discussion

The serum levels of ferritin and B12 did not appear to change the mRS or GOS scores at six months among the IA patients included in the present analysis. Although the serum levels of ferritin were not observed to be a proper indicator of the

Table 4 Model 1: Logistic regression with serum B12 as an independent variable. Model 2: Multivariate logistic regression with serum B12, age, hypertension, and aneurysm rupture as independent variables

Model 1		
Coefficients	**Estimate**	***p*-value**
Intercept	−0.534	–
Serum B12 (for every 100 pg/mL)	−0.001	0.987
Model 2		
Coefficient	**Estimate**	***p*-value**
Intercept	−4.364	–
Serum B12 (for every 100 pg/mL)	0.082	0.513
Age (> 60 years)	1.263	0.189
Aneurysm rupture	0.938	0.335

patient's functional outcome, they might still be correlated in some way with the formation and progression of IAs. In its conjugated form, heavy-chain ferritin (HFn) may contribute to a better magnetic resonance imaging (MRI) examination, since it is associated to inflammation and angiogenesis, being a positive indicator of atherosclerosis and aneurysm diseases.[9] Ferritin oxidates and stores redox-active iron, reducing oxidative stress, which is linked to heme and endoplasmic reticulum stress. These processes are correlated to vasculopathies such as atherosclerosis, diabetes, and vascular brain events, such as IAs.[19] Higher serum levels of ferritin in the cerebrospinal fluid have been reported after the occurrence of SAH, which is one of the most dangerous consequences of IA rupture.[10] In adults, high serum levels of ferritin are related to Kawasaki disease, a syndrome associated with coronary artery aneurysms.[11] Finally, total iron binding capacity (TIBC) has been reported to be significantly and inversely associated with IA rupture, but no significant association regarding the serum levels of iron and ferritin were observed.[20]

Just like the serum levels of ferritin levels, those of vitamin B12 do not seem to determine the prognosis of IA patients, but could be associated with IA pathogenesis. Vitamin B12 analog neutralizes radicals, preventing aortic wall degeneration by scavenging free radicals and having antioxidant properties.[21] Pyridoxal 5-phosphate (vitamin B6) is an independent risk factor for abdominal aortic aneurysm (AAA).

Aneurysm are formed after the elastic lamellae of the vascular wall are degraded and the collagen production is enhanced. Vitamin B6 is responsible for lysyl oxidase, the enzyme that leads to cross-linking collagen and elastin, enabling the formation of aneurysms. Lower levels of B6 inhibit lysyl oxidase and prevent the formation of AAAs.[22]

Homocysteine

Homocysteine is an amino acid, and its irregular metabolism can lead to high pathological levels. Hyperhomocysteinemia is associated with atherosclerosis, hypertension, vascular calcification, and aneurysm formation. The pathogenic mechanism of hyperhomocysteinemia involves oxidative stress, generating vascular inflammation, stress of the endoplasmic reticulum, methylation, and demethylation of genes, altering their expressiveness, and altering protein functions.[23] High homocysteine levels have been reported in 68% of AAA patients.[24] However, there is no consensus in the literature regarding the relationship between vitamin B12 and homocysteine levels. Even though some articles argue that there is no relationship between B12 and homocysteine and, accordingly, neither there is one between B12 and aneurysms,[25–27] others support the hypothesis that higher levels of B12 generate lower levels of homocysteine; therefore, they indicate vitamin supplementation as a protective tool.[24,28,29] Moreover, a significant inverse correlation between B12 levels and the maximum diameter of unruptured AAAs has been reported.[30]

Limitations of the Study

A limitation of the present study is that data was only collected from one reference center in the city of São Paulo, Brazil. Another limitation is that the study involved prospective collection of data from charts, which makes certain biases inevitable. Also, some charts were lacking information. Furthermore, only a minority of patients met all inclusion criteria, and some were lost follow-up before the analysis at six months, which resulted in a small sample, restricting the strength of the conclusions of the present article. However, to the best of our knowledge, the present is the first study to analyze the influence of the serum levels of ferritin and B12 in the functional outcome of patients with ruptured and unruptured IAs.[31]

Conclusion

The serum levels of ferritin and B12 levels do not seem to have an impact on the long-term outcomes after SAH. Despite that, ferritin and B12 may still be associated with the pathophysiological process of aneurysm formation, since they are correlated to the inflammatory process and homocysteine levels. Therefore, broader future investigations regarding these relationships may still be promising.

Ethical Standards

The present research project was approved by the Ethics and Research Committee of HCFMUSP (online registration CAPPesq: 15226–approved on 06/20/2016); it is registered on Plataforma Brasil under CAAE number: 61719416.6.0000.0068.

Disclosure

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

Financial Support

The authors declare that they have received no financial support pertaining to the present article.

Originality

The present manuscript is a unique submission and is not being considered for publication in any other source in any medium.

Conflict of Interests

The authors have no conflict of interests to declare.

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Dosage of Alcohol, Cocaine and Marijuana in Patients with Moderate and Severe Traumatic Brain Trauma Attended at the Hospital of Clinics of the Federal University of Uberlândia

Dosagem de álcool, cocaína e maconha em pacientes com traumatismo cranioencefálico moderado e grave atendidos no Hospital de Clínicas da Universidade Federal de Uberlândia

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Arq Bras Neurocir 2023;42(4):e316–e322.

Abstract

Introduction In Brazil, there are 125,000 hospitalizations a year for traumatic brain injuries (TBI) at a high socio-economic cost, causing serious and permanent sequelae, often associated with the use of alcohol, cocaine and marijuana.

Objective to discover the epidemiological characteristics of patients with moderate and severe TBI, treated at the Emergency Room of the Hospital of Clinics of the Federal University of Uberlândia (UFU), and their association with the use of alcohol, cocaine and marijuana.

Material and Methods saliva and urine samples were collected from 80 patients with moderate and severe TBI, aged $\geq$18 years, between September 2020 and December 2021. Research was made into the use of alcohol, cocaine and marijuana, using chromatographic immunoassay test kits.

Results A total of 28 cases (35%) were positive for alcohol, 22 cases for marijuana (27.5%) and 23 cases for cocaine (28.7%). The average age was 41 years old, with a predominance between 20 to 49 years old and of the male sex (90%). Accidents occurred mainly at night (52.5%) and on weekdays (65%). The most frequent cause of

Keywords
- cranio cerebral trauma
- alcohol intoxication
- cocaine
- marijuana

received
October 18, 2022
accepted
March 7, 2023

DOI https://doi.org/10.1055/s-0043-1776791.
ISSN 0103-5355.

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

accident was transport (53.8%), followed by falls (22.5%) and aggression (16.2%). Of the transport accidents, motorcycle and automobiles accidents predominated (28.75%). Overall mortality was 16.2%, with zero positive cases for alcohol, 17.4% positive for cocaine and 27.3% positive for marijuana.

Conclusion we observed an association between TBI, alcohol, marijuana and cocaine, as well as an increase in cocaine and marijuana cases when compared with a study performed at this institution in 2003.

Resumo

Introdução No Brasil, ocorrem 125 mil internações por ano por traumatismo cranioencefálico (TCE) com alto custo socioeconômico, causando sequelas graves e permanentes, muitas vezes associadas ao uso de álcool, cocaína e maconha.

Objetivo Conhecer as características epidemiológicas dos pacientes com TCE moderado e grave, atendidos no Pronto Socorro do Hospital de Clínicas da Universidade Federal de Uberlândia (UFU), e sua associação com o uso de álcool, cocaína e maconha.

Material e Métodos Foram coletadas amostras de saliva e urina de 80 pacientes com TCE moderado e grave, com idade entre 18 anos, entre setembro de 2020 e dezembro de 2021. Foi pesquisado o uso de álcool, cocaína e maconha, por meio de kits de testes cromatográficos de imunoensaio.

Resultados Um total de 28 casos (35%) foram positivos para álcool, 22 casos para maconha (27,5%) e 23 casos para cocaína (28,7%). A idade média foi de 41 anos, com predomínio entre 20 a 49 anos e do sexo masculino (90%). Acidentes ocorreram principalmente à noite (52,5%) e em dias úteis (65%). A causa mais frequente do acidente foi transporte (53,8%), seguida de quedas (22,5%) e agressões (16,2%). Dos acidentes de transporte predominaram os acidentes motociclísticos e automobilísticos (28,75%). A mortalidade geral foi de 16,2%, com zero casos positivos para álcool, 17,4% positivos para cocaína e 27,3% positivos para maconha.

Conclusão Observamos associação entre TCE, álcool, maconha e cocaína, bem como o aumento de casos de cocaína e maconha quando comparado com um estudo realizado nesta instituição em 2003.

Palavras-chave
- traumatismo cranioencefálico
- intoxicação alcoólica
- cocaína
- maconha

Introduction

Traumatic brain injury (TBI) is one of the biggest causes of mortality in the modern era. Young men are more involved in most statistics, perhaps because they take more risks in traffic and are more likely to use alcohol and illicit drugs.[1,2] TBI is considered a major public health problem worldwide, as it incurs high socioeconomic costs, requiring prolonged hospitalizations and specialized treatments.[3] It is estimated that in Brazil the annual costs of hospitalization for patients suffering from traumatic brain injury are US$ 70,960.0004 or 376,698,256.00 reais (US dollar exchange rate as on 08/07/2022; source: Web site of the Central Bank of Brazil – bcb.gov.br). Among the most common causes of TBI are transport accidents, falls, assaults and being run over. Added to these factors is the use of alcoholic beverages and drugs such as marijuana and cocaine. In Brazil, there are very few publications referring to moderate and severe TBI associated with the use of alcohol and illicit drugs. The present study aims to describe the epidemiological characteristics of patients with severe and moderate TBI, treated at the emergency room of the Hospital of Clinics, UFU (Federal University of Uberlândia), from September 2020 through to December 2021 (period of the Covid-19 pandemic) and their associations with the use of alcohol, cocaine and marijuana.

Methods

Study Delimitation and Population

A descriptive, cross-sectional, qualitative and quantitative study was performed on individuals treated at the Emergency Room of the Hospital of Clinics (HC) of the Federal University of Uberlândia (UFU), with a diagnosis of severe and moderate TBI, over the period from September 1st, 2020, through to December 31st, 2021, aged 18 years or over. Severe injuries were classified as those with a score of 3 to 8 and moderate those with a score of 9 to 12 on the Glasgow Coma Scale (GCS) (►**Fig. 1**).

The study was approved by the Ethics and Research Committee of the Federal University of Uberlândia, under CAAE (Certificate of Ethical Presentation) no. 29782820.0.0000.5152 and notion no. 4.041.608, and in all cases an informed consent statement was collected.

BEHAVIOR	RESPONSE	
Eye opnening response	4- spontaneously 3- to speech 2- to pain 1-no response	
Best verbal response	5- fully oriented 4- confused 3-inappropriete words 2-incomprehensible sounds 1-no response	
Best motor response	6- obeys command 5- moves to lacalize pain 4- flex to withdraw from pain 3- abnormal flexion 2- abnormal extension 1-no response	

Total Score – Best response - 15
Comatose - 8 or less
Totally inresponsive - 3

Fig. 1 Glasgow Coma Scale.

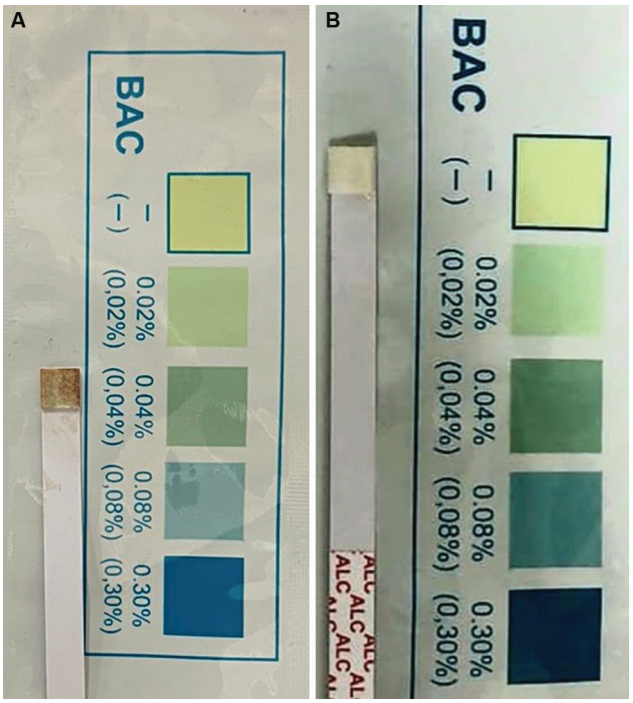

Fig. 2 (A) Image of positive and negative tests for marijuana and cocaine: there was the appearance of a red line on C (control) and no appearance of a line for THC, indicating a positive test for marijuana. (B) Image of positive and negative tests for marijuana and cocaine: there was the appearance of a red line on C (control) and for THC, but not for cocaine, indicating a positive result for this drug. (C) Image of positive and negative tests for marijuana and cocaine: there was only the appearance of a red line on C and no appearance of a line on THC and COC, indicating a positive result for marijuana and cocaine. (D) - Image of positive and negative tests for marijuana and cocaine: appearance of a red line on C, THC and COC, indicating a negative test. C – control. COC –cocaine. THC - tetrahydrocannabinol.

Data Collection and Variables Studied

The sample collection was performed exclusively by the same previously trained residents of the Neurosurgery Department of the Hospital of Clinics during the whole period, following the instructions on the test package.

Patients, immediately after initial care, were submitted to the saliva alcohol test using the Assure Saliva Alcohol Test, produced by Assure Tech (Hangzhou) Co. Ltd. This is a chromatographic immunoassay test based on an alcohol-sensitive enzyme reaction. It consists of a plastic strip with a small highly specific pad fixed on the tip containing Tetramethylbenzidine, Alcohol Oxidase, Peroxidase and other additives. Once this pad comes into contact with fresh saliva, it changes color depending on the concentration of alcohol present (►**Fig. 3a**).

For the qualitative measurement of cocaine and marijuana metabolites in urine, the Assure Multi 2 Test was used, produced by Assure Tech (Hangzhou) Co. Ltd. The test is an immunoassay based on the principle of competitive binding. This test consists of placing three drops of urine in a cassette filled with anti-marijuana and anti-cocaine antibodies. If these drugs are present in the patient's urine, it will produce a red line in the control region and will not appear at the indicated location for the drugs, thus indicating a positive test (►**Fig. 2a and –2b**).

Information related to the trauma was collected using a questionnaire made specifically for this purpose (Annex 2).

Statistical Data Analysis Methods

Qualitative data were described with absolute and relative frequency. Quantitative data were described with the mean and 95% confidence interval error for the mean (normally distributed data) or were described with the median and interquartile range (non-normal distribution). When necessary for the analyses, discrete or continuous quantitative

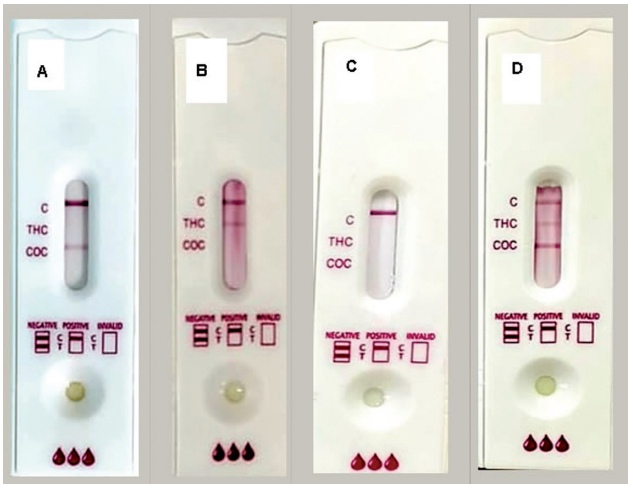

Fig. 3 (A) Image of positive and negative tests for alcohol: A- Test showing a greenish coloration of the strip pad, indicating positivity for alcohol at a concentration of 0.04%. (B) – Image of positive and negative tests for alcohol: test showing no change in coloring, therefore negative for alcohol.

Table 1 Descriptive Analysis of Variable Data

Variable	Modality	n (%)
Sex	Female	8(10%)
	Male	72(90%)
Location	Other	29(36.3%)
	Uberlandia	51(63.7%)
Time of Accident	Daytime	38(47.5%)
	Nighttime	42(52.5%)
Day of the Week	Weekend	28(35%)
	Midweek	52(65%)
Holiday	Yes	4(5%)
	No	76(95%)
Typeof Accident	Aggression	13(16.2%)
	Run over	6(7.5%)
	Fall	18(22.5%)
	Transport	43(53.8%)
Victim	Passenger	5(6.2%)
	Driver	40(50%)
Vehicle	Motorbike	23(28.75%)
	Car	23(28.75%)
	Other*	6(7.5%)
Use of Seatbelt	No	7(30.4%)
	Yes	1(4.34%)
Use of Helmet	No	8(34.7%)
	Yes	13(56.3%)
Alcohol	No	52(65%)
	Yes	28(35%)
Marijuana	No	58(72.5%)
	Yes	22(27.5%)
Cocaine	No	57(71.3%)
	Yes	23(28.7%)
Brain Injury	Diffuse Injury**	10(12.5%)
	Contusions	3(3.8%)
	Bruising	6(7.5%)
	Traumatic SAH	24(30%)
	Multiple Injuries***	37(46.2%)
Severity	Moderate	14(17.5%)
	Severe	66(82.5%)
Surgery	No	58(72.5%)
	Yes	22(27.5%)
Evolution	Death	13(16.2%)
	Release	67(83.8%)
Resuscitation at the Site of the Accident	Yes	11(13.8%)
	No	69(86.2%)
Alcohol and Cocaine	Yes	9(11.2%)
	No	71(88.8%)
Cocaine and Marijuana	Yes	15(18.7%)
	No	65(81.3%)
Alcohol and Marijuana	Yes	7(8.7%)
	No	73(91.3%)
Alcohol, Marijuana and Cocaine	Yes	7(8.7%)
	No	73(91.3%)
Agression	Yes	13(83.7%)
	No	67(16.3%)
No drug use	Yes	33(41.25%)
	No	47(58.75%)

Abbreviation: SAH, Subarachnoid Hemorrhage.
Key: n: number of patients. Other*: truck (1), bus (1) and bicycle (4).
Diffuse injury**: cerebral o edema and diffuse axonal injury.
Multiple injury***: associations between focal lesions.

variables were dichotomized for better description of the data due to representativeness or adjustment to inferential analyses.

To compare the data of the quantitative variables between the two groups, the data for each group were tested for normality using the Shapiro-Wilk test. Where both groups were normal, the differences between the means were tested with Student's *t*-test for homogeneous and/or heterogeneous variances, and when at least one of the groups was not normal, the medians were compared using the unpaired Wilcoxon test (Mann-Whitney).

The independence between the groups and qualitative variables was tested with the Chi-Square test of independence (when expected frequencies were greater than five) or with Fisher's Exact test (when at least one of the expected frequencies was less than five). The Chi-Square test had continuity correction in the 2×2 contingency Tables (2 rows by 2 columns).

For all analyses the data were analyzed in SPSS software version 19.0 or in the R environment (R CORE TEAM 2019). A significance of 5% was adopted for all analyses.

Results

Of a total of 168(one hundred and sixty-eight) patients treated at the ER of the Hospital of Clinics with a diagnosis of moderate and severe TBI over the period of the 1st of September 2020 to the 31st of December 2021, 5(five) patients were excluded for being underage and 8(eight) patients were excluded for having died shortly after initial care. Of the remaining 155(one hundred and fifty-five) patients, 80(eighty) were studied, which represent 51.6% of all patients treated over this period.75(seventy-five) patients were excluded, being that for 18 (eighteen) of

Table 2 Descriptive analysis of the stratified database in patients with alcohol, marijuana and cocaine consumption (qualitative variables)

Variable	Modality	No	Yes	
		n (%)	n (%)	Statistics(*p*)
Type of Accident	Aggression	7(13.5%)	6(21.4%)	X^2 =1.131 0.77
	Run over	4(7.7%)	2(7.1%)	
	Fall	13(25%)	5(17.9%)	
	Transport	28(53.8%)	15(53.6%)	
Evolution	Death	13(25%)	0(0%)	0.003
	Release	39(75%)	28(100%)	
Agression	No	45(86.5%)	22(78.6%)	0.362
	Yes	7(13.5%)	6(21.4%)	

Abbreviations: n, number of patients; X^2, Chi-square statistic; *p:* probability.

them, the person responsible for the patient was not present at the time of initial care and for 57(fifty-seven), the accompanying person did not agree to sign the consent forms. Thirty-three (41.25%) tested negative for any of the drugs. Forty-seven patients (58.75%) tested positive of those, 28 (twenty-eight) were positive for alcohol, 23(twenty-three) for cocaine and 22(twenty-two) for marijuana. As for the isolated use of substances, 18(eighteen) patients tested positive only for alcohol, 4 (four) for cocaine and 5 (five) for marijuana. Twenty patients tested positive for a combination of the three drugs (►**Table 3**).

Of these 80(eighty) patients, 72(90%) were male and eight (10%) were female. The average age was 41.9 years old. Fifty-one patients (63.7%) were from Uberlândia and 29 patients (36.3%) were from other locations. The accidents occurred predominantly at night (52.5%) and on midweek days (65%).

The most common types of accident were transport accidents (53.8%) and falls (22.5%), followed by aggression (16.2%) and being run over (7.5%). Regarding the types of vehicles, accidents involving motorbikes and cars were of a similar incidence (28.75%) and others (bicycle/4, truck/1, tractor/1) 7.5%. In 40 cases (50%) the victim was the driver of the vehicle and in five (6.2%), a passenger. One case was not informed. As for seat belts, just 1.2% of patients were wearing one, 8.7% were not, and 90.1% was not informed. Of 23 motorbike accidents and 5 bicycle accidents, 13(thirteen) patients were wearing a helmet,8(eight) were not, and 7 (seven) were not informed. Regarding the types of brain injury shown on tomography, multiple injuries (more than one type of injury) were predominant (46.2%), followed by traumatic subarachnoid hemorrhage (30%), diffuse injuries (12.5%), bruising (7.5%) and contusions (3.8%). Of the 80 patients tested, 82.5% presented severe TBI and 17.5% moderate TBI. Surgical treatment was performed on 27.5% of the patients. Only 13.85% of the patients were resuscitated on the site of the accident. The total mortality rate was 16.2% and 83.8% of patients were released (►**Table 1**).

The cocaine and marijuana tests performed on urine samples and the alcohol on saliva samples were then analyzed in the emergency room and their images recorded (►**Fig. 1**). Positive testing for alcohol was found in 28 patients (35%). Marijuana and cocaine were detected in 22 (27.5%) and 23 (28.7%) of patients, respectively (►**Table 1**). As for the patients under the influence of alcohol, transport accidents were predominant in 15 (53.6%) followed by aggression in 6 (21.4%), with a zero hospital mortality rate and an average number of days of hospitalization of 23.98 ± 5.94 (►**Table 3**).

Table 3 Descriptive analysis of the stratified database in patients with alcohol, marijuana and cocaine consumption (quantitative variables)

Drug	Variable	No		Yes		Statistic
		Average ± CI95%	Median (IQR)	Average ± CI95%	Median (IQR)	*Z(P)*
Alcohol	Age (Years)	42.42 ± 4.37	42(18)	40.93 ± 6.04	39(26)	701(0.785)
	Duration of Hospitalization	23.98 ± 5.94	20(28)	25.71 ± 11.04	13(31)	699.5(0.774)
Marijuana	Age (Years)	44.88 ± 4.19	43.5 (21)	34.05 ± 5.15	34 (19)	386 (0.007)
	Duration of Hospitalization	25.21 ± 6.39	18(28)	22.95 ± 10.41	14(27)	591(0.612)
Cocaine	Age (Years)	44.04 ± 4.21	43 (20)	36.61 ± 5.96	36 (23)	484.5 (0.069)
	Duration of Hospitalization	22.77 ± 6.18	14(26)	29.09 ± 11.02	21(34)	546.5(0.246)

Abbreviations: IQR, interquartile range; *p,* probability; *Z*, statistic *Z* approximate for the Mann-Whitney test.

In patients positive for cocaine use, the rate of transport accidents was 43.5%. Assaults totalled 21.7% and mortality was 17.4%, with an average length of hospitalization of 22.7 ± 6.18 (►**Table 3**). Among those positive for marijuana, transport accidents also predominated (50%), followed by aggression and falls (22.7%), with six deaths and an average number of days of hospitalization of 25.21 ± 6.39 (►**Table 3**). When analyzing the variables age and length of hospitalization for the three drugs tested, no significant differences were observed (►**Table 3**).

Among the 9 (nine) patients positive for the concomitant use of alcohol and cocaine, 5 (five) were victims of transport accidents, 2 (two) of aggression, 1 (one) of being run over and 1 (one) of falling, with a mortality rate of zero and a mean of 23.69 ± 5.32 days of hospitalization. Regarding the association between alcohol and marijuana, of 7 (seven) patients, transport accidents predominated at 5 (five), followed by aggression at 1 (one) and falling at 1 (one), with no cases of being run over in this association. Mortality was zero, with an average length of hospitalization of 24.52 ± 6.04 days. For the 15 (fifteen) patients with positive association between cocaine and marijuana, 6 (six) were victims of a transport accident, 5 (five) of a fall, 3 (three) of aggression and 1 (one) of being run over. Mortality was 13.3% and the average hospital stay was 25.32 ± 6.04 days. We also observed the concomitant use of the three tested substances, alcohol, marijuana and cocaine, in 7 (seven) patients, with a predominance of transport accidents at 5 (five), aggression at 1 (one) and a fall at 1 (one). Nobody was run over in this association. Mortality was zero and the average length of hospitalization was 24.52 ± 5.45 days.

Discussion

Samples from 80 patients were analyzed and we found 28 cases (35%) positive for alcohol in saliva. The average hospitalization was 25.71 ± 11.04 days to 23.98 ± 5.94 days for those not under the influence of alcohol, with no statistical difference (►**Table 3**). It is interesting to note that hospital mortality was zero in patients positive for alcohol, in contrast to a mortality of 25% (13 cases) in those negative for alcohol. Mortality is related to the severity of the trauma and to other associated injuries, and not necessarily to the use of alcohol.[5,6] Alcohol causes psychoactive effects such as euphoria, disinhibition, drowsiness and inattention[7]and is associated with more than 50% of injuries that require admission to trauma centres,[8] however its effect is temporary due to its short life. We chose to use a test for measuring alcohol in saliva and not in blood (alcoholaemia), as it is a non-invasive method of low technical complexity, it does not require storage of the collected material, and the result is obtained immediately.

We found positivity for alcohol in 35% of the patients evaluated, data similar to those of Lindembaum (1989).[1] Other studies found positivity in 22.8% and 37% respectively.[9,10] Our values are similar to those found in these same bibliographic citations.[9,10] When comparing our data with those found by Faria (2008)[11] who observed a positive blood alcohol level of 39.3%, it can be inferred that under the conditions of the dry law, there is no significant difference. Our study was performed under Decree 6,489 of 19/06/2008, which in turn became Law 11,705, popularly known as the Dry Law, and other laws that prohibited the sale of alcohol due to the Covid-19 pandemic. We expected that the ban on the sale of alcoholic beverages in this period would lead to a reduction in the percentage of positivity, which did not happen.

Research performed in the city of Seattle, Washington, USA, studying TBI patients admitted to a neurosurgical intensive care unit, mentions the need to measure blood alcohol. Signs such as agitation, tachycardia and hypertension can manifest in both alcohol intoxication and intracranial hypertension, which could confuse the diagnosis and delay treatment.[12]

We found 27.5% of positive cases for marijuana, practically, in absolute terms, triple the cases found by Faria (2011).[13] Hawley (2018)[14]in the state of Colorado, USA, identified in his work that 74% of patients with severe and moderate TBI had used marijuana, of those, 63% having used for recreational purposes, 72% to reduce anxiety and stress, and 55% to control insomnia. We did not collect data on our patients' activities. Faria (2008)[11]observed that this event occurred in male patients, during the night, on weekends, and mainly within an age group from 50 to 59 years old. Our study showed a higher incidence of TBI at night on weekdays, which differs from other studies.[3,15] There was a predominance in the age groups from 21 to 25 years old and from 36 to 40 years old for marijuana. The observed mortality was 27.3% and 14.3%[16]respectively. Regarding the types of accidents, we observed that in this group that transport accidents corresponded to 50%, followed by falls and assaults at 22.7% each. The average length of hospitalization was 25.21 ± 6.39 days.

There are few studies in Brazil relating the use of cocaine to TBI, probably due to underreporting and a lack of health policies that involve research in emergency units as a routine of care. We found that 28.7% of the patients in our study tested positive for cocaine, a higher frequency than that found by Faria,[12] which was 13.9%. In both, the use predominated in males and in young people. In these cases, transport accidents were the most common type. Faria observed a positive association between cocaine and trauma from aggression, when compared with other causes.[13] In our study, the main cause was transport accidents (43.5%), followed by falls (26.1%) and aggression (21.7%). A survey showed that 29.5% of cocaine-dependent individuals reported having suffered TBI during their lifetime compared with the 8% control,[17] emphasizing the importance of this association.

Faria[16] reports in his study that the associations between alcohol and cocaine and between alcohol and marijuana were the most frequent, followed by the association of the three drugs. We found positivity in the association between alcohol and cocaine at 11.25%, alcohol and marijuana at 8.75%, and alcohol, marijuana and cocaine at 8.75%.

A previous study found aggression to be the most common cause of trauma associated with the use of alcohol, marijuana

and cocaine.[1] In the current study, we found transport accidents to be the most common cause, followed by aggression and falls.

Studies performed in the USA showed that 35 to 80% of all patients hospitalized for trauma tested positive for illicit drugs.[18,19] In Brazil, despite intensive surveillance by the authorities in the fight against drug trafficking (80,607 tonnes of cocaine and 27,124 tonnes of marijuana were seized from 2020 to November 2021),[20] the presence of marijuana and cocaine associated with severe and moderate TBI may be underestimated. We emphasize that in our country there is no obligation to investigate these drugs in the emergency care departments of our hospitals.

Conclusion

An association was observed between the use of alcohol, cocaine and marijuana with moderate and severe TBI in patients attended at the Emergency Room of the Hospital of Clinics of the Federal University of Uberlândia. The percentage of patients positive for cocaine (28.7%) and marijuana (27.5%) increased when compared with a study performed at this institution in 2003, when positivity was observed for cocaine (13.9%) and marijuana (8.2%). A future study will be necessary to investigate the causal nexus of these associations.

Limitations

1. Difficulty in acquiring tests for the dosage of alcohol in saliva and for the dosage of cocaine and marijuana in urine during the period of the Covid-19 pandemic.
2. Several family members or guardians were either not identified or refused to sign the consent form.
3. Difficulty in implementing a routine for collecting the tests in the emergency room.

Financial Support
The author did not receive financial support.

Conflict of Interest
No conflict of interest to declare.

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Factors Related to the Recurrence of Low-grade Gliomas

Fatores relacionados à recorrência dos gliomas de baixo grau

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Arq Bras Neurocir 2023;42(4):e323–e327.

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Abstract

Objective To identify the determining factors for reoperation in patients with low-grade gliomas, taking into account the degree of resection, and to analyze the histological aspects, observing possible transformations with signs of malignancy in the tissue samples.

Materials and Methods The sample consisted of 40 cases of low-grade glioma that were operated on at Hospital das Clínicas de Botucatu between 2013 and 2019.

Results The mean follow-up was of 37 months, and the sample was composed of 28 men and 12 women with a mean age at the first surgery of 43.1 ± 15.6 years. Epileptic seizures were observed in 31 (77.5%) patients. According to the histological classification, half of the patients presented oligodendroglioma (50%), of grade II in most cases (97.5%). Total or subtotal resection was achieved in 22 (55%) patients. Only one patient underwent radiotherapy, and two underwent chemotherapy. Reoperation was performed in 20 (50%) patients. The median interval between the first surgery and the reapproach was of 16 (range: 0–77) months. In the second approach, the histological classification was of astrocytoma in 4 (20%) cases, oligoastrocytoma in another 4 (20%), oligodendroglioma in 7 (35%), and glioblastoma in 5 (25%) cases. The only variable associated with the need for reoperation was the degree of resection after the first surgery ($p = 0.013$).

Conclusions Total resection of low-grade gliomas, when feasible, should be performed to avoid recurrence.

Keywords
- gliomas
- low grade
- microsurgery

Resumo

Objetivo Apontar os fatores determinantes para a reoperação em pacientes com gliomas de baixo grau considerando o grau de ressecção, e analisar os aspectos histológicos, observando possíveis transformações com sinais de malignidade nas amostras teciduais estudadas.

Materiais e Métodos A casuística foi composta por 40 casos de gliomas de baixo grau operados no Hospital das Clínicas de Botucatu de 2013 a 2019.

Resultados O tempo médio de seguimento de foi de 37 meses, sendo a amostra composta de 28 homens e 12 mulheres com idade média à primeira cirurgia de

Palavras-chave
- gliomas
- baixo grau
- microcirurgia

received
September 22, 2022
accepted
March 7, 2023
article published online
October 27, 2023

DOI https://doi.org/10.1055/s-0043-1776283.
ISSN 0103-5355.

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

43,1 ± 15,6 anos. Crises epilépticas foram observadas em 31 pacientes (77,5%). Na classificação histológica, a metade dos pacientes apresentou oligodendroglioma (50%), sendo de grau II na maioria dos casos (97,5%). Ressecção total ou subtotal foi atingida 22 pacientes (55%). Apenas um paciente foi submetido a radioterapia, e dois, a quimioterapia. Reoperação foi realizada em 20 pacientes (50%). O intervalo mediano entre a primeira cirurgia e a reabordagem foi de 16 (variação: 0–77) meses; na segunda abordagem, a classificação histológica foi de astrocitoma em 4 casos (20%), oligoastrocitoma em outros 4 (20%), oligodendroglioma em 7 casos (35%), e glioblastoma em 5 casos (25%). A única variável que apresentou associação com a necessidade de reoperação foi o grau de ressecção da primeira cirurgia ($p = 0,013$).

Conclusão A ressecção total dos gliomas de baixo grau, quando factível, deve ser buscada com a finalidade de evitar a sua recorrência.

Introduction

Low-grade gliomas correspond to several histological types, with an emphasis on grade-II astrocytomas, oligodendrogliomas, and oligoastrocytomas.

With the advances and easier access to neuroimaging tests, early diagnosis as well as the diagnosis of asymptomatic patients, has increased. As a result, total or even supratotal resections were possible in a higher percentage of cases.

The results of the surgical treatment improved in terms of neurological and oncological aspects. In the oncological aspect, the patients started to present a lower rate of recurrence and malignancy. In the neurological aspect, fewer deficits and a lower incidence of epilepsy is observed in the postoperative period.[1]

Tumor recurrence patterns are varied. They may occur after malignant transformation, at the surgical site, or even at a site distant from the original location.[2]

Despite surgical resection, which can be total, subtotal or biopsy alone, the incidence of postsurgical recurrence is high, and it depends on the extent of the resection, malignant transformation of the neoplastic tissue, and use or absence of adjuvant treatments, such as radiotherapy and chemotherapy.[3] The adjuvant treatment with chemotherapy and radiotherapy can be indicated in cases of recurrence of low-grade gliomas submitted to a second surgery or not.[4]

For some authors,[5] reoperation for recurrent low-grade glioma is strongly indicated and should be as radical as possible. For others,[6] there is no strong evidence to recommend reoperation, and further clinical studies on the subject are required. The indicated treatments must be individualized considering the patient's age, the extent of the resection, the histological classification of the tumor, the quality of life, and the patient's preference.[7]

A detailed neuropsychological evaluation must always be performed in these patients, with a comparison of the pre- and postoperative periods, to enable the characterization of the initial deficits secondary to the tumor lesion itself and its postoperative alteration.[8]

Despite the well-defined goal of the surgery for low-grade glioma, the management of the cases of recurrence is still controversial.[9] The location of these tumors is a relevant factor in the indication of the first surgery and even in the case of recurrence. Some authors[10] advocate the surgical approach even in complex areas from anatomical and functional points of view, such as the insula.

The recurrence patterns of low-grade glioma vary considerably, and the management at this stage of the evolution of the disease is complex, which reinforces the recommendation for the most radical resection possible in the first surgery.[11]

Objective

The main objective of the present study was to determine the factors associated with tumor recurrence in low-grade glioma. The secondary objectives were to characterize the population of patients with recurrent glioma according to their demographic data, characterize, from a histopathological point of view, the recurrent low-grade gliomas according to the findings of the first surgical intervention, characterize the degree of resection (total resection, resection, subtotal resection, and biopsy alone) in the first surgical intervention, characterize, also from a histopathological point of view, the tumors observed in the second and occasional third surgical interventions, determine whether a supporting treatment was performed (chemotherapy and/or radiotherapy) between the first and second surgical interventions, and determine the interval between the first and second surgical interventions.

Materials and Methods

This retrospective cohort study was conducted in the Hospital of Clinics at Botucatu Medical School, São Paulo State University, Brazil. We recovered the data from the medical records of patients ($n = 40$) submitted to resection of low-grade gliomas between 2013 and 2019. Preoperative variables, such as age and sex, were the factors considered in the present study. Aspects of the first surgery, such as the degree of resection, the postoperative treatment, and the performance or absence of radiotherapy and chemotherapy, were

Table 1 Clinical features of the patients ($n = 40$)

Variable	
Male sex	28 (70%)
Age in years (mean ± SD)	43.1 ± 15.6
Seizures	31 (77.5%)
Side	
Right	18 (45%)
Left	19 (47.5%)
Midline	3 (4.5%)
Histological classification	
Astrocytoma	13 (32.5%)
Oligodendroglioma	20 (50%)
Oligoastrocytoma	13 (32.5%)
Degree of resection	
Total	8 (20%)
Subtotal	14 (35%)
Partial	11 (27.5%)
Biopsy	7 (17.5%)
Reoperation	20 (50%)

Abbreviation: SD, standard deviation.

also considered. The histopathological findings of the first and second surgeries were compared. The interval between the two surgeries was also evaluated.

Biopsy was performed by craniotomy and was considered a primary treatment. The degree of resection was classified by the surgeon. Reoperation was only considered when tumor growth was observed. Surgeries for residual tumors or surgery for complications of the procedure were not considered reoperations.

The distribution of the data was assessed using the Shapiro-Wilk test. Comparisons between the groups were performed using the *t*-test or Mann–Whitney tests according to data distribution. The Chi-squared and Fisher exact tests were used to compare the categorical data. The level of statistical significance was set at 5%. The statistical analyses were performed using the IBM SPSS Statistics for MacBook (IBM Corp., Armonk, NY, United States) software, version 24.0. The present study was approved by the institutional Ethics in Research Committee under registration number 51843121.8.0000.5411.

Results

We included 40 patients (28 men and 12 women), with a mean follow-up of 37 months, and a mean age at the first surgery of 43.1 ± 15.6 years. Epileptic seizures were observed in 31 (77.5%) patients, and the right and left sides were similarly affected. According to the histological classification, half of patients had oligodendroglioma (50%), of grade II in most cases (97.5%). Total or subtotal resection was achieved in 22 (55%) patients. Only one patient underwent radiotherapy, and two underwent chemotherapy. Reoperation was performed in 20 (50%) patients. ►**Table 1** shows the patients' clinical and demographic data. No differences were observed regarding the histological classification and sex, age, tumor laterality, degree of resection, or need for reoperation (►**Table 2**).

Comparing patients who did or did not require reoperation, there was no difference between sexes ($p = 0.301$), mean age ($p = 0.517$), and affected hemisphere ($p = 1.00$). The only variable associated with the need for reoperation was the degree of resection after the first surgery ($p = 0.013$), and none of the patients who underwent total resection required a reapproach (►**Fig. 1**).

None of the patients submitted to complete resection were reapproached during the follow-up, and the proportion of patients who required a reapproach was higher among those who underwent partial resection or biopsy alone.

The median interval between the first surgery and the reapproach was of 16 (range: 0–77) months. In the second approach, the histological classification was of astrocytoma in 4 cases (20%), oligoastrocytoma in another 4 (20%), oligodendroglioma in 7 (35%), and glioblastoma in 5 (25%)

Table 2 Comparisons between clinical variables and histological classification of the gliomas

Variable	Astrocytoma ($n = 13$)	Oligodendroglioma ($n = 20$)	Oligoastrocytoma ($n = 7$)	*p*-value
Male sex	8 (61.5%)	16 (80%)	4 (57.1%)	0.467
Age in years (mean ± SD)	41.4 ± 17.2	46.4 ± 15.0	36.7 ± 13.8	0.337
Left hemisphere	6 (46.2%)	11 (50%)	2 (28.6%)	0.205
Degree of resection				
Total	3 (23.1%)	4 (20%)	1 (14.3%)	0.675
Subtotal	4 (30.8%)	7 (35%)	3 (42.9%)	
Partial	2 (15.4%)	6 (30%)	3 (42.9%)	
Biopsy	4 (30.8%)	3 (15%)	0 (0%)	
Reoperation	7 (53.8%)	8 (40%)	5 (71.4%)	0.340

Abbreviation: SD, standard deviation.

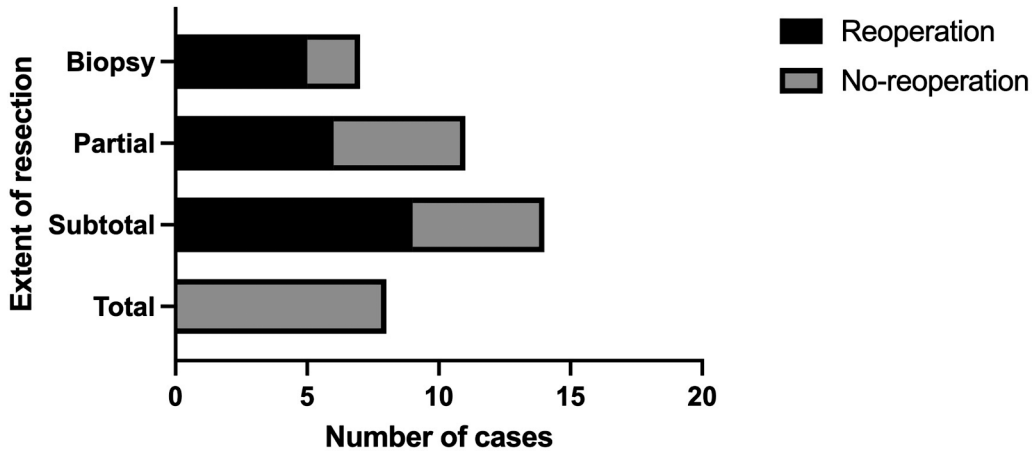

Fig. 1 Number of cases that required reoperation according to the degree of resection of the first surgery.

cases. As for the grads, 7 cases were grade II, 8 were grade III (40%), and 5 were grade IV.

No association was observed between the original histological classification and the change in grade ($p = 0.494$). There was also no association between the degree of surgical resection and histological transformation ($p = 0.425$).

Discussion

Low-grade gliomas account for 10% to 20% of all primary brain tumors. The median survival time is of 4.7 to 9.8 years. The aim of the treatment is to prolong survival while maintaining a good quality of life. Recent data[1,5,7] have favored early surgical resection. Additional chemotherapy or radiation therapy is recommended for high-risk patients.[12]

From an epidemiological point of view, the present series differs from those in the literature[13] because of the predominance of men, and it agrees with the literature considering the age of onset of symptoms (mostly in the beginning of the fifth decade of life). This is also in agreement with the literature because clinically, oligodendrogliomas present with epileptic seizures.[14,15] In the present study, there was no predominance of a single cerebral hemisphere in the cases analyzed.

The treatment of low-grade gliomas aims to prevent recurrence and malignant transformation; knowing the determining factors of these events is of fundamental importance to determine the best treatment strategies.[16] Diffuse low-grade gliomas can recur in different histological patterns and different degrees of malignancy. Radical surgery at the time of the initial diagnosis seems to determine a better prognosis for recurrence from a histopathological point of view.[16]

Regarding the histological type, most cases in the series were of grade-II oligodendroglioma, and cases of grade-II astrocytoma were less frequent. Histological classification has long guided the treatment of gliomas. However, classification through molecular biology has increased the knowledge of the nature of these tumors. The 2016 WHO classification integrates the histological and molecular findings of gliomas.[17] Molecular analysis has only recently been incorporated into our service; therefore, we did not present this analysis.

In the present series, the degree of resection was total in 20% of the cases, and none of them presented recurrence, corroborating the literature reports relating total resection to better prognoses.[3,5]

Some authors[18] have compared the performance of biopsy with surgical resection and observed better results in terms of survival and seizure control in patients undergoing more extensive surgeries. However, it should be considered that total resections are usually performed in gliomas located in non-eloquent areas, which eventually favors supratotal resection.

In the present series, regarding the interval between the first and second surgeries, the brevity of the period (16 months on average) should be highlighted, which may be related to the malignant transformation of gliomas to grades III (8 cases) and IV (5 cases). In cases of recurrence, histopathological transformation to grades of greater malignancy is very frequent (65% of the cases in the present series).

Radiotherapy and chemotherapy after the first surgery were performed in in one and two patients respectively who had undergone partial or even total resection. Such complementary treatment is often indicated due to recurrence, regardless of tumor malignancy.[12] The absence of molecular biology analysis of the tumors, the small number of cases, and certain methodological aspects are limitations of this study.

Conclusion

Total resection of low-grade gliomas, when the tumor does not occupy eloquent areas of the brain, should be performed to prevent recurrence and provide a better prognosis for these patients.

Conflict of Interests

The authors have no conflict of interests to declare.

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Use of Connectomes in Deep Brain Stimulation for the Treatment of Obsessive-Compulsive Disorder

Uso de conectomas na estimulação cerebral profunda para tratamento de transtorno obsessivo-compulsivo

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Arq Bras Neurocir 2023;42(4):e328–e336.

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Abstract

Obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by the performance of repetitive behaviors in response to an obsession, which currently ranks as the tenth cause of disability in the world. Patients who are refractory to conventional treatment are candidates for the neurosurgical treatment of deep brain stimulation (DBS). In this procedure, electrodes are implanted in specific anatomical brain targets. The present systematic literature review aimed to describe the main connectomes and associate them with their respective targets involved in DBS for the treatment of OCD, to understand the connectomes related to OCD and their contributions to DBS, and to describe the main targets used in DBS surgery for OCD. Based on the present results, the stimulated targets that showed better clinical outcomes were the anterior limb of the internal capsule, the nucleus accumbens, the subthalamic nucleus, and the ventral capsule/striatal capsule. The target associated with the worst clinical results was the posterior limb of the anterior commissure. The variable stimulation of certain regions of the brain determines different clinical results. However, an individualized investigation of the OCD patient is essential for choosing the best target for DBS.

Keywords

- obsessive-compulsive disorder
- OCD
- deep brain stimulation
- DBS
- connectome

Resumo

O transtorno obsessivo-compulsivo (TOC) é uma doença psiquiátrica caracterizada pela realização de comportamentos repetitivos em resposta a uma obsessão, que atualmente se enquadra como a décima causa de incapacidade do mundo. Pacientes refratários ao tratamento convencional são candidatos para o tratamento neurocirúrgico de estimulação cerebral profunda (ECP). Neste procedimento, eletrodos são implantados em alvos anatômicos específicos do cérebro. A presente revisão sistemática da literatura teve como objetivo descrever os principais conectomas e associá-los aos seus respectivos alvos envolvidos no ECP para o tratamento de TOC, compreender os conectomas relacionados ao TOC e suas contribuições para o ECP e descrever os

Palavras-chave

- transtorno obsessivo-compulsivo
- TOC
- estimulação cerebral profunda
- ECP
- conectoma

received
May 24, 2022
accepted
June 21, 2022

DOI https://doi.org/10.1055/s-0042-1756143.
ISSN 0103-5355.

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

principais alvos utilizados na cirurgia de ECP para TOC. Com base nos nossos resultados, os alvos estimulados que apresentaram melhores resultados clínicos foram o membro anterior da cápsula interna, o núcleo accumbens, o núcleo subtalâmico e cápsula ventral/cápsula estriatal. O alvo associado aos piores resultados clínicos foi o membro posterior da comissura anterior. A estimulação variável de determinadas regiões do cérebro determina resultados clínicos diferentes. No entanto, uma investigação individualizada do paciente com TOC é essencial para a escolha do melhor alvo para ECP.

Introduction

Obsessive-compulsive disorder (OCD) is a chronic neuropsychiatric condition characterized by performing repetitive behaviors in response to an obsession or obeying rules that have to be applied thoroughly.[1] Obsessions are mental events such as thoughts, ideas, and images that generate discomfort. Compulsions are repetitive behaviors or mental acts that occur to reduce the discomfort and anxiety caused by obsessions or a ritual to prevent some feared event or situation.[2] These rituals are not manias and cause suffering and damage, mainly because they consume the time of the individuals.[3] According to the World Health Organization (WHO), OCD is currently the tenth cause of disability in the world.[3]

Among the most prevalent obsessions of OCD are afflictions with dirt or contamination, somatic obsessions, aggressive obsessions, and self-extermination. The most common compulsions are: frequently washing objects and hands, likely causing dermatitis; counting; obeying symmetry such as the position of books, clothes on a clothesline, among others; collecting and not getting rid of mostly unnecessary objects; and several other rituals such as remembering, touching, and praying.[3]

The psychological changes of OCD are experienced as obsessions and/or compulsions responsible for mental discomfort such as anxiety. The disorder can affect the social (isolation), affective (family overload), and professional areas (unemployment), and this may lead to financial dependence and personal dissatisfaction. In addition, a significant evolution to depression throughout life in patients with OCD has been reported. Another aggravating factor is that, most often, patients make the disorder a secret due to denial of the disease, because of shame or fear of judgment, making the diagnosis and treatment more difficult. This disorder has significant epidemiological data associated with depression, suicide, and anxiety.[3]

From the pathophysiological perspective, OCD occurs due to the abnormal functioning of anatomical structures in the brain, causing deficits in the neurocircuits and neurotransmitters. Neuroimaging of patients with OCD detects hyperactivity of the orbitofrontal cortex (OFC), both in resting and active states. Thus, the corticostriatothalamocortical neurocircuitry is a good parameter to identify the pathophysiological cause of OCD.[3]

Based on the baseline model of OCD, the basal ganglia would not select cortical impulses, affecting the thalamic activity. Consequently, the excitatory impulses from the thalamus would reach the OFC, intensifying certain cravings that would be considered irrelevant in the absence of OCD.[4] The individualized assessment of symptoms, the degree of perception by the patient, and the extent of comorbidity are equally important, since OCD is quite heterogeneous and each type of neurobiological alteration has its specific brain circuits.[5]

The diagnostic criteria for OCD, in general, are: presence of obsessions, compulsions, or both; the obsessions or compulsions take time or cause relevant suffering or damage to social development, professional performance, or in other areas; the obsessive-compulsive symptoms are not physiological effects of a substance or other medical condition and the agitation is not best understood by symptoms of another mental disorder.[1] The differential diagnosis should be made by means of a general psychiatric evaluation to distinguish OCD from other psychiatric conditions or the absence of them. Intrusive thoughts and repetitive behaviors that are time-consuming ($>$ 1 hour per day), and that generate substantial distress or functional impairment are characteristic of OCD.[5]

Patients with refractory OCD, who remain severely impaired despite having been exposed to first- and second-line therapies, are candidates for the neurosurgery approach, a procedure that changes the activity of the neural networks involved in the illness. It is important to note that presenting with severe symptoms is a necessary requirement, but not sufficient to undergo this type of neurosurgery. The severity of OCD is usually scored using the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), a 40-item scale encompassing 20 questions for obsessions and 20 for compulsions that patients should answer. High Y-BOCS scores reveal more severe OCD symptoms.[6]

It is known that 20 to 30% of OCD patients are refractory to drug or cognitive behavioral therapies. Given this reality, a possible treatment of choice is deep brain stimulation (DBS).[5] It consists of reversible stimulation for the treatment of resistant neurological disorders by delivering electrical currents to the brain using electrodes connected to implanted pulse generators. These electrodes are permanently applied to specific anatomical targets.[7] The stimulation is defined with focal, adjustable, and reversible neuromodulation.[8] The

electric field generated by DBS is three-dimensionally sent throughout the brain. The neurons directly affected by the stimulation influence the activity of the network, and the response of the network depends on the types of neurons affected and their interconnections.[7] In general, the effects are mild, transient, and reversible after shaping the stimulation properties. An efficient programming of the electric current that shapes the magnetic field of DBS aims to ensure a better prognosis.[8]

This surgical procedure has been used for $\sim$ 30 years to regulate defective brain networks caused by various diseases such as Parkinson disease and essential tremor.[9] In 2009, the United States Food and Drug Administration, the American federal government agency that regulates food, drugs, cosmetics, and medical products, approved DBS as a treatment for severe OCD.[10]

A 60% response rate has been reported in patients submitted to this neurosurgery. From a prognostic perspective, the anterior limb of the internal capsule (ALIC), the nucleus accumbens (NAcc), and the cingulum are targets that show good postoperative responses. Studies of neuroimaging and anatomical connectivity of OCD patients have pointed to alterations in the frontostriatothalamocortical network. This anatomical connectivity can be determined by diffusion-weighted imaging, acquired by magnetic resonance imaging (MRI), and followed by tractography reconstructions to provide the trajectory and density of the white matter of the brain. Additionally, functional connectivity, via functional MRI, has also been used to guide the implantation of electrodes in DBS.[11]

Given that OCD is a very heterogeneous psychiatric disorder that involves a dysfunction of the whole brain network, there is not a single universal target for its modulation in DBS. The importance of identifying these patient-specific connectivity profiles suggests the feasibility of a personalized DBS.[12] Hence, functional imaging supports the analysis of these correlations with the detection of several directly stimulated fibers and their corresponding cortical or subcortical regions modified by DBS. Furthermore, diffusion tensor imaging tractography facilitates the detection of axonal trajectories around DBS electrodes.[7]

Therefore, the present systematic literature review aimed to describe the main connectomes and associate them with their respective targets involved in DBS for the treatment of OCD, understand the OCD-related connectomes and their contributions to DBS, and describe the main targets used in DBS surgery for OCD.

Methods

The present systematic literature review was performed searching on the Public/Publisher MEDLINE (PubMed), Scientific Electronic Library Online (SciELO), Virtual Health Library (VHL), Cochrane Library, and Portal de Periódicos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior do Ministério da Educação (CAPES/MEC, in the Portuguese acronym) databases applying the protocol of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13] The following descriptors searched on the Descriptors of Health Sciences (DeCS) and associated with the Boolean operators AND and OR were employed: (*obsessive compulsive disorder* OR *OCD*) AND *connectome* AND (*deep brain stimulation* OR *DBS*). For article selection, five inclusion criteria were elected: 1. full-length original articles; 2. studies performed in humans; 3. studies that responded to the proposed objectives; 4. articles published in the past 10 years (2011 to 2021); and 5. articles in English, Portuguese, or Spanish. The exclusion criteria were: 1. review articles; 2. meta-analyses; and 3. duplicate articles.

Results

In total, 238 studies were found in the initial search. Before screening, 124 articles were excluded after applying the filters "full text," "human," "last 10 years," and "English, Portuguese, Spanish," whereas 18 were excluded because they were duplicates. Therefore, 96 records were selected for careful reading of the titles and abstracts, 81 of which were excluded for not meeting the inclusion criteria, and 15 were assessed for eligibility. Finally, after the exclusion of 1 more record, 14 articles were included in the qualitative analysis (►**Fig. 1** and ►**Table 1**).

Several studies have already demonstrated that DBS is a promising procedure for the treatment of refractory OCD with the reduction of symptoms.[18] Based on the analysis of the selected articles, the main targets used in DBS for the treatment of OCD were the ALIC, the subthalamic nucleus (STN), and the NAcc.

In a retrospective cohort with a sample of 50 patients who underwent stimulation of different targets to control OCD, namely ALIC, STN, NAcc, and ALIC-STN, similar results were found for all of them. The best clinical result, however, was observed with the stimulation of the hyperdirect pathway, which was connected from the dorsal anterior cingulate cortex (ACC) to the STN. Conversely, the posterior limb of the anterior commissure showed the worst clinical results. Although different targets were used, they all converged to the same fiber bundle, called the ventral tegmental area projection pathway, with modulation of both ALIC and STN. This tract interacts with multiple brain areas, resulting in clinical improvement of OCD symptoms over time.[23] Another study including this same cohort of patients showed that different targets share the same network, that is, although the targets of choice were ALIC, STN, NAcc, or STN-ALIC, they connected to common brain areas, including the insula, the superior frontal gyrus, the ACC, and the anterior thalamus.[24]

In a study conducted in Germany, 22 patients, all with severe OCD refractory to treatment according to Y-BOCS, underwent DBS in the ALIC/NAcc. These targets were chosen from a normative and patient-specific connectome. A fiber bundle was evidenced within the ventral ALIC, which crosses the ventral striatum (VS), next to the stria terminalis bed, which connects the medial prefrontal cortex (PFC) to the thalamus. In a volume of activated tissue, this bundle of fibers reached apical and posterior white matter areas of the NAcc, leading to a significant improvement in the clinical

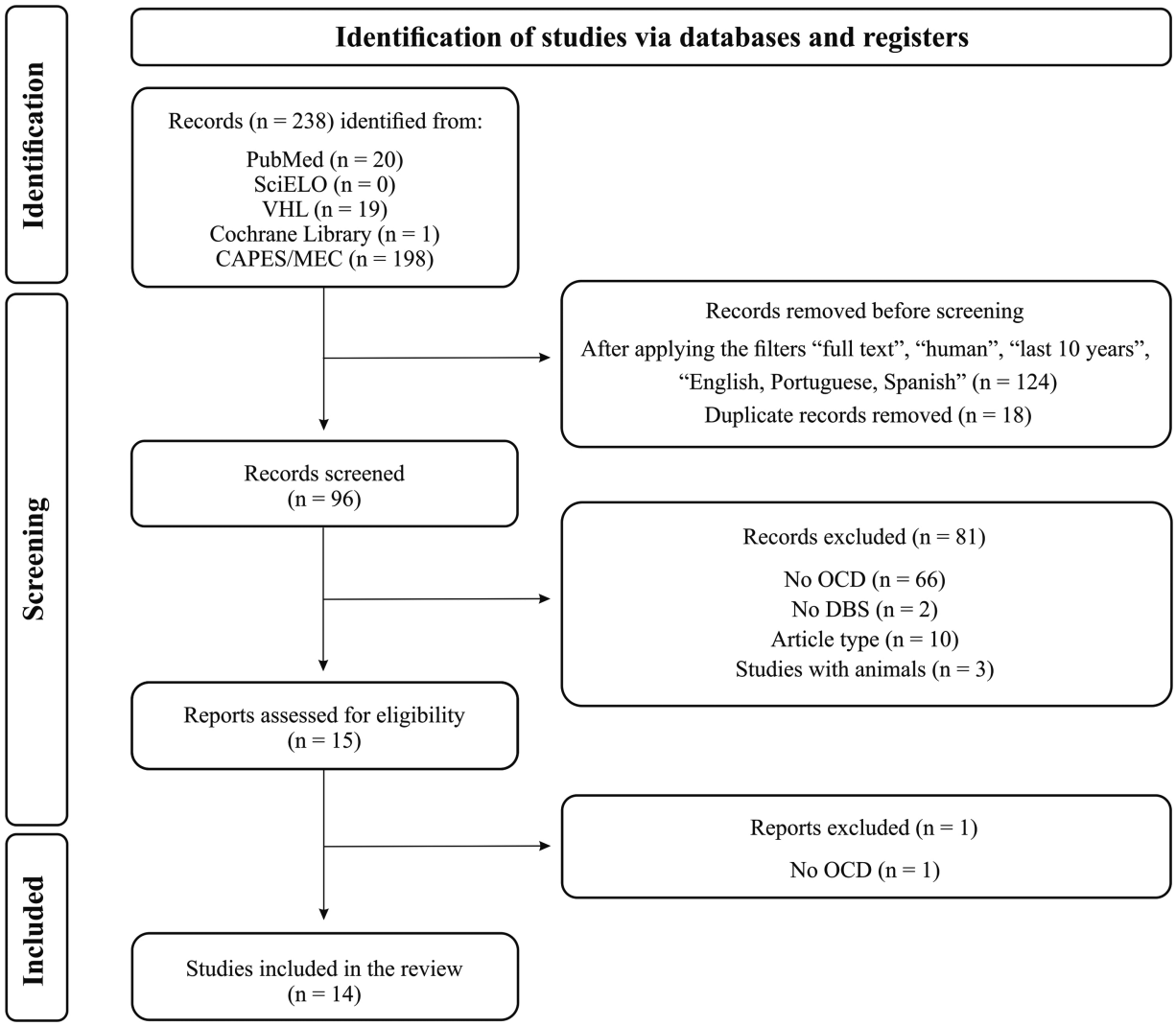

Fig. 1 Flow diagram showing the study design following to the protocol of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13] CAPES/MEC, Portal de Periódicos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior do Ministério da Educação; DBS, deep brain stimulation; OCD, obsessive-compulsive disorder; PubMed, Public/Publisher MEDLINE; SciELO, Scientific Electronic Library Online; VHL, Virtual Health Library.

symptoms analyzed, with the participation of both medial and lateral PFC in positive results. Nevertheless, the tract in flux to the medial prosencephalic bundle, to the posterior limb of the anterior commissure, and to the fibers within the inferior lateral fascicle were associated with negative results. After 1 year, an improvement in the symptoms associated with OCD was observed after DBS in the ALIC/NAcc with the insertion of electrodes in the frontostriatothalamic pathway.[19] From a physiological point of view, another study also admitted abnormalities in the frontostriatal circuitry linked to OCD.[17]

In another retrospective cohort, including eight patients diagnosed with severe OCD based on the Diagnostic and Statistical Manual of Mental Disorders: Fifth Edition (DSM-5) [1] and a Y-BOCS score of at least 30/40, the ventral capsule (VC)/VS target was chosen. The inclusion criteria were persistence of symptoms for a minimum of 5 years, accompanied by intolerance to 2 selective serotonin reuptake inhibitors, clomipramine, antipsychotic medications, and cognitive behavioral therapy. At the end of the study, 5 patients responded to surgery, with a mean drop of 16.6 in total Y-BOCS, whereas 3 patients continued nonresponsive; that is, a 63% response rate was achieved. In this sample that underwent stimulation in the VC/VS, it was observed that an ALIC subpart, which connects the PFC with the STN in front of the medial nucleus of the thalamus, is associated with a favorable clinical response to refractory OCD. The fibers unfavorable to a decrease in Y-BOCS were those in the posterior limb of the anterior commissure that connect with the bilateral temporal cortices and the cingulum fiber bundles.[26]

In a diffusion MRI analysis of 29 healthy patients, 29 human connectomes were constructed. Among these patients, the case of a 30-year-old individual with OCD symptoms since adolescence caught the attention of the researchers. Therefore, DBS surgery was proposed due to the fact that, previously, the patient had responded neither to medication such as clomipramine and serotonergic agents, nor to cognitive behavioral

Table 1 Articles selected for the present systematic literature review

Study design	Sample	Target stimulated in DBS	Conclusions	Reference
Case studies	29 controls, 1 patient	VC/VS	The current surgical model is based on identifying identical stereotaxic coordinates for different patients in the VC/VS target. However, it has been observed that the individual connectome approach is crucial to improve the accuracy of DBS for the treatment of OCD	Makris et al.[14]
Clinical study	8 patients	NA	Using specific mapping of each patient's brain, the goal is to obtain brain network models for a personalized stimulation, improving the surgical intervention	Muldoon et al.[15]
Comparative study	842 controls	ALIC	Due to the high variability of the frontal structural connectivity of te ALIC, tractography and individual analysis of the connectomes of each patient corroborate a better neurosurgical direction	Nanda et al.[16]
Construction of a whole-brain rs-fMRI-based biomarker using a data-driven approach	108 patients	NA	Construction of a biomarker to better understand OCD	Takagi et al.[17]
Discussions about how to interpret results from the recent pivotal trials of DBS for OCD and depression, views on neuromodulation for psychiatric disorders, criteria for moving forward with new trials, the best way of confirming safety and efficacy of these therapies, and the next steps in the journey to new neuromodulatory therapies for OCD	NA	NA	DBS has shown promising results for several psychiatric disorders	Bari et al.[18]
Cohort	Total of 22 patients, 13 females	ALIC, NAcc	Stimulation pathways that are more closely connected to the frontothalamic pathway predict varying degrees of relief in clinical symptoms	Baldermann et al.[19]
Descriptive study	8 patients	slMFB	HAMLET refines the surgical fiber of the slMFB through deterministic tractography and therefore assists in accurate surgical planning	Coenen et al.[20]
Cohort	200 patients	NA	Regions targeted for OCD converge on subcortical portions of the reward network that is associated with OCD	Coenen et al.[21]
Precision functional mapping	NA	NA	The diverse clinical responses of DBS occur due to nonspecific stimulation of subparts of brain structures	Greene et al.[22]

Table 1 (*Continued*)

Study design	Sample	Target stimulated in DBS	Conclusions	Reference
Retrospective cohort	Total of 50 patients: $n = 22$, ALIC-DBS, in Colony, Germany; $n = 14$, STN-DBS, in Grenoble, France; $n = 8$, bilateral NAcc, in Madrid, Spain; $n = 6$, STN-ALIC, in London, United Kingdom	ALIC, STN, NAcc, STN-ALIC	Electrode activation of the STN and the ALIC enhances their connection with various parts of the brain. Modulation of the STN and the ALIC is linked to the same fiber bundle that responds to clinical improvements	Li et al.[23]
Retrospective cohort	Total of 50 patients: $n = 22$, ALIC-DBS, in Colony, Germany; $n = 14$, STN-DBS, in Grenoble, France; $n = 8$, bilateral NAcc, in Madrid, Spain; $n = 6$, STN-ALIC, in London, United Kingdom	ALIC, STN, NAcc, STN-ALIC	A group of functionally connected brain regions was identified; thus, regardless of the target region of choice, good results were obtained	Li et al.[24]
Randomized, double-blind, sham-controlled trial	9 patients	BNST/NAcc	BNST target stimulation showed better results compared with placebo	Mosley et al.[25]
Retrospective cohort	8 patients	VC/VS	VC/VS neuromodulation has shown good clinical results and is linked to the neuronal networks responsible for symptoms of OCD	van der Vlis et al.[26]
Prognostic study	8 patients	VC/VS	It has been held that the connection of the anterior cingulate cortex to the thalamus and the basal ganglion are part of the DBS response in the VC/VS target	Widge et al.[27]

Abbreviations: ALIC, anterior limb of the internal capsule; BNST, bed nucleus of the stria terminalis; DBS, deep brain stimulation; HAMLET, Hierarchical Harmonic Filters for Learning Tracts from Diffusion Magnetic Resonance Imaging; NA, not available; NAcc, nucleus accumbens; OCD, obsessive-compulsive disorder; rs-fMRI, resting-state functional magnetic resonance imaging; slMFB, superolateral medial forebrain bundle; STN, subthalamic nucleus; VC/VS, ventral capsule/ventral striatum.

therapy. The surgery included bilateral VC/VS implantation and, after 6 months, following proper adjustments, a decrease by 35% in Y-BOCS was noted, as well as improvements in quality of life. It is known that DBS in this region establishes reciprocal excitation between the OFC and the thalamus, and consequently weakens abnormal activity within the OFC-caudate-pallidal-thalamic circuit. Therefore, the orbitofrontal-thalamic connections are important in the pathophysiology and clinic of OCD, since these fibers connect to several thalamic nuclei, primarily the dorsal medial, intralaminar midline, medial pulvinar, and anterior medial nuclei. Nonetheless, these fibers that cross the VC/VS region display high variability between individuals, so their most precise and individual localization determines a better post-surgical outcome.[14]

In a normative cohort encompassing 200 patients, with data collected from the Human Connectome Project (HCP), 4 networks associated with OCD were described, namely affect, reward, cognitive control, and default. Patients diagnosed with OCD exhibit cognitive inflexibilities related to the cognitive control network. Furthermore, the target regions in OCD have fibers confluent to the subcortical parts that belong to the reward network, since this interacts with the affect system in dynamic equilibrium. Another important point of the study was the analysis of eight projection points, all of which pass through the anterior branch of the internal capsule and reach the frontal cortex. In parallel, the reward and affect network tracts are also located in the ALIC, in a ventral/inferior position, while the cognitive control network tract is positioned more dorsally.[21]

The precision functional mapping of 10 individuals evidenced that regions of the subcortex are connected to multiple cortex networks. The subcortical structures have several functions, one of which is acting in the reward network. The most commonly affected subcortical fiber bundles among individuals may explain the different psychiatric disorders involved and are targets for improving subcortical interventions in DBS.[22]

In one analysis using diffusion imaging, a sample of eight patients presenting with OCD underwent DBS in the VC/VS region. The average improvement in Y-BOCS was 46.6%. The targets with positive responses were the cingulate and lateral OFC, whereas the ones that caused negative responses were the medial OFC and the ventrolateral PFC. The authors reaffirmed the relevance of the relationship between the circuits connecting the ACC to the thalamus and the basal ganglia to the response of electrode deployment in the VC/VS in DBS. Individual variability of fiber passage in the internal capsule was supported, ratifying that patient-specific imaging plays a crucial role in the accuracy of surgical target choice.[27]

In a randomized, double-blind, sham-controlled study conducted with nine Australian participants diagnosed with refractory OCD based on criteria defined by the DSM-5[1] and severity based on Y-BOCS and preoperative neuroimaging by structural MRI, the effects of DBS on the bed nucleus of the stria terminalis (BNST) was analyzed. Thus, from stimulation of this target, a 49.6% reduction in the Y-BOCS of the participants was noted.[25]

In a study with 842 HCP controls, portions of the ALIC were compared using diffusion tensor tractography to analyze structural patterns of frontal connectivity, in addition to the prefrontal-subcortical tracts. From these, 40 individuals in which the subdivisions of the ALIC diverged were randomly selected. However, there were sites of compatibility, mainly in the region connected to Brodmann's area 11 located in the OFC, which is a target widely used in DBS for OCD. Furthermore, the presence of a tract that crosses the ALIC and connects the prefrontal and subcortical regions was observed. The involvement of the ALIC in the pathophysiology of neuropsychiatric conditions is notorious, and dysfunctions in this portion produce cognitive and limbic feedback. Multiple diffusion imaging has evidenced that fractional anisotropy is abnormal in the ALIC of patients with OCD. Functional imaging studies have also shown that metabolic activity is increased in OCD patients at rest in nodes of the frontal subcortical circuits spanning the OFC, the PFC, and the thalamus.[16]

Aiming to identify connectome architecture more precisely, one study used a novel tract learning algorithm named Hierarchical Harmonic Filters for Learning Tracts from Diffusion Magnetic Resonance Imaging. This device tracks complex fiber bundles more finely than tractography. To better understand the region of the superolateral medial forebrain bundle in DBS for OCD and major depression, the technique was able to refine surgical planning discarding excess fibers, thus improving the accuracy of targeting in psychiatric disorders.[20]

Another study identified that variable stimulation of certain regions of the brain determines different clinical results. Thus, the specific regional stimulation of each individual can determine better prognoses.[15]

Discussion

The main focus of the present study was to analyze the main targets used in DBS in individuals presenting with OCD. In accordance with this systematic literature review, the ALIC connected to its different subparts is a promising region to achieve clinical response in patients affected by this neuropsychiatric condition.[19,26] As already elucidated in previous studies, the corticostriatothalamic networks cross the ALIC and its abnormalities are, therefore, involved in the pathophysiology of OCD.[28] In contrast, the posterior limb of the anterior commissure, the medial prosencephalic bundle, and the fibers of the inferior lateral fascicle were the targets most related to unsatisfactory results in DBS for OCD.[11,19,24,26]

Regarding its pathophysiology, OCD is associated with the basal ganglia, the caudate nucleus and putamen, the STN, the globus pallidus, and the substantia nigra. Alterations in the frontocorticostriatothalamocortical circuitry are the main evidence of the behavioral aspects of OCD, already confirmed in other research.[2,17,19] The excitatory impulses from the thalamus would be activated, since the caudate nucleus would not be able to stop the cortical impulses correctly, reaching the OFC. Therefore, the OFC would present an excitatory overload, which would make it impossible for the patient with OCD to

defocus attention from insignificant concerns.[2] This circuit is essential for behavioral or cognitive responses inasmuch as it processes information in the cortex.[29]

In healthy individuals, the direct pathway is constituted by striatal activation, through the glutamatergic output of the OFC and ACC, consequently increasing the excitatory glutamatergic output of the thalamus to the frontal cortex. This pathway, in turn, is recontroled by the indirect pathway, which does not happen satisfactorily in OCD patients. Consequently, the STN excites the globus pallidus interna and the substantia nigra reticulata, which inhibit the thalamus. Furthermore, when the STN receives projections from the cortex, it forms the hyperdirect pathway. With the hyperactivation of the orbitofrontal-subcortical pathway come excessive preoccupations with a threatening content, characterizing the obsessions and later the compulsions, compatible with the neutralization of the supposed threat.[11] As results have shown, the stimulation of this hyperdirect pathway has been promising in DBS for OCD.[23]

Patients with intractable OCD must meet the following eligibility criteria to be candidates for DBS: have OCD as the main diagnosis, have Y-BOCS $\geq$ 28 (or $\geq$ 14 if only obsessions or only compulsions are present), have made adequate use of at least 3 serotonin reuptake inhibitors (at least 1 with clomipramine), present with severe OCD symptoms even if they have already received psychomedical treatment for at least 5 years, have had at least 2 escalation strategies, present with refractoriness to treatment, have completed 20 hours of OCD-specific cognitive behavioral therapy, be between 18 and 75 years old, provide informed consent and awareness of surgical outcomes.[5]

From a neuroimaging perspective, HCP presented the architecture, organization, topography, and connectivity of the brain in MRI. Among its contributions to the scientific community, HCP has enhanced neuroimaging data, improving the understanding of various neuropsychiatric disorders.[30] The use of DBS for the treatment of both OCD and other brain disorders has benefited from these connectomic discoveries, since the high definition of specific networks provided by these neuroimaging and tractography data for each patient allows the refinement of surgical targeting and, as a consequence, a better therapeutic response.[31]

Searching for neurosurgical refinement, the individualization of DBS, possible because of the precision of neural networks among the various targets, enables the acquisition of a circuit that is more suitable for each patient according to their profile and symptom development. In parallel, the excitation of various portions of the involved tract excels over a fixed anatomical locus for a more favorable clinical response. Neuromodulation procedures must also target underlying dysfunctional neural networks that cause other behavioral effects. Hence, consideration of individual characteristics is critical for the most accurate choice of the common neuronal network.[11]

Conclusion

The main targets that provided the post-DBS clinical improvements found in the reviewed literature were the ALIC, the STN, the NAcc, the VC/VS, and the BNST. In addition to the presurgical choice of a target, insight into the common neural network and the underlying networks to which the various targets of choice relate is critical. Consequently, the modulation of this common tract from the different DBS stimulation sites is able to reduce OCD symptoms.

Furthermore, the variability of both the symptoms and the anatomical portion of the structures involved among individuals with OCD, as verified by neuroimaging, results in different profiles of specific connectivity. Therefore, the connectomic science, along with the advances in neuroimaging, play a fundamental role in the understanding of the affected neuronal networks. Because of this, before performing DBS, it is fundamental to do an individualized analysis of the neural connections in the brain for a more precise procedure. Given the facts presented herein, the combination of normative and patient-specific connectomes can result in a more personalized, and therefore more effective, DBS procedure for the treatment of refractory OCD patients, less susceptible to readjustments and side effects.

Conflict of Interests

The authors have no conflict of interests to declare.

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Literature Review: Role of Neurosurgery in Leptomeningeal Carcinomatosis

Crítica literária: Papel da neurocirurgia na Carcinomatose Leptomeníngea

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Arq Bras Neurocir 2023;42(4):e337–e342.

Abstract

Introduction Leptomeningeal carcinomatosis results from metastatic neoplastic cells that reach the leptomeninges through the cerebrospinal fluid. The presentation of the disease is variable, making prognosis challenging. However, the presence of intracranial hypertension is common, which has prompted new treatments to mitigate this effect.

Objective To report the role of neurosurgery in the treatment of leptomeningeal carcinomatosis, as well as its advances.

Methodology Literature review with a search of the PubMed database, between 2011 and 2021, using the following descriptors: *Neurosurgery*, *Leptomeningeal Carcinomatosis*, *Cerebrospinal* and *Treatment*. A total of 42 articles were found, 16 of which were selected.

Results The shunt insertion considerably improved the effects of cranial hypertension, increasing the average survival time of patients by 3.5 months after surgery. The

Keywords
- neurosurgery
- leptomeningeal carcinomatosis
- cerebrospinal
- treatment

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received
April 17, 2022
accepted
July 12, 2022
article published online
October 18, 2023

DOI https://doi.org/10.1055/s-0042-1758210.
ISSN 0103-5355.

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

Ommaya reservoir is also a viable option due to its convenience and safety. The V-Port, on the other hand, has overcome the challenges of conventional devices, with shorter operating times (42 minutes), smaller skin incisions, and no reports of postoperative infection.

Conclusion Devices for the treatment of leptomeningeal carcinomatosis have been steadily improving, simplifying surgical procedures and benefiting patients.

Resumo

Introdução A carcinomatose leptomeníngea resulta de células neoplásicas metastáticas que atingem as leptomeninges através do líquido cefalorraquidiano. A apresentação da doença é variável, tornando o prognóstico desafiador. No entanto, a presença de hipertensão intracraniana é comum, o que levou a novos tratamentos para mitigar esse efeito.

Objetivo Relatar o papel da neurocirurgia no tratamento da carcinomatose leptomeníngea, bem como seus avanços.

Metodologia Crítica literária com busca na base de dados PubMed, entre 2011 e 2021, utilizando os seguintes descritores: Neurocirurgia, Carcinomatose Leptomeníngea, Cefalorraquidiana e Tratamento. Foram encontrados 42 artigos, dos quais 16 foram selecionados.

Resultados A inserção do shunt melhorou consideravelmente os efeitos da hipertensão craniana, aumentando o tempo médio de sobrevida dos pacientes em 3,5 meses após a cirurgia. O reservatório de Ommaya também é uma opção viável devido à sua conveniência e segurança. O V-Port, por outro lado, superou os desafios dos dispositivos convencionais, com tempos de operação mais curtos (42 minutos), incisões cutâneas menores e sem relatos de infecção pós-operatória.

Conclusão Os dispositivos para o tratamento da carcinomatose leptomeníngea vêm melhorando constantemente, simplificando os procedimentos cirúrgicos e beneficiando os pacientes.

Palavras-chave
- neurocirurgia
- carcinomatose leptomeníngea
- cefalorraquidiano
- tratamento

Introduction

Leptomeningeal carcinomatosis (LC) was first reported in 1870 by the Swiss pathologist Karl Joseph Ebert as an attack on the meninges by metastatic tumors.[1] In the first publication on this disease, Ebert highlighted that the absence of localized signs and its variable nature made diagnosis difficult.[2] Then, in 1902, the term leptomeningeal carcinomatosis was proposed by Siefert, who described its clinical presentation.[1]

Leptomeningeal carcinomatosis, also known as meningeal metastasis, is a consequence of tumors that metastasize. The main tumors capable of evolving into a this metastasis are lung cancer, breast cancer, and malignant melanoma.[3,4] The most common symptoms include headache, nausea, and vomiting.[5] Some cases may also include fever, relative devascularization, signs of meningeal irritation, increased stiffness, and alteration of the cranial nerves; furthermore, in more severe cases, convulsions and changes in the level of consciousness may occur.[3] It is well known that the majority of symptoms presented by patients are a consequence of increased intracranial pressure (ICP) and the presence of hydrocephalus (HCP). Moreover, the increase in ICP and HCP reduces the effectiveness of treatment (uneven distribution of drugs given via intrathecal or intraventricular administration) and contributes to a poor prognosis in patients with leptomeningeal carcinomatosis.[5]

The most important diagnostic measures are clinical evaluation, magnetic resonance imaging (MRI), and analysis of the cerebrospinal fluid (CSF), as it is extremely important to perform a full neurological examination to correctly identify the pathology.[6,7] Disease progression can be well demonstrated through MRI, which is considered useful for the diagnosis of this disease.[8] Additionally, leptomeningeal carcinomatosis is being increasingly diagnosed in patients with cancer due to improved detection through the routine use of MRI.[9,10] It is important to stress that, in some cases, the diagnosis may not be totally accurate, when the disease is not suspected or when there are flaws in the imaging examinations.[11]

The incidence of leptomeningeal carcinomatosis normally varies according to the type of primary tumor, occurring in approximately 5 to 8% of patients with solid tumors and 5 to 15% of patients with hematologic neoplasia. Although nearly all systemic tumors metastasize into leptomeninges, the most common solid tumors in these instances include lungs, breasts, and melanoma. Incidence by tumor type is 5 to 8% for metastatic cancers of the breast, 9 to 25% for cancer of the

lungs (greater in small-cell lung carcinomas), and 6 to 18% for melanomas.[12]

As far as survival rates are concerned, approximately 10% may survive for a year, though this varies according to the type of primary tumor.[6] However, neither age nor gender were related to survival.[13] On the other hand, the average survival period of leptomeningeal metastasis patients who do not receive treatment is just 4 to 6 weeks, though survival may be extended to between 4 and 6 months, depending on the treatment afforded.[11]

The available options for the treatment of leptomeningeal metastasis are intrathecal (IT) chemotherapy, systemic therapy, radiotherapy, and surgery. In the case of HCP or symptoms resulting from focal lesions, surgery, and radiotherapy are recommended.[11] The factors influencing the choice of treatment depend on the type of primary tumor and the attack pattern of the disease. Accordingly, treatment must be personalized.[6]

Of the surgical methods available, the CSF shunt is an effective palliative procedure, capable of alleviating the symptoms and improving patients' quality of life.[14,15] Various shunt types exist, including the ventriculoperitoneal shunt (VPS) and the lumboperitoneal shunt (LPS). Both safely divert the flow of CSF from a ventricle or spinal arachnoid space to the peritoneal space. The indication for each shunt type should be made according to patients' condition, with the LPS being more suitable when communicating HCP is involved, and when the patient cannot be subjected to cranial surgery. The VPS, on the other hand, does not possess so many restrictions and may be used regardless of whether the HCP is communicating or noncommunicating.[5]

Accordingly, the aim of this study is to perform a literature review on the role of neurosurgery in the treatment of leptomeningeal carcinomatosis, to explain the advances and new possibilities that have been emerging for the treatment of the disease in the surgical setting.

Methodology

For the bibliographic review, a search of the PubMed database was made, encompassing publications between 2011 and 2021. The following descriptors were employed: *neurosurgery*, *leptomeningeal carcinomatosis*, *cerebrospinal*, and *treatment*. In total, there were 42 results, from which 16 articles were selected. Among the 26 articles that were excluded, 25 did not involve surgical treatment, and 1 was unavailable.

Results

Of the 16 articles selected for the current review, 9 produced consistent results and showed detailed data of the operations, as displayed in ►**Table 1**, 7 dealt with VPS and LPS, 1 was a case report on the Ommaya reservoir, and 1 was a case series study in respect of the V-Port.

In terms of shunt insertion technique, according to the literature analyzed, an improvement was seen in patients' conditions with increased rates of survival. In the retrospective study conducted by Zhao et al., in which 6 individuals were assessed, it was possible to note a reduction in intracranial hypertension, which consequently improved patients' quality of life.[17]

Additionally, according to the retrospective analysis of Kim et al.,[5] and the systematic review of Yoshioka et al., analyzing 70 and 14 individuals respectively, the shunt was effective in the treatment of HCP, improving patients' symptoms and prolonging their life expectancy.

In the study published by Murakami et al.,[14] it was shown that 87.5% (7⁄8) of patients obtained an improvement in headaches after the shunt had been inserted. Moreover, according to Lin et al.,[19] in their case-control study with a sample of 42 individuals, the insertion of the shunt had a significant impact on increased patient survival rates. In the systematic review conducted by Mitsuya et al.,[11] an average increase in life expectancy of 3.5 months was observed, postsurgery.

Thus, it is possible to determine that shunt surgery is effective in the treatment of the signs and symptoms of leptomeningeal carcinomatosis. According to the results of the study conducted by Le Rhun et al.,[10] the symptoms of 93% of patients improved on using the ventriculoperitoneal shunt.

Regarding complications involving shunt, the main ones listed by Kim et al.[5] involves hemorrhages, infections, shunt malfunction and risk of transferring cancerous cells to the peritoneal region. In their study, 51 patients underwent VPS, and 19 LPS, with 8 patients developing infections. Additionally, there was a need to review the procedure in 24% of the patients, either due to malfunction, infection, or symptoms of excessive drainage; 6 patients required a second revision surgery and 2 required a third.

As for the comparison of results obtained between the VPS and LPS, Kim et al.[5] observed that there was no significant difference in mean survival between patients undergoing VPS and LPS procedures. On the other hand, patients who underwent LPS required more evaluations for surgical revision, due to higher rates of malfunction and infection, according to a study by Kim et al.[5] Therefore, in the review by Zhao et al.,[17] they pointed out advantages in cooperate the use of LPS with Ommaya reservoirs.

In the study by Li et al.,[18] the Ommaya reservoir was considered a safe option for administering IT chemotherapy, all the more so when compared with administration via lumbar puncture. Other studies did not note any complications relating to the Ommaya reservoir. The advantages include it being a safer, more convenient procedure, with minimal pain for the patient and the possibility of draining the CSF with the device, if necessary.

According to Byun et al.,[9] the average duration of surgery is 16 to 38 minutes. Regarding the main complications, in the studies by Murakami et al.[14] and Magill et al.,[16] there were no reports of complications such as infection, misalignment or obstruction of the tube, intracranial hematoma, or liquor fistula. The incidence of infection was relatively low, all the more so when compared with the LPS, ranging from 5% to 8%. There was no need for revision surgery, in patients who received the Ommaya reservoir, 7.5% required revision surgery for VPS insertion due to an increase in ICP.

Table 1 Description of operations found in the literature

Author	Type of study	Sample	Operation	Outcome
Zhao et al. (2017)	Retrospective analysis	6	Shunt	Alleviation of ICP, reduction in mortality and incapacity through intracranial hypertension, and improved quality of life in patients with cancer.
Seon et al. (2019)	Retrospective analysis	70	Shunt	80% died during the follow-up period, 48% due to progression of the LC and 23% due to progression of the systemic disease; the reason for death was unspecified in 29% of cases. The VPS or LPS are effective for patients with HCP. There was an acceptable level of complications.
Murakami et al. (2018)	Clinical study	11	Shunt	An improvement in symptoms was observed in 9 patients, and severe headache relief was reported in 7 of the 8 patients. This is an effective palliative surgical option for alleviating the symptoms.
Lin et al. (2011)	Retrospective case-control study	24	VPS	The insertion of the VPS resulted in a very low rate of postoperative complications (8.3%), as well as the absence of infection and no perioperative deaths. The patients enjoyed a longer overall average survival.
Yoshioka et al. (2021)	Systematic review of case series	14	Shunt	The shunt is an effective procedure, including for the palliative treatment of HCP symptoms.
Mitsuya et al. (2019)	Systematic review of case series	31	Shunt	There was a functional improvement of 90.3% in patients, with an increase in survival of 3.5 months after shunt surgery.
Byun et al. (2018)	Case series	9	V-Port	This implantable reservoir was superior to the others as it is safe, easy to palpate and more durable to large-bore needles.
Li et al. (2020)	Case report	1	Ommaya reservoir	The Ommaya reservoir had a positive effect when used to administer IT chemotherapy.
Le Rhun et al. (2016)	Systematic review of case series	59	VPS	Symptoms improved in 93% of the patients; complications were observed in 11.8% of the patients.

Abbreviations: HCP, hydrocephalus; ICP, intracranial pressure; IT, intrathecal; LC, leptomeningeal carcinomatosis; LPS, lumboperitoneal shunt; VPS, ventriculoperitoneal shunt.

With the aim of refining the existing implantable reservoirs, Byun et al.[9] evaluated the V-Port (►**Fig. 1**), which demonstrated better performance than all the other options. It stood out on account of its safety and more simplified technical operation, with a low average duration of operation (42 min) and smaller skin incisions. Furthermore, the study did not observe complications such as infection, skin problems related to the V-Port, or postoperative intracranial hypertension. As for the need for revision surgery, out of a total of 9 patients, 7 (77.78%) were subjected to liquor drainage at least once to control ICP, and 2 patients (22.22%) did not have ICP controlled by intermittent drainage.

►**Table 1** summarizes the principal operations analyzed, indicating the study type, sample size, operation performed, and the respective outcome.

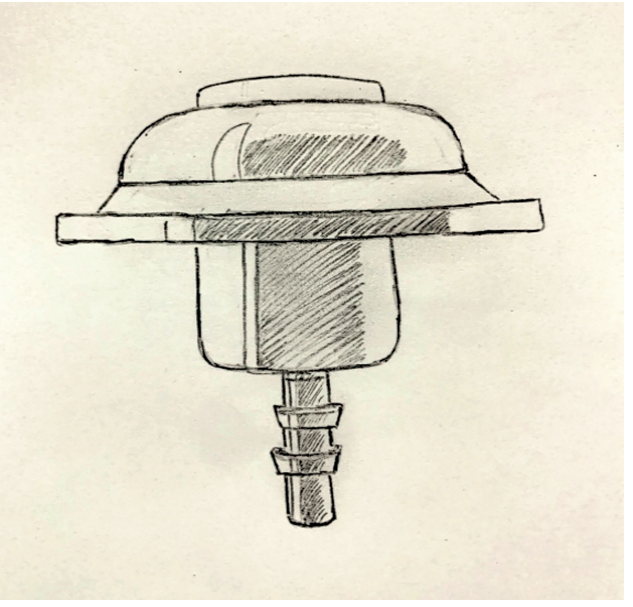

Fig. 1 Image of V-Port.

Discussion

Leptomeningeal carcinomatosis (LC) is the result of cancerous cells infiltrating the meninges, bringing about aseptic inflammation in these structures.[17] The growth of these cells

may be focal and/or diffuse, with the potential formation of different sizes of nodule.[8] This condition continues to be one of the most challenging complications of cancer, as it involves a complex diagnostic process, poor prognosis, negative impact on patients' quality of life, and uncertain responses to cytotoxic treatment or standard targeted therapy.[12]

Treatment

Treatment options for leptomeningeal carcinomatosis have been limited to the effective administration of drugs, although not all patients achieve a good outcome with these types of therapy. Therefore, after the disease is diagnosed, the ideal treatment continues to be the consensus recommendation of specialists in the respective cases. However, although treatment options remain limited, advances in molecular and genetic studies into leptomeningeal carcinomatosis have been generating new, clinically effective treatment options, and better ways to predict patients' response to treatment.[12]

Ommaya Reservoir

One of the treatment options for leptomeningeal carcinomatosis is the administration of IT chemotherapy. This method manages to circumvent the blood-brain barrier and minimize the systemic side effects. The drugs may be administered via lumbar puncture or through the surgical insertion of a reservoir which, with the use of a catheter, directly feeds the ventricular system (Ommaya reservoir). The most commonly used drugs are methotrexate (a folate antagonist), thiotepa (an alkylating agent), cytarabine (a pyrimidine analogue), and sustained-release liposomal cytarabine.[12]

In a retrospective analysis of 50 patients, 34 received treatment (IT chemotherapy with liposomal cytarabine or methotrexate, systemic chemotherapy, or radiotherapy) and 16 simply received support and palliative measures. The results showed that overall average survival for patients receiving treatment was 21.2 weeks, compared with 6.38 weeks for patients who did not treat the disease.[13]

Various retrospective studies have demonstrated the positive impact on the survival rates of patients receiving conventional chemotherapy treatment.[12] However, in the quest to find more effective drugs, the study conducted by Yoshioka reported survival of a year for patients who received targeted molecular treatment postoperatively, compared with 3.7 months for patients receiving only radiotherapy.

There are limitations to the conventional methods of antineoplastic treatments, given that they are uncapable of attaining effective concentrations due to the blood-brain barrier. Accordingly, Ommaya reservoirs tend to be more advantageous in administering IT chemotherapy, both in terms of the operation and the safety of the patient.[18]

Thus, the insertion of an Ommaya reservoir for LC is a surgical option for the administration of IT chemotherapy. However, one study found that 8 out of 107 patients (7.5%) who received the Ommaya reservoir for LC-related HCP, required revision surgery to insert a VPS due to the increase in ICP.[14]

Ventriculoperitoneal Shunt (VPS) and Lumboperitoneal Shunt (LPS)

As far as the surgical insertion of shunts is concerned, studies have shown that this technique can alleviate symptoms arising from high ICP. Of the 5 patients treated using shunt surgery, observed in a retrospective analysis, all of them displayed the shunt in the computed tomography of the skull after the operation. The positioning of the tube was correct and there was no operative bruising. Furthermore, no shunt-related infections were reported for any of the patients.[17]

One study indicated there are three aspects that contribute to a better outcome after shunting, namely: treatment with TKIs (Epidermal growth fator receptor [EGFR] tyrosine kinase inhibitors), good ECOG (Eastern Cooperative Oncology Group) performance status (the scale evaluates how the disease affects patients' everyday life skills) and controlled extracranial cancer. Of the two shunt types, lumboperitoneal and ventriculoperitoneal, the former is more effective in unfavorable conditions, precisely because it is less invasive than the latter.[11]

The VPS technique was assessed in 59 patients suffering from leptomeningeal carcinomatosis with a condition of HCP, 40 with brain metastasis and 19 with primary brain tumors. The average duration of the surgery was 50.4 minutes. Symptoms improved in 93% of the patients. Following an average follow-up of 6.3 months, 7 patients suffered complications (11.8%). The average survival of patients who received the shunt was 6.4 months. The LPS, which is less invasive, is also a good option for the treatment of intracranial hypertension.[10]

Even though shunt surgery is a relatively simple neurosurgical procedure, the number of patients receiving it is lower than the rate of increase in ICP. As the prognosis of patients with LC is poor, for the most part the treatment of choice is not surgical intervention. Moreover, complications with hemorrhaging, infection, shunt malfunction, and the risk of transferring cancerous cells to the peritoneal region cause some doctors to opt not to carry out CSF shunts on their patients.[5]

In one study, 70 patients who had previously had cancer (lung cancer, breast cancer, among others) were analyzed. The main brain tumors were glioma and medulloblastoma. A total of 51 patients received a VPS, while 19 had a LPS. Following surgery, preoperative symptoms diminished in 35 patients, remained stable in 24, and did not improve in 11 patients. Shunt malfunctions and infections occurred in 8 patients, and 17 patients had to be assessed due to shunt malfunction or excessive drainage. Average overall survival was 8.7 months from the diagnosis of LC and 4.1 months after shunt surgery.[5]

Both the VPS and the LPS succeeded in safely diverting the flow of CSF from a ventricle or spinal arachnoid space to the peritoneal space. Each shunt system has its advantages and disadvantages, and, for this reason, the choice should be tailored to each patient. In general, the LPS is used in cases of communicating HCP and in patients who are not suitable for cranial surgery (i.e., idiopathic intracranial hypertension with ventricular cleft) or who wish to avoid cranial surgery. The VPS, on the other hand, can be used regardless of whether the HCP is communicating or noncommunicating.[5]

A study analyzed shunt surgeries performed on 11 patients with an average age of 58. The average Karnofsky performance status (KPS) was 40; 8 patients (73%) were treated with the VPS and 3 (27%) with the LPS. There were no reports of postoperative infections in any of the patients. The average KPS was 60 after shunt surgery. Furthermore, none of the patients developed infiltration of cancerous cells to the peritoneal region after surgery.[14]

It may be concluded, therefore, that surgery to insert the VPS or LPS shunt is useful for patients with HCP caused by LC, improving their symptoms and prolonging overall survival.[5] The shunt proved to be an effective therapeutic procedure with regard to the alleviation of symptoms given that 100% of patients showed improvedKPS.[15] Therefore, this procedure should be considered for palliative surgical treatment of leptomeningeal carcinomatosis.[14]

Advances in Treatment

New improved techniques aiming to diverting CSF are in development, one of which is the insertion of an on/off valve in conjunction with the programmable ventriculoperitoneal valve (RO-VPS). The major advantage of this system is its reduced handling, as well as enabling the management of the concentration of chemotherapy drugs in the CSF in a more stable way.[19]

To overcome the obstacles involved with the Ommaya reservoir, Byun et al. developed the V-port, which is equipped with a noncollapsible port with a titanium connector where the ventricular catheter is inserted. This device is made out of polysulfones and epoxy instead of silicon, making it more durable to the various bores and larger needles, as well as being more easily palpated and having a lower risk of drug leakage. It also stood out because of the short duration of operations reported by neurosurgeons, the absence of complications resulting from the V-Port, and the lack of malfunction complaints.[9]

Treatment Decision

Lastly, whenever viable, treatment with the intraventricular shunt was the preferred option over IT therapy in the lumbar region, as per the study performed. In the event of shortcomings with lumbar puncture, 22.5% preferred IT chemotherapy and only 15.5% believed that radiotherapy should always be performed.[6]

Conclusion

Leptomeningeal carcinomatosis continues, therefore, to be a challenge to medicine due to the difficulty of diagnosis and treatment. However, it should be noted that the field of neurosurgery has been developing techniques capable of improving its clinical condition and increasing both the quality of life and life expectancy of patients. Furthermore, the available neurosurgical procedures have different purposes. Shunts are considered an effective option in the management of HCP, while reservoirs are used for infusion of drugs and are not very viable for the treatment of HCP. Therefore, neurosurgery plays a significant role in the treatment of meningeal carcinomatosis, precisely because it is able to improve the patients' prognosis.

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Traumatic Carotid Artery Dissection — A Case Report

Dissecção traumática de artéria carótida – Um relato de caso

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Arq Bras Neurocir 2023;42(4):e343–e347.

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Abstract

Traumatic carotid artery dissection (TCAD) usually occurs after a direct cervical trauma or blunt trauma that causes hyperextension and excessive rotation of the neck. The most frequent presentation of TCAD is stroke, with 80% of patients developing a stroke in the first week after the trauma. Recent data indicate that symptoms start later in non-survivors (19.5 hours after trauma) compared with survivors (12.5 hours). In this case report, a young boy, 14 years-old, developed TCAD after he fell from his bike. He developed ischemic stroke symptomatology in the eighth day of hospitalization, with full recovery of symtoms after acetylsalicylic acid (AAS) administration. The use of antithrombotic medication is recommended, aiming for better neurological outcomes and prevention of stroke in TCAD patients, as highlighted by our case. However, the treatment recommendations are based on observational studies and expert opinion, owing to the lack of concrete data on the treatment of carotid artery blunt trauma. New studies and data are required to improve diagnosis and treatment of TCAD.

Keywords
- traumatic carotid artery dissection
- pediatrics

Resumo

A dissecção traumática da artéria carótida (TCAD) geralmente ocorre após um trauma cervical direto ou contuso que gera hiperextensão e rotação excessiva do pescoço. A apresentação mais frequente da TCAD é o acidente vascular cerebral (AVC), com 80% dos pacientes desenvolvendo um AVC na primeira semana após o trauma. Dados recentes indicam que os sintomas começam mais tardiamente nos não sobreviventes (19,5 horas após o trauma) do que nos sobreviventes (12,5 horas). Apresentamos o caso de um jovem de 14 anos que sofreu TCAD após cair da bicicleta. Ele desenvolveu sintomatologia de AVC isquêmico no oitavo dia de internação, com recuperação completa dos sintomas após administração de ácido acetilsalicílico (AAS). O uso de medicação antitrombótica é recomendada, visando melhores resultados neurológicos e prevenção do AVC em pacientes com TCAD, como destacado em nosso caso. No entanto, as recomendações de tratamento são baseadas em estudos observacionais e opinião de especialistas, devido à falta de dados concretos sobre o tratamento do trauma contuso da artéria carótida. Novos estudos e dados são necessários para melhorar o diagnóstico e tratamento do TCAD.

Palavras-chave
- dissecção da artéria carótida interna
- pediatria

received
April 4, 2022
accepted
June 21, 2022
article published online
October 20, 2023

DOI https://doi.org/10.1055/s-0042-1755453.
ISSN 0103-5355.

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

Introduction

Internal carotid artery (ICA) dissection can occur spontaneously or as a result of a traumatic event. These events are separate clinical entities, with different mechanisms and predisposing factors. Traumatic carotid artery dissection (TCAD) is usually secondary to blunt trauma that causes excessive hyperextension or rotation of the neck or a direct blow to the anterolateral aspect of the neck.[1] It is present in about 2.6% of all severe blunt trauma patients, and in 2.7% of patients with multisystemic traumatism.[2] Traumatic carotid artery dissection can be asymptomatic in some cases, but the majority of patients develop ischemic stroke sooner or later. Mortality can be as high as 40%.[3] The onset of symptoms is highly variable, initiating immediately (in up to 10% of all cases) or only after several months.[1,3–5] As mentioned previously, risk factors for spontaneous carotid artery dissection (SCAD) and TCAD differ, and conditions such as systemic arterial hypertension, cigarette smoking, collagen-related diseases, and other general vascular risk factors, not always contribute to the occurence of TCAD, especially in younger patients.[4] We describe the case of a young male patient with TCAD and delayed onset of symptoms.

Case Report

A previously healthy 14-year-old male patient came to the emergency room after falling from his bike while riding. He reported posttraumatic amnesia, which led to a computed tomography (CT) scan that revealed a small extradural hematoma (8 mm) in the right temporal pole (►**Fig. 1**), without any associated fractures, and a small hypodense area in the right frontal lobe, seemingly without cause. The neurosurgical team was called to evaluate this patient, and no surgery was indicated, but he was admitted for observation. Two days after hospitalization, a sequential CT scan was performed, confirming that the epidural hematoma remained stable, and the patient asymptomatic. On the 5th day of admission, the patient developed aphasia and paresis in the left arm, followed by loss of consciousness, which led to the presumptive diagnosis of seizure, and treatment with intravenous phenytoin (20 mg/Kg), followed by maintenance dosage. On the 8th day of hospitalization, the patient presented a new episode of aphasia, but this time with hemiparesis on the left side. A new course of phenytoin was prescribed, but without resolution of the symptoms. A magnetic resonance imaging (MRI) was performed (►**Fig. 2**), demonstrating an area that was hyperintense in the diffusion-weighted imaging (DWI), and hypointense in the apparent diffusion coefficient (ADC) map, suggesting an acute ischemic area, with correspondence on fluid attenuation inversion recovery (FLAIR). A complementary computed tomography angiography (angio-CT) scan was performed (►**Fig. 3**), demonstrating an imagiologic pattern suggestive of carotid artery dissection. The artery caliber started to reduce at the C1 segment, keeping the smaller size up to the C6 segment, with no signs of pseudoaneurysm or rupture of the vessel, with the dissection being classified as type 2 on the Denver scale. After the diagnosis was made, treatment with 100 mg of acetylsalicylic acid was immediately initiated. The patient evolved with amelioration of the symptoms after 5 days of pharmacological treatment and physical therapy, being discharged thereafter.

At the outpatient follow-up consultation 1 month after discharge, the patient referred no symptoms, with resolution of every neurological deficit. The patient remains using the same medication, and a 3-month follow-up angio-CT scan demonstrated that the dissection remained stable, with no need for further treatment indication. Clinical follow-up with the neurosurgery team is ongoing.

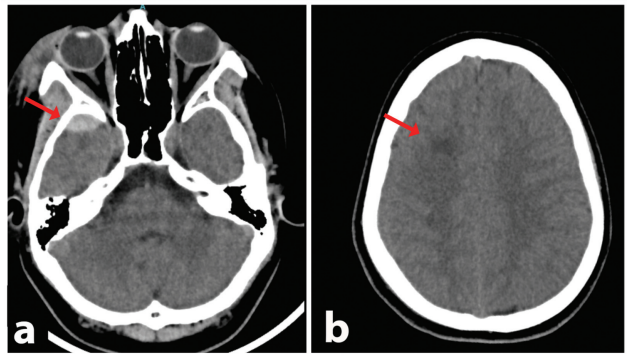

Fig. 1 Initial head computed tomography scan, performed on admission. **(a)** Axial plane image, showing a small (8 mm) epidural hematoma in the middle cranial fossa on the right side (red arrow). **(b)** Axial plane image, showing a small, nonspecific, hypodense subcortical lesion in the right frontal lobe (red arrow). Aside from the aforementioned features, no alterations could be seen.

Discussion

About 1 to 2.6% of blunt trauma patients develop TCAD.[2] Dissection occurs when the artery is excessively stretched, or it may result from a direct blow to the anterolateral aspect of the neck. The stretching mechanism usually occurs during excessive hyperextension and contralateral rotation of the head and is probably associated with the direct contact of the artery with the lateral processes of the cervical vertebrae in the majority of cases, which contributes to the artery's injury. These phenomena lead to laceration of the artery's intimal layer, which can be worsened by its blood flow. The trauma mechanisms involved are diverse, going from high speed automobilistic accidents to more trivial traumas, such as falling from a bike.[1,6–8] The main risk factors for TCAD differ from those related to SCAD, with the conventional cardiovascular risk factor being unimportant in the former, with the exception of diagnosed migraine and connective tissue disease.[1,4]

The incidence of stroke after TCAD can be as high as 60 to 80%, depending on the population studied.[1,3] The onset of the ischemic symptoms varies widely, from immediate onset to symptoms that take months to present. Nevertheless, it usually occurs in between the 1st hour and 7 days after the trauma.[5,9–12] The average onset time of symptoms is also different in patients that survive from those that do not survive (12.5 vs 19.5 hours, respectively). Since immediate

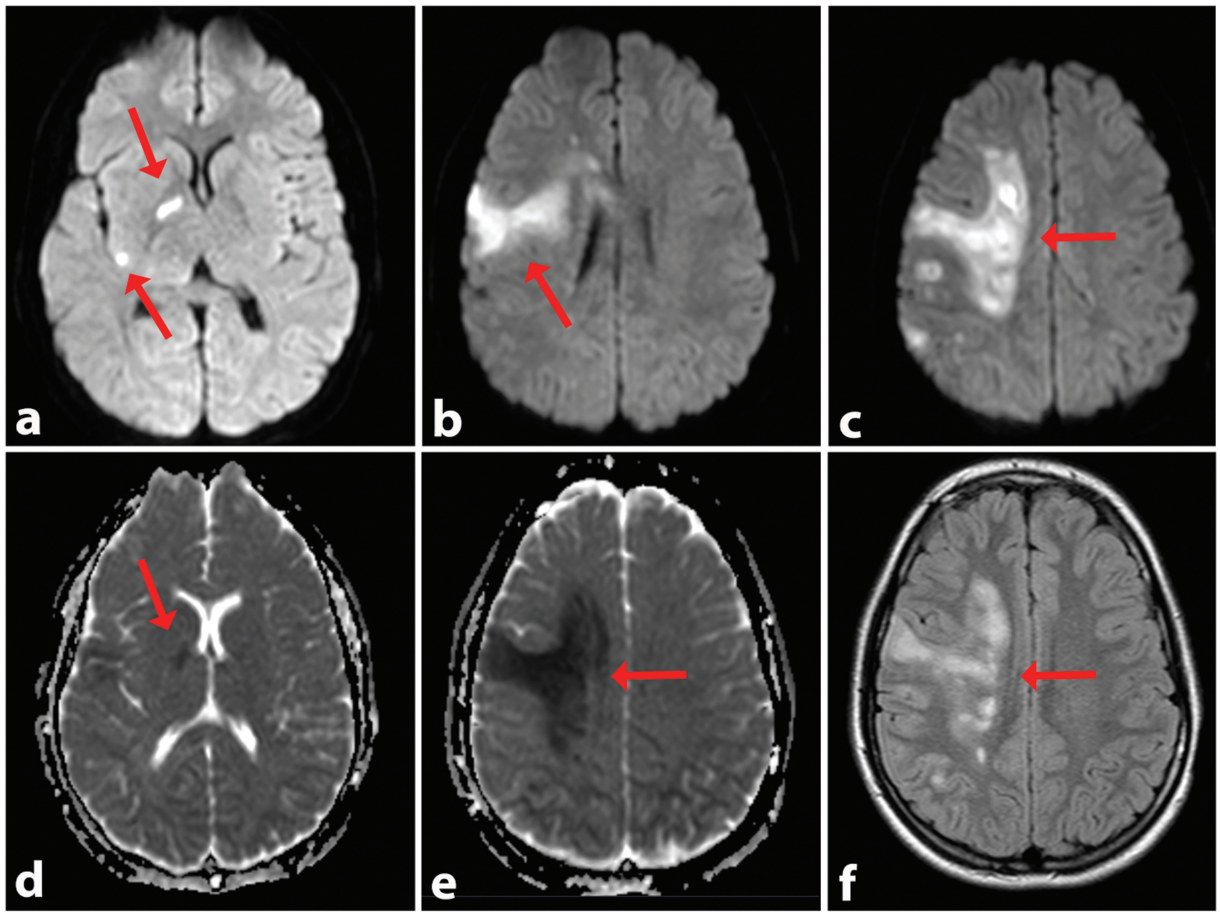

Fig. 2 Magentic resonance imaging performed on the eighth day. All figures are on the axial plane. **(a,b,c)** Diffusion-weighted imaging imaging showing hyperintense areas on the right middle cerebral artery vascular territory, suggestive of acute ischemia (red arrows). **(d,e)** Apparent diffusion coefficient map imaging showing hypointense signal on the middle cerebral artery vascular territory (red arrows), confirming the suspicion of acute ischemia. **(f)** Fluid attenuation inversion recovery sequence, evidencing perilesional edema in the ischemic territory (red arrows).

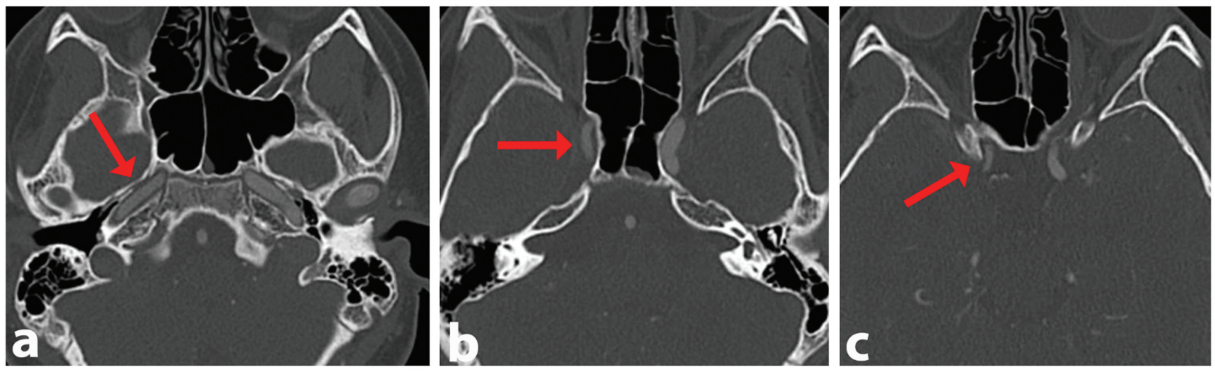

Fig. 3 Angio computed tomography scan. All figures are on the axial plane. **(a)** This image shows a subtle narrowing in the petrous segment of the right internal carotid artery (ICA) (red arrow). **(b)** Shows a more pronounced narrowing of the right ICA (red arrow). **(c)** Shows a narrowing in the intracranial portion of the right ICA (red arrow).

onset of symptoms occurs in only 10% of cases, serial repetition of the neurological examination is extremely important in diagnosis and clinical follow-up.[1]

In severe trauma, screening for TCAD is often recommended since, although uncommon, TCAD has high morbidity and mortality rates (up to 43%). The gold standard for TCAD diagnosis is digital subtraction angiography; however, angio CT scan is also indicated for screening, albeit with some controversy regarding its sensitivity.[1,3] Aside from ischemic symptoms, TCAD can also present with Horner syndrome (due to a cervical hematoma mass effect) and cranial nerve palsy, but these are not as common. Additionally, the Denver

Table 1 Blunt carotid arterial injury grading scale

Injury grade	Description	AIS 90 score	
		Intracranial	Cervical
I	Luminal irregularity or dissection with < 25% luminal narrowing	3	3
II	Dissection or intramural hematoma with > 25% luminal narrowing, intraluminal thrombus, or raised intimal flap	3	3
III	Pseudoaneurysm	3	3
IV	Occlusion	4	3
V	Transection with free extravasation	5	4

[a]Add 1 point if neurologic deficit (stroke) is not head-injury related.

group described a variety of signs and symptoms associated with carotid lesions. Cervical, buccal or nasal bleeding, carotid murmur, growing cervical hematoma, focal neurological deficits and neuroimaging studies (MRI or CT scans) with ischemic findings, in the context of trauma, are highly suggestive of TCAD, and indicate the need for further investigation even in trauma cases that are not considered severe.[1,13] In our case, no clinical signs were present initially, or they were attributed to the epidural hematoma, a fact that withheld earlier investigation for TCAD. However, the initial CT scan showed a small, nonspecific hypodense lesion on the right frontal lobe (►**Fig. 1b**) that was not given much attention at that moment. In retrospect, it is clear that it was an ischemic finding, highly suggestive of TCAD. This goes to show that a small inattention can lead to a delayed diagnosis of a severe disease.

The Denver group also developed a scale that quantifies the risk of stroke and death in patients with blunt carotid trauma (►**Table 1**). Grade-I lesions are determined as an angiographic aspect of irregularity of the wall of the vessel or dissection causing at least 25% of luminal stenosis. Grade-II lesions include those with intraluminal thrombus, elevated intimal flap, dissections, or intramural hematoma with narrowing of luminal vessel bigger than 25%. The presence of a pseudoaneurysm is classified as grade III, and vessel occlusion as grade IV. When transection of the vessel occurs, it is defined as grade V.[6,9]

The treatment for TCAD is still a matter of debate. The majority of the studies are observational, and the recommendations are derived from these studies as well as expert's opinions. One point of convergence is that the use of antithrombotic drugs, usually acetylsalicylic acid (AAS), is superior to expectant conduct. Surgery or endovascular carotid treatment can also be performed, but its role is still not well established. Due to the severity of the disease and the possibility of progression of the dissection, some authors recommend performing a follow-up angiographic study at the end of the higher risk period for development of neurological symptoms (7th day).[7,14]

Conclusion

Traumatic carotid artery dissection has a low incidence but is capable of resulting in serious neurological deficits and death. Fortunately, in the present case, the delay in the TCAD diagnosis did not significantly worsen the patient's outcome, but one should remember that this was an exception. The delay happened even in the presence of a highly suggestive sign of TCAD, which goes to show that suspicion levels should always be high in trauma patients. Ours was not, and so the diagnosis was delayed for several days. After diagnosis, the treatment should be promptly initiated. There are no clear and quality evidence-based treatment indications for the diagnosis and management of TCAD patients. We would like to highlight the lack of evidence about TCAD treatment in the literature as well as the need for further research on the subject.

Conflict of Interests

The authors have no conflict of interests to declare.

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Reactivation of Tumor-like Chagas Disease in the Central Nervous System in Cardiac Transplant Patients: A Case Series and Literature Review

Reativação pseudotumoral da doença de Chagas no sistema nervoso central em pacientes transplantados cardíacos: Série de casos e revisão de literatura

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Arq Bras Neurocir 2023;42(4):e348–e353.

Abstract

Introduction Chagas disease is an important public health problem in Latin American countries, affecting ~ 6 million people within the region. In patients with chronic Chagas disease who undergo some type of immunosuppression reactivation of the acute form may occur, and manifestations involve many organs, including the central nervous system. Tumor-like brain reactivations are well described in patients with acquired immunodeficiency syndrome; however, this is a very rare event among Chagasic patients immunosuppressed after a heart transplantation.

Case Report We describe three cases of cardiac transplant patients who had a tumor-like intracranial lesion, whose biopsies were compatible with Chagas disease. All 3 patients were treated with benznidazole, and 2 of them presented parameters of cure after 60 days of treatment, while 1 required a 2nd cycle of treatment.

Discussion A tumor-like Chagas disease reactivation in the central nervous system may happen in heart-transplant patients and, due to the multiple differential diagnoses, we believe that brain biopsies should be considered when feasible.

Keywords
- Chagas disease
- central nervous system diseases
- heart transplantation
- immunosuppression therapy

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received
June 6, 2022
accepted
June 21, 2022

DOI https://doi.org/10.1055/s-0042-1756210.
ISSN 0103-5355.

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

Resumo

Introdução A doença de Chagas é um problema de saúde pública relevante nos países da América Latina, afetando aproximadamente 6 milhões de pessoas na região. Em pacientes com a forma crônica da doença submetidos a algum tipo de imunossupressão, a reativação da forma aguda pode ocorrer e cursar com manifestações que envolvem vários órgãos, incluindo o sistema nervoso central. A reativação cerebral pseudotumoral é bem descrita em pacientes imunossuprimidos pela síndrome de imunodeficiência adquirida; contudo, é um evento raro entre os pacientes imunossuprimidos após transplante cardíaco.

Relato de caso São relatados três casos de transplantados cardíacos que apresentavam uma lesão tumoral intracraniana, cujas biópsias eram compatíveis com a doença de Chagas. Todos os 3 pacientes foram tratados com benznidazol, e 2 deles apresentaram parâmetros de cura após 60 dias de tratamento, enquanto 1 exigiu um 2° ciclo de tratamento.

Discussão A reativação pseudotumoral da doença de Chagas no sistema nervoso central pode acontecer em pacientes submetidos ao transplante cardíaco e, devido aos múltiplos diagnósticos diferenciais, acreditamos que a biópsia cerebral deve ser considerada quando viável.

Palavras-chave

- doença de Chagas
- doenças do sistema nervoso central
- transplante de coração
- imunossupressão

Introduction

Chagas disease (CD) or American trypanosomiasis is a zoonosis caused by the protozoan *Trypanosoma cruzi*. It is an important public health problem in Latin American countries, affecting ~ 6 million people within the region.[1] This disease presents an acute phase that is usually asymptomatic or oligosymptomatic and, in the absence of specific treatment, lasts 8 to 12 weeks. Once the host's immune response is able to reduce the replication of the parasite, the patient enters the chronic phase, which persists for his entire life. The chronic form of the disease comprises an asymptomatic latency period that can last for several years. The symptomatic chronic manifestation occurs in ~ 20 to 30% of those infected, with heart and gastrointestinal disease being its most common forms.[2]

The heart is the most affected organ in the chronic symptomatic phase of CD.[3] In patients with the chronic form and some type of immunosuppression, reactivation of the acute form may occur with manifestations involving various organs, such as the heart, skin, and the central nervous system. In advanced cases of Chagasic cardiomyopathy, heart transplantation is the chosen procedure, and these patients are at risk of reactivation as a result of the immunosuppressant therapy.

Three cases of patients who have undergone heart transplantation due to Chagasic cardiomyopathy and evolved with neurological symptoms are described. They underwent brain biopsy, and the result was compatible with cerebral CD. Furthermore, a literature review was performed through the PUBMED database searching for articles in English, Portuguese, and Spanish, with no date limit. The descriptors used were: *Chagas disease*, *American trypanosomiasis*, *central nervous system*, *cardiac transplant* and *immunosuppression*.

Case Reports

Case 1

A 47-year-old male patient was admitted to the emergency room after his first generalized tonic-clonic seizure. He was alert, oriented, afebrile, without focal neurological deficits and without neck stiffness. The patient had undergone a heart transplant 7 months prior to admission due to Chagasic cardiomyopathy. He reported daily headache that started after the transplant, with a worsening in intensity in the last 3 days, associated with apathy and behavioral changes. In addition, he had chronic renal failure and cataracts. The patient was taking the following medications: cyclosporine 200 mg/day, mycophenolate mofetil 2 g /day, tacrolimus 4 mg/day, prednisone 10 mg/day, diltiazem 10 mg/day, simvastatin 20 mg/day, metformin 500 mg/day, alendronate 70 mg/week, calcium carbonate 1,000 mg/day, and sulfamethoxazole-trimethoprim 400/80 mg/day.

The computed tomography (CT) scan without contrast showed left frontal hypodensity associated with perilesional edema. The magnetic resonance imaging (MRI) showed an expansive left frontal lesion with hyposignal in T1, heterogeneous enhancement by gadolinium, perilesional edema, and absence of restriction to diffusion (►**Fig. 1**). The patient underwent a lumbar puncture that showed an opening pressure of 23 cmH2O, and the other results of biochemistry, cytology, and microbiology were normal. Serological tests for toxoplasmosis and human immunodeficiency virus (HIV) tests were negative.

Due to the atypical lesion in an immunosuppressed patient with a history of CD, a brain open biopsy was chosen. Concomitantly, empirical treatment with benznidazole 300 mg/day was started. Histology showed neutrophilic and histiocytic inflammatory infiltrate, mainly perivascular, associated with amastigotes nests, compatible with CD

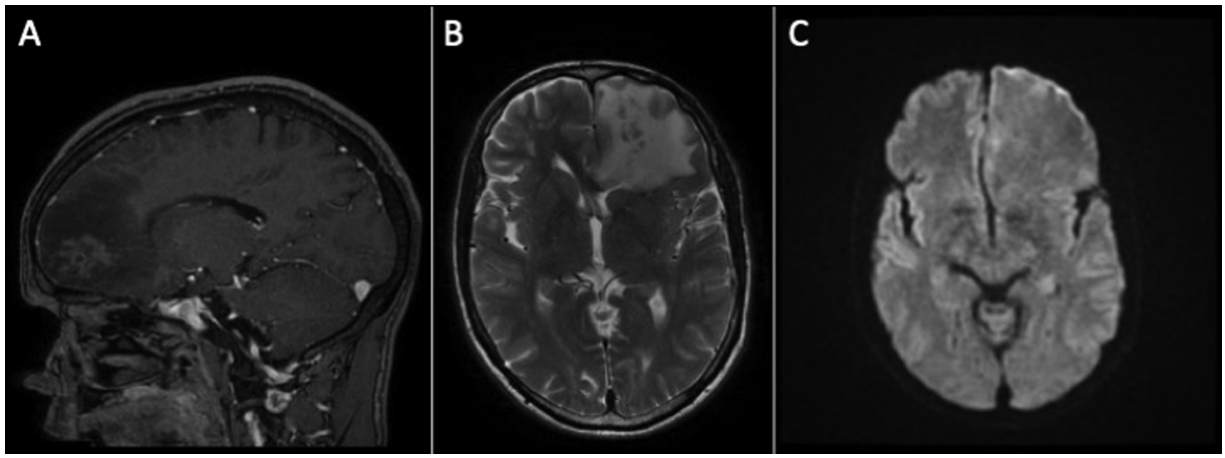

Fig. 1 Brain magnetic resonance imaging (MRI) of the case 1. (A) T1-weighted MRI with gadolinium. Note the heterogeneous contrast enhancement. (B) T2-weighted MRI shows heterogeneous lesion with intense perilesional edema. (C) Diffusion-weighted imaging MRI showing absence of restriction on diffusion.

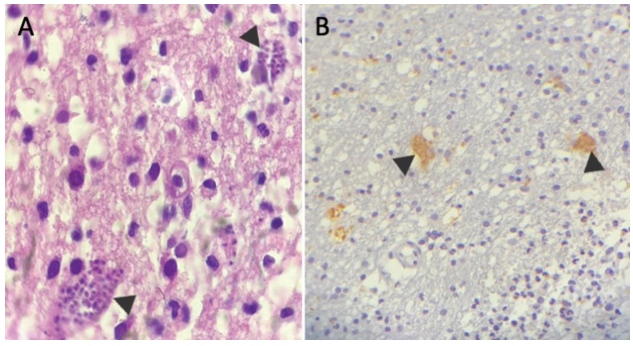

Fig. 2 (A) Hematoxylin-eosin stain with inflammatory infiltrate and amastigotes nests (arrows). (B) Immunohistochemistry analysis positive for the presence of *T. cruzi* (arrows).

(►**Fig. 2A**). Immunohistochemistry confirmed the diagnosis (►**Fig. 2B**). The patient was treated with benznidazole for 60 days and showed complete improvement. He had no new neurological symptoms after 3 years of follow-up.

Case 2

A 48-year-old female patient was admitted to the emergency department with left fasciobraquiocrural hemiparesis and dysarthria initiated in the last hours. There was a report of progressive headache of about 4 months of evolution and chronic hepatitis B being treated with entecavir. She underwent a heart transplant 4 months before admission as a result of Chagasic cardiomyopathy. The immunosuppression regimen was performed with cyclosporine 200 mg/day, prednisone 10 mg/day, and mycophenolate mofetil 2 g/day.

Image propaedeutic showed an extensive lesion in the right temporo-parietal region with the predominantly annular enhancement by gadolinium (►**Fig. 3**). Serological tests for toxoplasmosis and HIV tests were negative. We opted for an open biopsy of the lesion. In the hematoxylin-eosin stain, numerous parasites were observed forming amastigotes nests (►**Fig. 4**). Immunohistochemistry confirmed the diagnosis of reactivation of CD. After diagnosis, treatment with benznidazole was started. After completing 60 days of treatment and partial improvement, the patient presented a further worsening of the deficit. Magnetic resonance imaging examination showed worsening of the lesions. The patient underwent a new benznidazole cycle with improvement of the condition but maintained a sequel motor deficit and dependence for basic activities.

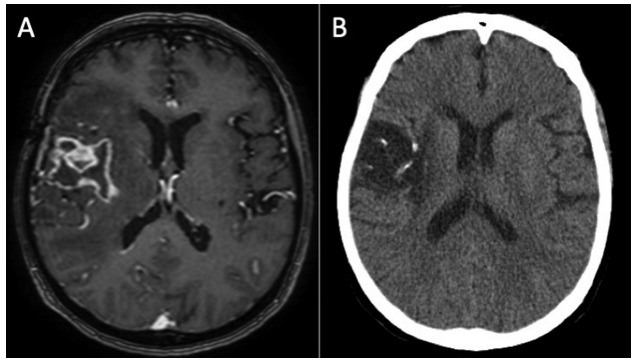

Fig. 3 (A) Magnetic resonance imaging of the brain in axial section in T1-weighted sequence with the presence of an expansive lesion with hyposignal and predominantly annular enhancement by gadolinium. (B) Computed tomography of the skull in axial section at the same level. Note non-specific hypodensity associated with intralesional bleeding.

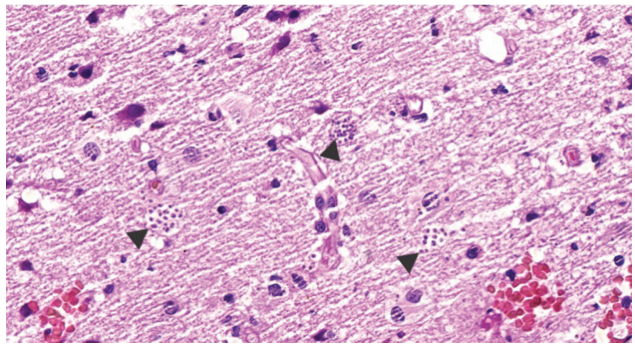

Fig. 4 Hematoxylin-eosin stain showing several nests of amastigotes (arrows) associated with inflammatory infiltrate.

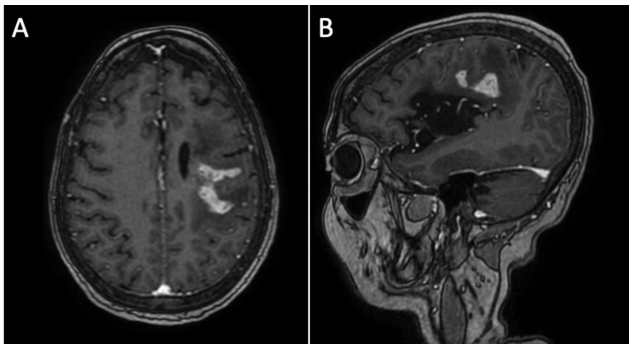

Fig. 5 Magnetic resonance imaging of brain in axial (A) and sagittal (B) section in T1-weighted sequence with presence of expansive lesion with hyposignal and heterogeneous enhancement by gadolinium.

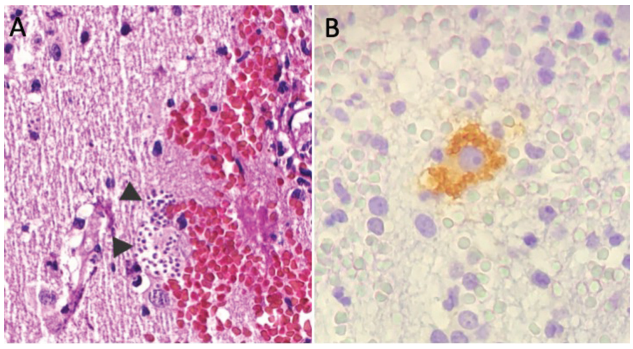

Fig. 6 (A) Hematoxylin-eosin stain with intracellular amastigotes (arrows) adjacent to an area of hemorrhagic necrosis. (B) Positive immunohistochemistry for *T. cruzi*.

Case 3

A female patient, 67 years-old, presented with a sudden onset of aphasia. She had undergone a heart transplant 4 months before admission due to Chagasic cardiomyopathy and used prednisone 5 mg/day, cyclosporine 150 mg/day, mycophenolate mofetil 1 g/day, and prophylaxis for neurotoxoplasmosis with trimethoprim sulfamethoxazole. Propaedeutics demonstrated a heterogeneous right frontal-temporal lesion with enhancement by paramagnetic contrast (►**Fig. 5**). Cerebrospinal fluid was not positive for research of *T. cruzi*, and biochemistry as well as cytology were normal. Serological tests for toxoplasmosis and HIV tests were negative. Cerebral open biopsy showed necrotizing encephalitis with the presence of amastigotes, and immunohistochemistry was positive for CD (►**Fig. 6**). The patient underwent treatment with benznidazole and maintained motor aphasia after 6 months of follow-up.

Discussion

In Latin America, Chagasic cardiomyopathy is the third most common cause of indication for heart transplantation.[4] Posttransplant immunosuppressive therapy increases the risk of *T. cruzi* infection reactivation, whose incidence after transplantation varies from 8 to 90%. This event is defined as an increase in parasitemia that can be detected by direct parasitological techniques or polymerase chain reaction (PCR), even in the absence of symptoms.[1,5,6]

Reactivation of CD is associated with immunodeficiency states, such as those caused by the acquired immunodeficiency syndrome (AIDS), hematological neoplasms, corticosteroid therapy, and other immunosuppressants, including in the context of solid organ transplantation.[7] General clinical manifestations observed include fever, myocarditis, symptoms suggestive of rejection or dermatological manifestations, including inflammatory panniculitis and skin nodules.[4] When the central nervous system is involved, the most common manifestations include headache, vomiting, seizures, and focal neurological deficits. The involvement of the central nervous system in reactivation is well described for patients with AIDS, accounting for up to 80% of cases.[8] In these patients, the most common form of presentation is meningoencephalitis, which may also present itself as tumor-like expansive lesions similar to abscesses, described by some authors as cerebral chagoma.[7,8] Cerebral chagoma is characterized by the presence of single or multiple nodular lesions with necrotic-hemorrhagic tissue, which are little and defined, but can evolve and reach bigger dimensions. These lesions are usually located in the white matter of the brain lobes, but they also affect the brainstem. Histologically, there is inflammatory infiltrate in the nervous and perivascular tissue, in addition to abundant intracellular amastigotes.[8] Magnetic resonance imaging reveals an expansive lesion with mass effect with T1 hyposignal, T2 hypersignal, and irregular or annular gadolinium enhancement, as shown in the cases described.

The first report of the brain tumor-like form reactivation of CD was made in 1973, by Queiroz,[6] in a patient with cutaneous T-cell lymphoma (mycosis fungoides). Since then, there have been several reports of cerebral chagoma in AIDS patients.[7,8,9,10,11,12,13,14,15,16,17] The cases of cerebral chagoma non-related to AIDS found in our review are summarized in ►**Table 1**. Among patients immunosuppressed for causes other than AIDS, the following was found: 1 patient using methotrexate due to rheumatoid arthritis;[18] 2 patients with leukemia;[19,20] 2 patients undergoing kidney transplantation;[21,22] and only 1 reported case of a patient who underwent a heart transplantation,[4] similar to our case. Such a complication in heart transplant patients is very rare. In a series of 107 heart transplantations over 25 years, it occurred to only 1 patient,[23] the same case described by Marchiori et al.[4] We present 3 transplanted and biopsied cases in the same hospital with an interval of 5 years between them. Like the case described by Marchiori et al. (2007), the reactivation in the 3 cases of our sample occurred in the first 7 months after transplantation.

The best treatment for CD in immunocompromised patients is still uncertain, since the available data are limited to observational studies. Two medications are described as effective in reactivation treatment, benznidazole and nifurtimox. In all 3 cases described in this report, treatment with benznidazole at a dose of 5 mg/kg/day for 60 days was used.[25,26] The mortality rate in cases of CD reactivation in patients with HIV is ~ 79%, with an average survival time of 21 days.[7] On the other hand, in reactivation after heart transplantation, the behavior is apparently more indolent,

Table 1 Tumor-like Chagas disease reactivation cases non-related to acquired immunodeficiency syndrome

Author, year	Sex	Age (years)	Base disease	Symptoms	Site of lesion	Treatment
Queiroz,[6] 1973	M	62	T-cells lymphoma	–	–	No
Salgado,[19] 1996	M	76	Lymphocytic leukemia	Intracranial hypertension	Right Parieto-occipital	Benznidazole 5 mg/kg/day
Marchiori,[3] 2007	M	46	Cardiac transplant, 7m	Left hemiparesis, dysarthria, dysphagia	Right fronto-parietal	No
Cohen,[20] 2010	F	15	Lymphoblastic leukemia	Headache, fever	Left occipital	Benznidazole 7 mg/kg/day
Cicora,[21] 2014	M	27	Kidney transplant, 6y	Intense headache	Right frontal	Benznidazole 7 mg/kg/day
Montero,[22] 2018	M	62	Kidney transplant, 3y	Left arm paresis, bradypsychia	Corpus callosum	Benznidazole 15 mg/kg/day
Kaushal,[18] 2019	F	88	Rheumatoid arthritis	Right-sided weakness, slurred speech	Bilateral frontoparietal	No

since all patients described in our series are alive and only one patient has severe neurological sequelae.

Conclusion

Heart transplantation is considered the gold standard for the treatment of severe Chagas cardiomyopathy. Although more common in patients with AIDS-related immunosuppression, tumor-like reactivation in the central nervous system may happen in heart-transplant patients. Therefore, due the multiple differential diagnoses in this context, we believe that brain biopsy should be considered when feasible.

Conflict of Interests

The authors have no conflict of interests to declare.

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Bilateral Cerebral Venous Thrombosis with a Rare Presentation in a COVID-19 Patient: A Case Report

Trombose venosa cerebral bilateral com apresentação rara em paciente com COVID-19: Relato de caso

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Arq Bras Neurocir 2023;42(4):e354–e357.

Abstract

Since the COVID-19 pandemic started, millions of peoples are involved. The presentation of the disease varies from mild respiratory symptoms and multiple organ failure to coma and death. Neurological symptoms such as headache or seizure are also coincident with COVID-19. Thromboembolic events increase in COVID-19 patients due to hypercoagulability and inflammation, particularly in severely ill patients. Thrombosis may cause venous thrombosis, pulmonary embolism, or cerebral sinus venous thrombosis (CSVT). Cerebral sinus venous thrombosis is a rare phenomenon that is usually found in critically ill patients with bad prognoses. In the present case report, we present a 40-year-old man with COVID-19 confirmed by real-time polymerase chain reaction (RT-PCR) who was admitted due to acute bilateral visual loss due to bilateral transverse sinus thrombosis. Pseudotumor cerebri disease was confirmed through high lumbar puncture. Early surgical intervention (optic nerve fenestration) was performed and, fortunately, his visual acuity improved. Cerebral sinus venous thrombosis is a rare incident in COVID-19 patients, but due to irreversible complications, an early diagnosis is fundamental. In any neurologic change in COVID-19 patients, CSVT must be considered. Also, prophylactic thrombolytic therapy should be kept in mind as the patient is admitted.

Keywords
- SARS-COV-19
- CSVT
- thrombosis
- pseudotumor cerebri
- venous thrombotic event
- visual loss

received
February 7, 2022
accepted
July 12, 2022
article published online
October 18, 2023

DOI https://doi.org/10.1055/s-0042-1756458.
ISSN 0103-5355.

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

Resumo

Desde o início da pandemia da COVID-19, milhões de pessoas estão envolvidas. A apresentação da doença varia desde sintomas respiratórios leves e falência de múltiplos órgãos até coma e morte. Sintomas neurológicos, como dor de cabeça ou convulsão, também coincidem com COVID-19. Os eventos tromboembólicos aumentam em pacientes com COVID-19 devido à hipercoagulabilidade e inflamação, particularmente em pacientes gravemente enfermos. A trombose pode causar trombose venosa, embolia pulmonar ou trombose venosa do seio cerebral (TVC). A trombose venosa do seio cerebral é um fenômeno raro, geralmente encontrado em pacientes gravemente enfermos e com mau prognóstico. No presente relato de caso, apresentamos um homem de 40 anos com COVID-19 confirmado por reação em cadeia da polimerase em tempo real (RT-PCR) que foi internado devido a perda visual bilateral aguda causada pela trombose bilateral do seio transverso. A doença pseudotumor cerebral foi confirmada através de punção lombar alta. Foi realizada intervenção cirúrgica precoce (fenestração do nervo óptico) e, felizmente, sua acuidade visual melhorou. A trombose venosa do seio cerebral é um incidente raro em pacientes com COVID-19, mas devido a complicações irreversíveis, um diagnóstico precoce é fundamental. Em qualquer alteração neurológica em pacientes com COVID-19, a TVCS deve ser considerada. Além disso, a terapia trombolítica profilática deve ser lembrada quando o paciente é internado.

Palavras-chave

- SARS-COV-19
- CSVT
- trombose
- pseudotumor cerebral
- evento trombótico venoso
- perda visual

Introduction

Since 2019, when COVID-19 spread around the world, ~ 250 million people were infected and ~ 5 million died. The disease causes multiple organ morbidity. The most common symptom of the disease is pulmonary involvement and pneumonia, which are fully studied. COVID-19 mostly presents with respiratory tract involvement such as cough and dyspnea accompanied by fever. The disease may also cause neurological manifestations such as decreased level of consciousness and myopathy.[1,2]

Some studies also reported involvement of the central nervous system (CNS).[3,4] The most common symptoms of CNS involvement consist of headache, decreased level of consciousness, seizure, and smelling impairment.[3] COVID-19 has been shown to cause coagulation impermanent, which can lead to cerebrovascular manifestations. Critically ill patients were reported as having developed ischemic and hemorrhagic stroke, which can burden the severity of the disease. The possible cause could be the hypercoagulation statue due to the cytokine storm produced by COVID-19.[4]

Venous thrombosis may occur anywhere in veins. The venous system of the brain may also be involved, resulting in cerebral sinus venous thrombosis (CSVT). The early diagnosis in COVID-19 patients is important considering that these patients are sedated intentionally to have a better pulmonary function.

The occurrence of CSVT as a complication of COVID-19 is rare, but some cases have been previously reported. Most of the cases presented with thrombosis in the sagittal sinus or unilateral sinus occlusion. In present study, a rare case of bilateral transverse sinus thrombosis in a COVID-19 patient is presented. The patient presented with bilateral visual loss due to bilateral occlusion of the transverse sinus as a complication of CSVT. The SARS-COV-19 virus activates many inflammatory factors that start a thrombosis cascade, such as angiotensin converting enzyme 2 (ACE2) and D-dimer.[5,6]

Case Presentation

A 40-year-old man was referred to our center due to blurred vision for 2 days before admission and a history of fever, malaise, and dry cough for 1 week before admission. The patient was admitted due to respiratory involvement in a COVID-19 hospital center. He had only a history of HTN, which was controlled with medication. At the time of admission, his vital signs were within the normal limits. The results of the laboratory tests performed upon admission were: blood glucose 250 mg/dL, white blood cell count 10, neutrophil lymphocyte ratio (NLR) 33, erythrocyte sedimentation rate (ESR) 93 mm/h, C-reactive protein (CRP) 6 mg/dL. The results showed hyperglycemia, leukocytosis, and increased NLR. The ESR showed a considerable increase, whereas CRP was slightly increased. Also, D-dimer, as an inflammatory factor, was increased. All laboratory data confirmed the inflammatory process which is consistent with COVID-19 infection. The patient underwent RT-PCR for diagnosis of the disease, whose positive result indicated the involvement of the SARS-COV-19 virus. Prophylactic treatment with enoxaparin for deep vein thrombosis (DVT) was administered subcutaneously during the course of the COVID-19 treatment. A thorax computed tomography (CT) showed bilateral patchy ground glass opacities throughout

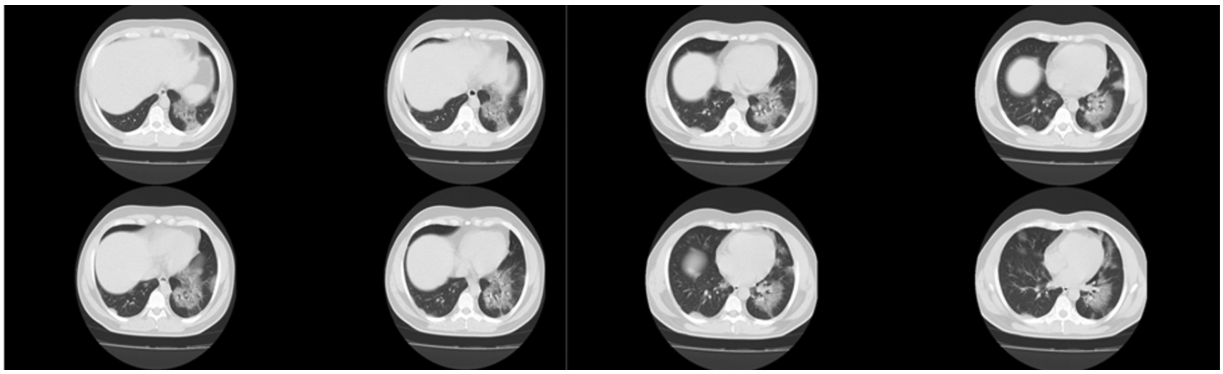

Fig. 1 Base line axial thorax computed tomography showing multiple bilateral ground-glass patchy opacities and subpleural effusion in both lungs, particularly in the upper lobe, with a fibrotic appearance in the left lung.

both lungs (►**Fig. 1**). The patient developed with sudden blurred vision and decrease in visual acuity of both eyes 1 week after admission due to the COVID-19 infection. When the patient was admitted to our center, his visual acuity was: No light perception (NLP) in the right eye and finger count (FC) in the left eye.

A noncontrast brain CT scan did not show any specific findings that could explain the decreased vision. There were no significant hyperdensities in the brain CT, but the patient had bilateral pupillary edema in the clinical examination, which, in concurrence with the presence of brain edema, was suggestive of pseudotumor cerebri (PTC) (►**Fig. 2**). A lumbar puncture (LP) was performed in the patient with an opening pressure of 40 cm h2o, confirming PTC. The patient underwent an ophthalmologic consultation that showed papillary edema grade 5 with no other problems. The visual field test showed bilateral visual loss. Magnetic resonance venography (MRV) was performed and showed bilateral transverse sinus (TS) thrombosis, which confirmed CSVT (►**Fig. 3**). The cerebrospinal fluid (CSF) analysis was normal and did not show anything indicative of encephalitis. Due to the high intracranial pressure (ICP) and to the sudden decrease in visual acuity, the patient underwent an emergency operation for optic fenestration. A serial LP was preformed, showing decreased CSF pressure. Medications, including enoxaparin, were continued until the patient was discharged 2 weeks after admission, when the respiratory clinical manifestations were improved, and VA were: 20/400 and 20/200.

Discussion

The neurological manifestations of COVID-19 vary from headache to encephalopathy with decreased level of consciousness and coma.[3] The SARS-COV-19 virus can involve the neurological system directly or affect the CNS through a severe inflammatory response which is started by systemic infection.[7] Cerebral sinus venous thrombosis is a rare phenomenon with an incidence rate of $\sim$ 0.5 to 1% of all strokes. The patients usually develop with neurological deficits such as motor deficit or decreased level of consciousness. The diagnosis is usually made by brain MRV or CTV. Computed tomography scans show wedge-shaped hypodensities in the involved areas, which explains the venous cause of thrombosis. The presentation of clinical symptoms depends on the site of thrombosis and occur due to brain edema and infarction. The severity of the disease depends on predisposing factors such as age, gender, and medical condition.[8,9]

COVID-19 has been shown to induce hypercoagulation statue by starting an inflammatory cascade that results in the

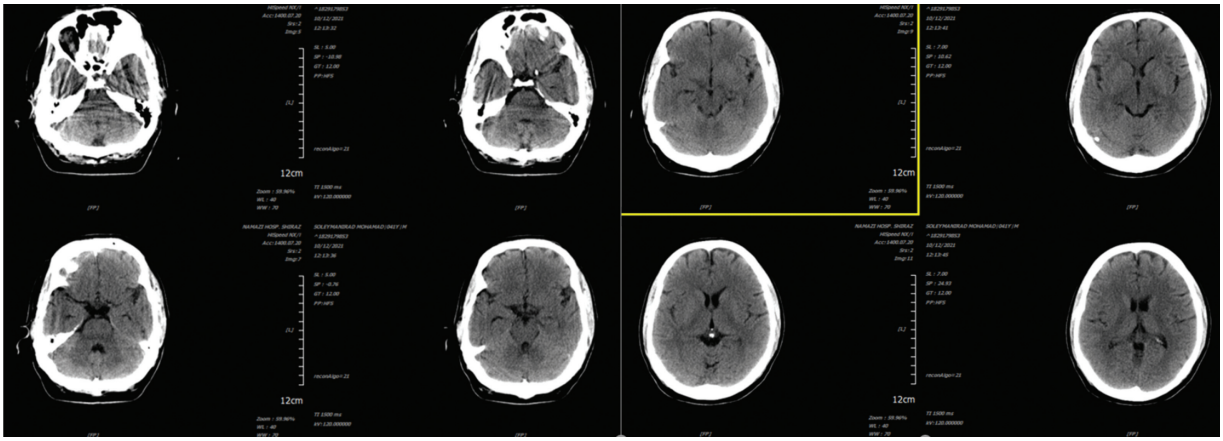

Fig. 2 Axial noncontrast brain computed tomography showing obliteration of the basal cisterna and narrowed sulcal spaces, which is suggestive of brain edema and in favor of PTC.

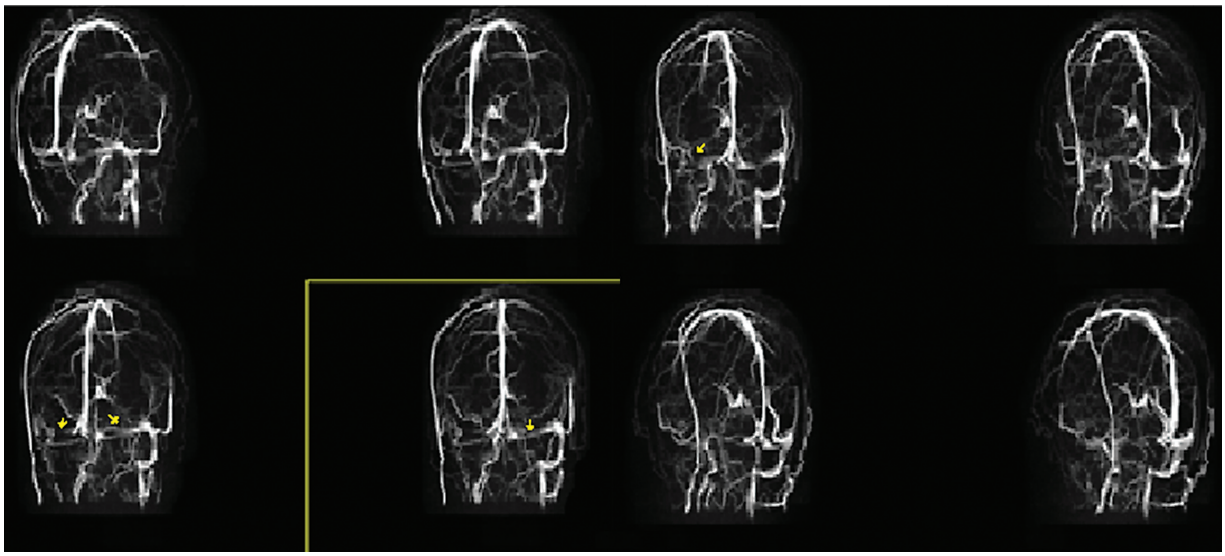

Fig. 3 Bilateral filling defect of both transverse sinuses (TS) are shown in magnetic resonance venography (MRV) that confirmed the diagnosis of cerebral sinus venous thrombosis. The hypodensities in the transverse sinuses are made by clot formation in the vein lumen. Due to acute occlusion, few collateral veins could be found. Also, partial filling defects in the right sigmoid and jugular veins were noted.

release of many cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-12 (IL-12), and interferon-γ (IFN-γ), which are associated with inflammation in pulmonary tissue and fibrosis. As shown in previous reports, the CRP, D-dimer and other inflammatory cytokine levels are high. Thrombosis may happen in the venous system everywhere in the body consisting brain venous system. The most common site of thrombosis in the brain is the superior sagittal sinus.[10]

Patients with predisposing factors like OCP who develop CSVT could be diagnosed due to typical neurological changes, but in severely ill patients, the level of consciousness may be decreased due to hypoxia or intentional anesthesia (to have a better pulmonary function). Therefore, the incidence of CSVT could be missed due to primary decreased LOC. Cerebral sinus venous thrombosis can increase ICP and cause irreversible damage to the brain, so an early diagnosis is fundamental.[11]

In the present case, the patient presented with sudden bilateral visual loss without any predisposing factors. Fortunately, considering that the patient had a good score in the Glasgow coma scale (GCS) and was admitted to the hospital early, the diagnosis was made with brain CT and lumbar puncture. The visual acuity of the patient returned to normal after proper treatment.

Conclusion

Sinus venous thrombosis is one of the uncommon presentations of COVID-19 that cause increased intracranial hypertension and visual loss. Early diagnosis and treatment are critical and can significantly improve the condition of the patient.

Funding
None.

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

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Unusual Anterior Neck Swelling: Cervical Spinal Cord Schwannoma

Incomum inchaço anterior do pescoço: Schwannoma da medula espinhal cervical

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Arq Bras Neurocir 2023;42(4):e358–e362.

Abstract

Schwannomas are typically solitary, well-encapsulated, benign tumors running along or attached to a nerve. An intradural-extramedullary cervical spinal schwannoma, which first manifests as a swelling in the anterior neck, has not been reported to the best of our knowledge. We present the case of a 69-year-old patient complaining of a gradually worsening painful left cervical swelling for over 8 years. First, a posterior spinal midline approach was performed for the resection of the tumor and the tumor portion in the vertebral canal was totally removed. The second operation, the anterolateral approach, was planned to be executed in a second surgical session. The patient was discharged from the hospital without neurological deficits. Histopathological diagnosis was a schwannoma. The first aim of surgery is to treat neurological deficits in patients with cervical intraspinal schwannomas with/without extension into the extravertebral paravertebral neck regions. The surgical strategy combines the posterior midline and the anterolateral cervical approaches in the same session or at different times.

Keywords
- cervical neuroma
- dumbbell schwannoma
- neck mass
- neck swelling
- spinal schwannoma

Resumo

Schwannomas são tipicamente tumores solitários, bem encapsulados e benignos que correm ao longo ou aderem a um nervo. Até onde sabemos, um schwannoma espinhal cervical intradural-extramedular que se manifesta pela primeira vez como um inchaço na região anterior do pescoço não foi relatado. Apresentamos o caso de um paciente de 69 anos com queixa de inchaço cervical esquerdo doloroso de piora gradual há mais de 8 anos. Primeiramente, uma abordagem da linha média da coluna vertebral posterior foi realizada para a ressecção do tumor, e a porção do tumor no canal vertebral foi totalmente removida. A segunda operação, via anterolateral, foi planejada para ser realizada em uma segunda sessão cirúrgica. O paciente recebeu alta hospitalar sem déficits neurológicos. O diagnóstico histopatológico foi um schwannoma. O primeiro

Palavras-chave
- neuroma cervical
- schwannoma com halteres
- massa cervical
- inchaço do pescoço
- schwannoma espinhal

received
May 1, 2021
accepted
August 6, 2021

DOI https://doi.org/10.1055/s-0043-1776790.
ISSN 0103-5355.

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

objetivo da cirurgia é tratar déficits neurológicos em pacientes com schwannomas intraespinhais cervicais com/sem extensão para as regiões extravertebrais do pescoço paravertebral. A estratégia cirúrgica combina a abordagem da linha média posterior e a abordagem anterolateral cervical na mesma sessão ou em momentos diferentes.

Introduction

Schwannomas are benign mesenchymal tumoral masses that originate from Schwann cells on the peripheral nerve sheath, including the spinal dorsal nerve roots.[1–3] Spinal schwannomas occur rarely and compress neighboring structures in the neck region.[4] An intradural-extramedullary schwannoma with a solitary extradural component anteriorly extended is a very rare entity.[5,6] It is unusual for an intraspinal schwannoma to present with a swelling in the neck. To the best of our knowledge, an intradural-extramedullary cervical spinal schwannoma which first manifests as a swelling in the anterior neck region has not been reported.

Clinical Presentation

Patient Characteristics

A 69-year-old right-handed man presented to our department complaining of a gradually worsening painful left anterior cervical swelling over 8 years. The mass was insidious and gradually increasing in size. Physical examination of the patient revealed an unusual palpable swelling, which was hard, non-pulsatile, and painless, in the left anterior neck region. The remainder of the physical examination was normal.

On neurological examination, muscle strength was normal and neither sensory deficiency nor pathological reflex was present. The patient had no dysphonia, syncopal attacks, dysphagia, or dyspnea. The magnetic resonance imaging (MRI) revealed an intradural extramedullary tumoral mass at the C2–C3 level(►**Fig. 1 A-B**). The tumor, which extends to the anterior neck region, was hypointense on T1-weighted magnetic resonance imaging (MRI) scans and hyperintense on T2-weighted MRI scans. It enhanced heterogeneously after administration of contrast media. The anterior-–posterior diameter of the lesion has reached ∼ 3 cm, with the spinal canal and the extension in the neural foramen, the total size reaching 6 cm. Computed tomography (CT) angiography showed no vascularization in the tumor, but an anterior displacement of the carotid sheath.

Surgical Procedure

Our surgical strategy combines the posterior midline approach and the anterolateral cervical approach at different times. First, a posterior spinal midline approach was performed for the resection of the tumor. The second operation, the anterolateral approach, was planned to be executed in a second surgical session. In the first operation, under general anesthesia, neuro-monitorization was used to monitor the intraoperative action potential of the trapezius and the upper limb muscles. A three-pin head holder was applied, and the patient was positioned prone. A two-level laminectomy at C2 and C3 was performed following a midline incision and a standard opening. A surgical microscope was introduced, and a longitudinal dural incision was made. This revealed the intradural part of the tumor, which was located under the C3 dorsal root and dentate ligaments

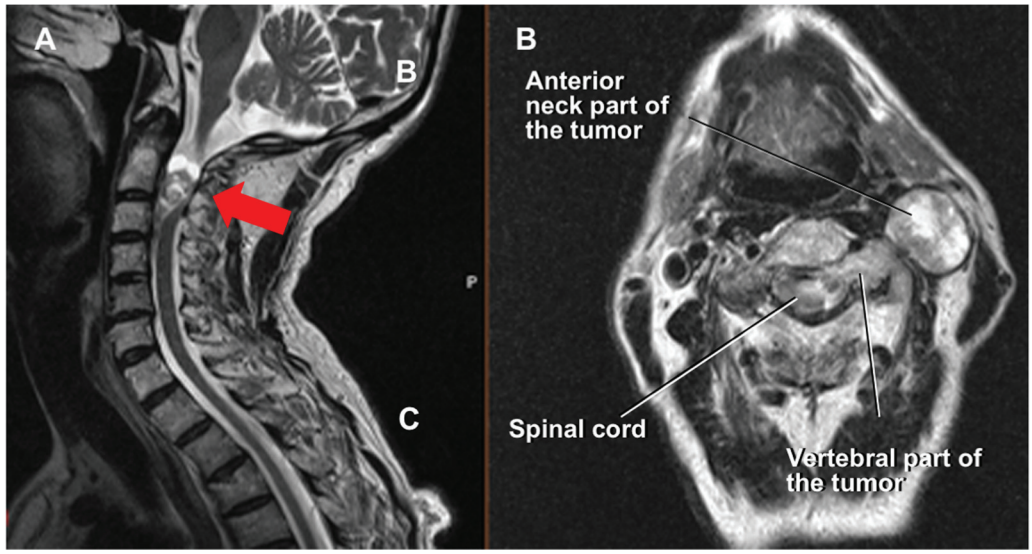

Fig. 1 Preoperative magnetic resonance images (MRIs): T2-weighted MRI in sagittal (**A**) and axial planes (**B**) and at the level of C3 corpus shows the tumor. (A; arrow)

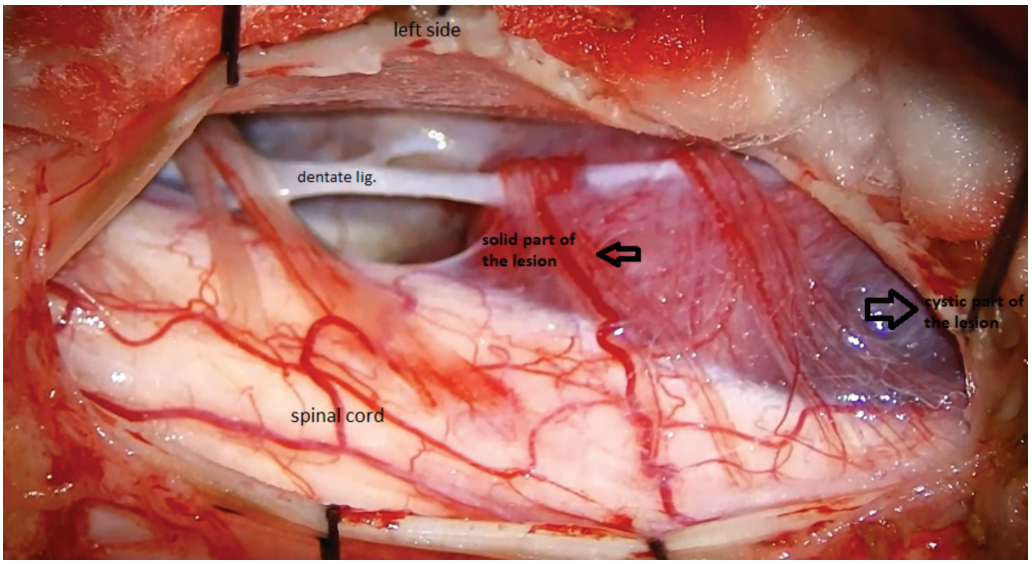

Fig. 2 Intraoperative view

(►**Fig. 2**). The tumor extended anterolaterally from the spinal cord, and this was evidenced by observation of the adjacent subarachnoid space. We removed the tumor in piecemeal fashion following a central debulking until total resection of the intraspinal part of the tumor was achieved. An ultrasonic aspirator was employed during tumor removal, which turned out to be insufficient due to a semi-fibrotic structure of the lesion. The tumor was not extremely hemorrhagic, and no evidence of tumor necrosis was observed either. Intraoperatively, it was consistent with a schwannoma, which was later confirmed with the histopathological examination.

Postoperative follow-up

Postoperative MRI images demonstrated a total removal of the tumor in the vertebral canal with the extraspinal anterior part of the tumor left untouched. (►**Fig. 3**). The patient was discharged from the hospital without neurological deficits.

Discussion

In literature, there are rare case reports of schwannoma, which manifest with cervical swelling, including the tongue, thyroid gland, intraparotid gland facial nerve, the cervical sympathetic chain, brachial plexus, and vagal nerve schwannomas.[3,7–14] But the anteriorly extended intradural extramedullary cervical schwannoma is uncommon.[15,16] In addition to this infrequency, in our case, the intradural extramedullary lesion has an anterior extension, which causes observable and palpable neck swelling. This clinical presentation for a spinal schwannoma is atypical.

To understand head and neck surgery and to perform systematic and safe excision of tumors, training in neuroanatomy of the neck region is essential.[17–20] A detailed knowledge of the complex topographic relationships between muscles, blood vessels, nerves, and lymph nodes will enable the surgeon to safely perform difficult and risky

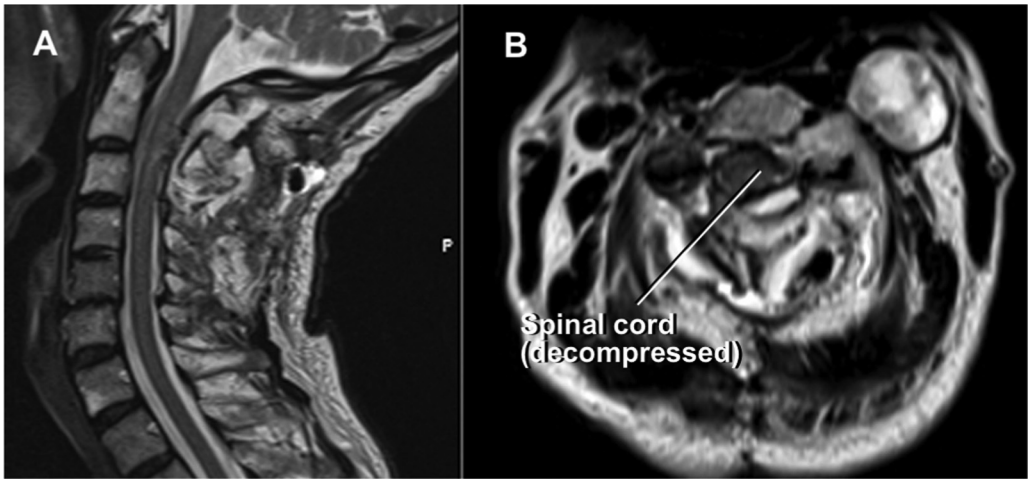

Fig. 3 Postoperative magnetic resonance images (MRIs). T2-weighted MRI in sagittal (**A**) and axial planes (**B**) and at the level of C3 corpus. The spinal cord is seen to be decompressed.

dissection in the head and neck region. In addition, a good knowledge of both anterior and posterior approaches—as well as their variations—to the neck region is crucial in choosing the most appropriate surgical method. Conventional treatment for spinal tumors includes open laminectomy.[21] However, a wide variety of alternative minimally invasive surgical techniques including laminoplasty and unilateral hemilaminectomy are used.[21–23]

The diagnosis of cervical schwannoma is difficult due to the fact that they are slowly growing tumors, and the medical history and clinical examination are not specific.[14] The symptoms are local pain or loss of sensation/strength due to intraspinal cervical spinal cord compression. However, asymptomatically, their volume may gradually increase and, although rarely, they may appear as cervical swelling.[24,25] After this stage, signs and symptoms are generally related to the size of the schwannoma, and symptoms such as dysphagia and dyspnea may appear due to the compression of the surrounding anatomical structures.[26] Magnetic resonance imaging and computed tomography (CT) angiography are very useful diagnostic tools for surgical planning, as they show the extension and vascularity of the tumor and its relationship with important functional structures in the neck.

Conclusions

The first aim of surgery is to treat neurological deficits in cervical intraspinal schwannomas with extension into the extra-vertebral paravertebral neck regions. Therefore, the surgical strategy combines the posterior midline and the anterolateral cervical approaches in the same session or at different times.

Ethical Issues

The ethical issues for the present study involving human subjects have been carefully considered in line with the Declaration of Helsinki (1964).

Authors' Contributions

Erkin Özgiray: Conceived the idea, collected data, performed the analysis, interpreted the results, wrote the text, performed a literature search, critically reviewed the intellectual content, and revised the text.

Cihat Karagöz: Analyzed and designed data, interpreted the results, performed a literature search, revised the text, and critically reviewed the intellectual content.

Serdar Bölük: Analyzed and designed data, interpreted the results, performed a literature search, and revised the text.

Naci Balak: Analyzed and designed data, interpreted the results, performed a literature search, revised the text, and critically reviewed the intellectual content.

Patient Consent

The patient signed the informed consent agreement of clinical images and data for medical use.

Financial Support

None.

Conflict of Intersts

The authors have no conflict of interests to declare.

Acknowledgments

None.

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Capítulo de livro

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

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Tese e dissertação

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Anais e outras publicações de congressos

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ISSN 0103-5355

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