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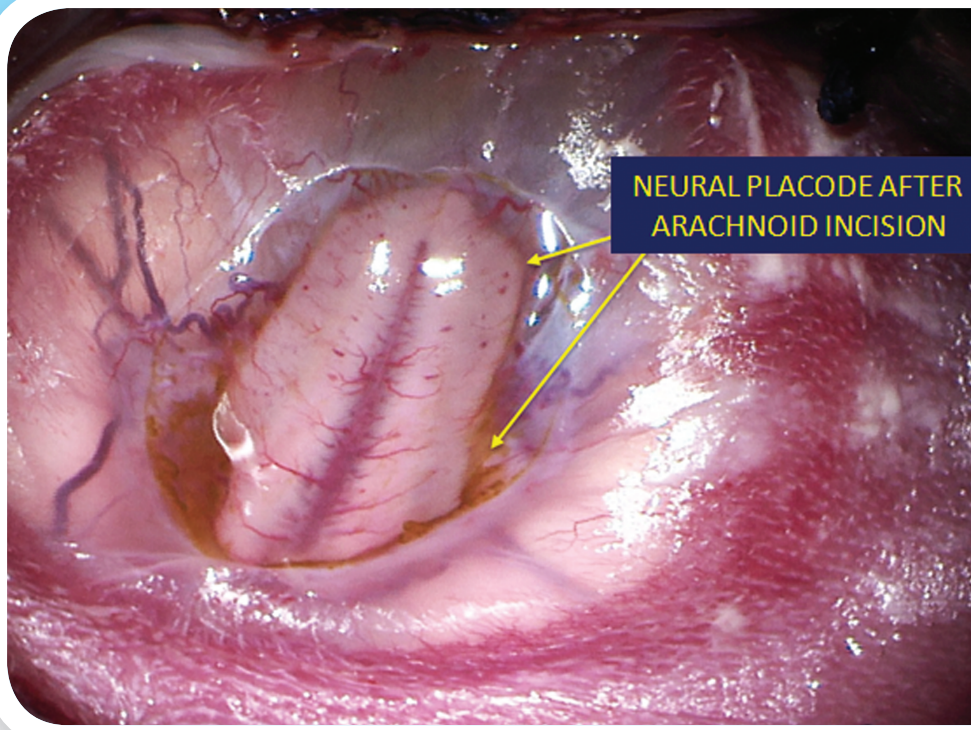

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Syringomyelia: Retrospective Analysis of 30 Surgically Treated Patients from the Northeast of Brazil

Siringomielia: Análise retrospectiva de 30 casos operados no nordeste brasileiro

Bruna Lisboa do Vale[1] Maurus Marques de Almeida Holanda[2] Marcelo Moraes Valença[3] Severino Aires de Araújo Neto[4]

[1] Discipline of Neurosurgery, Department of Neurology and Neurosurgery, Universidade Federal de São Paulo, São Paulo, SP, Brazil
[2] Discipline of Neurology, Department of Internal Medicine, Medical Sciences Center, Universidade Federal da Paraíba, João Pessoa, PB, Brazil
[3] Neurosurgery Unit, Department of Neuropsychiatry, Health Sciences Center, Universidade Federal de Pernambuco, Recife, PE, Brazil
[4] Discipline of Radiology, Department of Internal Medicine, Medical Pessoa, PB, Brazil

Address for correspondence Bruna Lisboa do Vale, Department of Neurology and Neurosurgery, Universidade Federal de São Paulo, Rua Napoleão de Barros, 715, 6o andar, São Paulo, SP, CEP 04024-002, Brazil (e-mail: bruna.lisboa@unifesp.br).

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Abstract

Introduction Syringomyelia is a chronic disease characterized by the presence of intramedullary cavity. Chiari malformation (CM) and basilar impression (BI) are conditions usually associated with syringomyelia. Its prevalence has wide geographical variation, being higher in the Northeast of Brazil, making it relevant to study the subject in this region.

Objective To analyze the frequency of signs, symptoms, and surgical aspects observed in patients undergoing decompressive treatment.

Methods We performed a retrospective analysis of the medical records of patients diagnosed with syringomyelia who received decompressive surgical treatment in various hospitals in João Pessoa, Paraíba, between 1994 and 2021.

Results Thirty patients were analyzed. Twenty-nine (96.7%) presented CM and 27 (90.0%) also presented BI. A wide variety of symptoms was found, with significant prevalence of muscle weakness, neck pain, and headache. Brevicollis, a finding considered typical of the Northeastern region and associated with craniocervical junction malformations, was present in 66.7%. The surgical technique used in 90% of patients was similar. Fourteen (46.7%) patients presented difficult craniocervical junction and 4 (13.3%) had occipital bone assimilation. Eighteen (60.0%) presented

Keywords
- craniocervical junction malformations
- syringomyelia
- Chiari malformation
- basilar impression
- surgery

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thickening of the arachnoid membrane. Postoperatively, there was clinical improvement in 21 patients (70%).

Conclusions The sample majorly had CM and BI associated with syringomyelia. High prevalence of signs and symptoms related to the Brazilian northeastern phenotype was also found. Syringomyelia, therefore, has peculiarities in the population of the Northeast of Brazil that, when described, allow better understanding of the pathology in this group.

Resumo

Introdução Siringomielia é uma enfermidade crônica caracterizada pela presença de cavidade intramedular. Costuma vir associada a condições como malformação de Chiari (MC) e impressão basilar (IB). Sua prevalência tem grande variação geográfica, sendo maior no nordeste brasileiro, o que torna relevantes estudos sobre o tema nessa região.

Objetivo Analisar a frequência de sinais, sintomas e aspectos cirúrgicos observados em pacientes submetidos a tratamento descompressivo.

Método Foi realizada análise retrospectiva das informações contidas nos prontuários de pacientes diagnosticados com siringomielia submetidos a tratamento cirúrgico descompressivo em vários hospitais de João Pessoa, Paraíba, entre 1994 e 2021.

Resultados Foram analisados 30 pacientes, dos quais 29 (96,7%) apresentaram MC associada e 27 (90,0%) também tinham IB. Houve grande variedade de sintomas, com importante prevalência de fraqueza muscular, cervicalgia e cefaleia. Brevicolia, um achado considerado típico do nordestino e associado a malformações da junção craniocervical, esteve presente em 66,7% dos pacientes. A técnica cirúrgica utilizada em 90% dos pacientes foi semelhante. Quatorze (46,7%) pacientes apresentaram junção crânio-cervical difícil; e quatro (13,3%) apresentaram assimilação do osso occipital. Dezoito (60,0%) apresentaram espessamento da membrana aracnoide. No pós-operatório, houve melhora clínica em 21 pacientes (70%).

Conclusão A expressiva maioria da amostra possuía MC e IB associadas à siringomielia. Nota-se também grande prevalência de sinais e sintomas relacionados ao fenótipo nordestino. A siringomielia, portanto, possui peculiaridades na população do Nordeste brasileiro que, ao serem descritas, permitem a melhor compreensão da patologia nesse perfil de pacientes.

Palavras-chave
- malformações da junção craniocervical
- siringomielia
- malformação de Chiari
- impressão basilar
- cirurgia

Introduction

Syringomyelia (SM) can be defined as the presence of a cavity in the spinal cord.[1] Its etiology can be classified as idiopathic when it is not possible to identify a cause; or as secondary to cerebrospinal fluid (CSF) obstruction. Syringomyelia is commonly associated with Chiari malformation (CM) and basilar invagination (BI), but it can also be attributed to inflammation, trauma, tumor, or local compression.[2]

The prevalence of SM varies from 0.9 to 8.4 per 100,000 individuals, according to ethnicity and geographic variation.[3,4] The Brazilian Northeast is considered one of the regions in the world with the highest number of cases of craniocervical junction malformation (CJM).[5,6] Local studies conducted by Silva et al.[6] and Alves et al.[7] relate this fact to the great presence of brachycephaly in the area, which is so easily noted that it became popular knowledge, with people from the Northeast of Brazil, sometimes being referred to, pejoratively, as "flat head" or "short neck."[5] Associated with this craniometric profile, there is a marked prevalence of platybasia and BI.[5] This propensity toward flattening of the skull base and its correlation with SM may explain its high frequency.

Considering that the pathogenesis of symptomatic SM in this particular population located in the state of Paraíba may be different from others, it is important to study the clinical and surgical aspects from this region, to provide personalized treatment and better comprehension of the disease.

Material and Methods

We performed a retrospective analysis of data contained in the medical records of patients diagnosed with SM by magnetic resonance imaging (MRI) undergoing decompressive surgical treatment in several hospitals of João Pessoa, PB, Brazil, between 1994 and 2021. The identification of other

malformations of the CJM was performed as follows: CM was diagnosed using MRI or during the surgical procedure; BI, according to MRI results or other imaging examination, or by measuring the lines of Chamberlain and McGregor. Patients who were lacking the necessary data in their medical records were excluded from the study.

The research was based on secondary data, ensuring privacy, confidentiality, and the non-use of information to the detriment of the subject, in accordance with Resolution 580/18, of the National Health Council, which establishes the ethical principles of research in human beings. The study was approved by the ethics committee of Hospital Universitário Lauro Wanderley.

Results

For this study, 30 patients (15 women, 15 men) with SM were analyzed, 29 (96.7%) of whom had associated CM and 27 (90.0%) also had BI. Clinically, 6 (20.0%) had syringomyelic pain. The average age was 38.2 years, ranging from 8 to 72 years old.

The period between the onset of symptoms and surgery was over 3 years in 14 patients (46.7%); from 2 to 3 years in 2 of them (6.7%); from 1 to 2 years in 6 (20%); and less than 1 year in 8 (26.7%).

Table 1 Clinical symptoms observed in 30 cases of syringomyelia

Symptoms	Cases number	%
Neck pain	20	66.7
Muscular weakness	20	66.7
Numbness of limbs	20	66.7
Headache	16	53.3
Rhinolalia	15	50.0
Dysphagia	12	40.0
Sexual potency disturbances	11	36.7
Stiffness of neck	10	33.3
Vertigo	10	33.3
Nasal reflux	6	20.0
Hearing loss	5	16.7
Apnea	5	16.7
Libido disturbances	4	13.3
Constipation	4	13.3
Menstrual disorders	4	13.3
Vicious position of the head	3	10.0
Dysarthria	3	10.0
Numbness of face	2	6.7
Ataxic gait	2	6.7
Decreased visual acuity	1	3.3
Drop attack	1	3.3
Difficult urination	1	3.3
Anhidrosis	1	3.3

Table 2 Clinical findings in 30 cases of syringomyelia

Findings	Number of cases	%
Brevicollis	20	66.7
Brachycephaly	19	63.3
Low hair implantation	12	40.0
Alteration of the posterior fossa	9	30.0
Hypertelorism	8	26.7
Painful limitation of the neck	7	23.3
Scoliosis	6	20.0
Prognathism	5	16.7
Craniofacial asymmetry	4	13.3
Accentuated lumbar lordosis	1	3.3
Equinovaro feet	1	3.3

The symptoms observed in the preoperative period are shown in ►**Table 1**; the clinical findings are in ►**Table 2**; and the signs found on physical examination in ►**Table 3**.

Regarding the surgical treatment of SM, 27 (90%) of the patients were operated in the concord position (prone position with the head flexed forward), and the other 3 (10%) in a sitting position. All were submitted to bone, dural, and neural decompression, characterized by posterior fossa craniectomy and high cervical laminectomy (C1 and C2) according to the degree of tonsil herniation in the CM (►**Table 4**). In the 29 cases (96.7%) in which CM was present, Y-shaped opening of the 4th ventricle dura and subpial aspiration of the cerebellar tonsils was performed; in many cases, a small membrane that occluded the foramen of Magendie was found. After opening, the tonsils were fixed laterally, and duraplasty with a synthetic dural substitute was performed (100% of cases); thus, the cisterna magna was remodeled, allowing a more physiological circulation of the cerebrospinal fluid (►**Fig. 1**).

About half of the sample—14 patients (46.7%)—had a difficult craniocervical junction, and 4 (13.3%) had occipital bone assimilation. Eighteen (60.0%) presented thickening of the arachnoid membrane.

With surgical treatment, there was clinical improvement in 21 patients (70%) and 9 (30%) did not suffer changes; there was no worsening in any of the cases studied.

Discussion

Rodrigues et al.[8] stated that SM is associated with CM (or other anomalies that occlude the foramen of Magendie) in ¾ of the cases.[8] In the present study, CM was present in 96.7% of the cases, which reinforces CM and other CJM as major factors for the development of SM in our population.

When characterizing our sample, sex parity was perceived, similar to some previous analyses, but different from others in which there is a predominance in females.[9]

Table 3 Clinical signs observed in 30 cases of syringomyelia

Signs	Number of cases	%
Hyperreflexia	28	93.3
Syringomyelic dissociation	24	80.0
Hypoesthesia	23	76.7
Hoffmann sign	17	56.7
Abolition of gag reflex	16	53.3
Abolition of palatal reflex	15	50.0
Nystagmus	14	46.7
Hypertonia	14	46.7
Paresis	14	46.7
Clonus	12	40.0
Babinski sign	9	30.0
Rossolimo sign	9	30.0
Paresis of soft palate	8	26.7
Exophthalmos	6	20.0
Hypoacusis	6	20.0
Atrophies	6	20.0
Abolition of abdominal reflexes	4	13.3
Lesion of the V nerve	3	10.0
Vestibular disturbances	3	10.0
Hypertelorism	2	6.7
Lesion of the spinal nerve	2	6.7
Lesion of the XII nerve	2	6.7
Cerebellar disturbances	2	6.7
Unsteady gait	2	6.7
Fasciculations	2	6.7
Lesion of the VII nerve	1	3.3

Table 4 Surgical findings in 30 patients with syringomyelia

Findings	Number of cases	%
Difficult atlanto-occipital joint	14	46.7
Thinning of the occipital bone	12	40.0
Thickening of the occipital bone	17	56.7
Dural adhesion	11	36.7
Arachnoid thickening	18	60.0
Degree of cerebellar tonsillar herniation		
0	1	3.3
C1	15	50.0
C2	14	46.7
C3	0	0.0
Tonsillar symmetry		
Symmetrical	13	43.3
Right > Left	3	10.0
Left > Right	13	43.3

Regarding age, the population analyzed was similar to or older in relation to others.[9–11] Regarding the period between the onset of symptoms and surgical approach, there was a great variety in our sample, as well as among previous studies.[9,10]

With regard to the clinical aspects, as in other studies with SM, a wide variety of symptoms could be noted among patients, with higher frequency of complaints of muscle weakness, pain, and headache.[9,10] Paresthesia, neck pain and cranial nerve involvement were also observed in a proportion similar to the one described in the literature.[10] Rare findings in our sample have also been observed in some patients in other studies, such as ataxic gait and vestibular disorders.[9]

Some findings, however, were markedly more significant in our population. Brevicollis, for example—which is a finding considered typical of the Brazilian Northeast and associated with CJM—, was present in 66.7% of our patients and only in 22% of patients by Mariani et al. (1991). In the same study, a prevalence of 74% of CM and 28% of BI was reported among cases of SM.[10] Bogdanov et al. (2002) reports presence of BI in 46% of patients with SM.[3] In our sample, however, 96.7% had CM, and 90% BI.

Alzate et al.[9] demonstrated statistically that, among patients with type I CM, the presence of scoliosis is a risk factor for the development of SM. In our sample, the prevalence of scoliosis was 20%, which is similar to or smaller than observed in previous studies.[3,9–11]

One of the most widely reported symptoms among authors is headache, which also had a high frequency in our sample. Headache associated with SM tends to respond very well to decompressive treatment.[9] This characteristic can have an important influence on the rate of clinical improvement obtained with surgery.

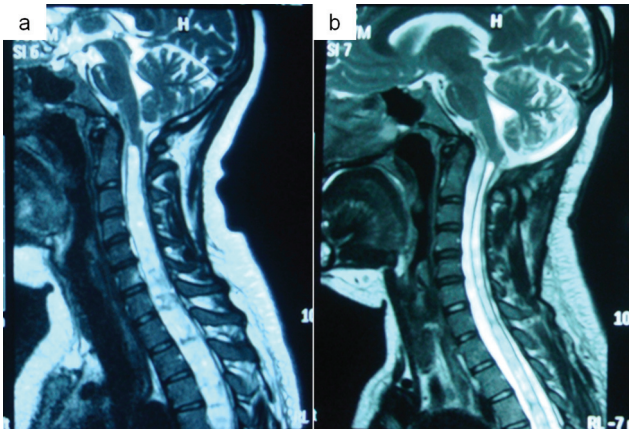

Fig. 1 (a) Preoperative magnetic resonance imaging showing extensive syringomyelia compressing the spinal cord. (b) Postoperative magnetic resonance imaging showing decompression of the spinal cord after the physiological return of the cerebrospinal fluid.

Generally, considering signs and symptoms of patients with SM, there is usually significant improvement in 50 to 90% of the cases with surgical treatment according to most studies.[9,12] In our sample, 70% of all patients showed improvement, and there was no worsening in any of the cases analyzed.

Considering the surgical outcomes, the study of Silva et al.[6] with 260 operated cases, in a population similar to ours, is certainly an important source of comparison for the obtained results. In it, 29.6% of patients had thin and 15% thickened occipital bone; similar to the results of Gonçalves et al. (2003), however, different from ours (40% and 56.7%, respectively).[6,12] Such variations are usually associated with greater technical difficulty in performing the craniectomy.[6]

Thickening of the arachnoid membrane was found in 60% of patients; similar to that observed by Silva et al. (1994), with 67.3%, and Gonçalves da Silva et al.,[12] with 67.9%.[6,12] In case series, this change was associated with an increased surgical risk.[10] It is also considered the most important factor for the development of neurological symptoms.[6] Thus, it is a frequent finding and has a great impact on the clinical picture of CJM. As for the topography of cerebellar tonsils, in our patients, there was symmetry in 43.3% of cases. This proportion approaches the one found in the literature.[6,13]

In our sample, there was clinical improvement in 70% of the operated patients, and outcome that was similar to the one found by Mariani et al.[10]

During the operative act, since the 1970s, duraplasty has been performed to increase the anatomical space of the posterior fossa, prevent cerebrospinal fluid leak, reduce arachnoiditis by preventing the penetration of blood in the manipulated region, recompose the pachymeninge, and protect the posterior fossa structures.[6,11,12] In the experience of Silva et al. (1994), duraplasty reduced the number of postoperative complications, especially mortality and the incidence of respiratory disorders.[6] Munshi et al. (2000) demonstrated that decompression of the posterior fossa with C1 laminectomy and dural graft caused hydromyelia to regress more quickly than with the same procedure without the use of dural graft.[11,12] In our sample, all patients treated with the decompressive procedure underwent duraplasty with a synthetic dural substitute. Another aspect of the surgical approach adopted in this sample was the aspiration of the herniated cerebellar tonsils. This procedure also had promising results presented by Silva et al.[6]

Note that our findings were similar to those of local studies but differed significantly from those of international studies. This can be related to the ethnic and geographic differences in SM incidence, which are associated with genetic and environmental differences.[3,4]

The average tonsillar position in asymptomatic individuals is another difference found between populations. Studies in normal patients have shown that the tonsillar position is usually higher in the Japanese population when compared with Euro-Americans: in these, more than 5% have tonsils between 1 and 5 mm below the FM, while in Japan, this prevalence is of only 0.24%.[13] This characteristic is especially relevant when it is pointed out that Japanese people are affected less frequently than Europeans with CM-related obstruction in the CSF pathways in FM, which explains the lower prevalence of SM in Japan (1.9 per 100,000) than in England or New Zealand (8.4 and 8.2 per 100,000, respectively).[13]

Among the regions identified globally as CM and SM clusters, there is the Brazilian Northeast, as already mentioned, some states in India, an area of Germany, and regions of Russia with a large proportion of Tatar.[13]

When studying the Tatar population, Bogdanov et al.[13] considered recommendation for surgery based on less objective criteria, as in groups with less than 5 mm descent of the tonsils, absence of SM, and predominantly subjective symptoms; but stressed that it is inappropriate to apply these criteria to populations in which the spread of CJM is not considered high.[13]

Furthermore, some studies suggest that cultural aspects present greater impact on the development of CJM than genetic and environmental. In the sample studied by Bogdanov et al.,[13] for example, 88% of symptomatic CM patients were male manual workers, who have done agricultural work all their lives. From this, the authors indicated that an occupation associated with physical tension imitating the Valsalva maneuver can lead to the development of SM in those who already had a posterior fossa underdeveloped.[13] Another fact that suggests that CM may be acquired, not congenital, is that the abnormal shape and position of the cerebellar tonsils disappears after simple extra-arachnoid decompressive surgery.[14]

Conclusions

There is great prevalence of signs and symptoms related do the Brazilian northeastern phenotype in patients with SM. This shows that regional determinants have an important role in the presentation of SM, thus requiring changes in treatment and prognosis.

Because it is usually associated with CM, in an even more expressive way in individuals from the Northeast of Brazil, surgical treatment of SM, in most cases, consists of suboccipital craniectomy, C1 laminectomy, and duraplasty.

Therefore, there are peculiarities in the Northeast of Brazil that, once described, allow for better understanding of SM.

Ethics Standards

This research was based on secondary data, ensuring privacy, confidentiality, and the non-use of information to the detriment of the subject, in accordance with Resolution 580/18 of the National Health Council, which establishes the ethical principles of research in human beings. The study was approved by the ethics committee of Hospital Universitário Lauro Wanderley.

Conflict of Interests

The authors have no conflict of interests to declare.

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Micro-Surgical Treatment of Fetal Myelomeningocele

Tratamento microcirúrgico da mielomeningocele fetal

Gabriel Mufarrej[1] Gonzalo Castillo[1] Maria Anna Brandão[1] João Ricardo Penteado[1] Jair Braga[2] Paulo Niemeyer Filho[1]

[1] Instituto Estadual do Cérebro Paulo Niemeyer, Rio de Janeiro, RJ, Brazil
[2] Maternity School, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, Brazil

Address for correspondence Gabriel Mufarrej, MD, Rua General Garzon 22 sala-411, Lagoa, Rio de Janeiro, Rio de Janeiro, Brazil 22470-010 (e-mail: gabrielmufarrej@gmail.com).

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Abstract

Introduction Myelomeningocele (MMC) is the most common malformation of the central nervous system compatible with life. We will report the results obtained with the prenatal closure of MMC at the Instituto Estadual do Cérebro Paulo Niemeyer (IECPN).

Objectives Clinical outcome of fetuses undergoing intrauterine MMC repair by the Peralta mini-hysterotomy. Monitor the reduction of Arnold-Chiari II secondary to MMC, reduction of hydrocephalus and also motor development in these children.

Methods Descriptive study of 26 cases with intrauterine MMC repair by mini-hysterotomy, or Peralta technique, performed at the IECPN from December 2017 to February 2020.

Results Between December 2017 and February 2020, 26 pregnant women with children with MMC were operated on using Peralta technique. Fetuses were born at an average gestational age of 34.2 weeks and 8% were born before 30 weeks of gestation. The average birth weight was 2096g. It was possible to observe a significant reduction in the occurrence of Arnold-Chiari II in these patients, as well as an evident improvement in motor function in the neurological examination of these babies at the end of the first month of life, where 20 of 23 babies had active movement in the lower limbs.

Discussion This study demonstrates the correction of fetal MMC through a mini-hysterotomy of 2.5 to 3.5 cm, developed in order to reduce maternal and fetal mortality. This mini-hysterotomy technique is not a minimally invasive procedure, as it is based on open surgery for the treatment of fetal MMC, as recommended by the Management of Myelomeningocele Study (MOMS).

Keywords
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- fetal surgery
- spina bifida
- Arnold Chiari II
- hydrocephalus

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Resumo

Introdução Mielomeningocele (MMC) é a malformação mais comum do sistema nervoso central compatível com a vida. Nós relataremos os resultados obtidos com o fechamento pré-natal da MMC no Instituto Estadual do Cérebro Paulo Niemeyer (IECPN).

Objetivos Desfecho clínico dos fetos submetidos a correção intrauterina de MMC por mini-histerotomia de Peralta. Monitorar a redução de Arnold-Chiari II secundária à MMC, redução da hidrocefalia e também o desenvolvimento motor nessas crianças.

Métodos Estudo descritivo de 26 casos com correção intrauterina de MMC por mini-histerotomia ou técnica de Peralta realizadas no IECPN no período entre dezembro de 2017 a fevereiro de 2020.

Resultados Entre dezembro de 2017 a fevereiro de 2020, 26 gestantes com filhos portadores de MMC, foram operadas utilizando-se a técnica de Peralta. Os fetos nasceram com uma idade gestacional média de 34,2 semanas e 8% nasceram antes das 30 semanas de gestação. O peso médio ao nascer foi de 2096 gramas. Foi possível observarmos uma significativa redução na ocorrência de Arnold-Chiari II nestes pacientes, bem como uma evidente melhora da função motora no exame neurológico destes bebês ao final do primeiro mês de vida, aonde 20 de 23 bebês apresentavam movimentação ativa nos membros inferiores.

Discussão Este estudo demonstra a correção da MMC fetal através de uma mini-histerotomia de 2,5 à 3,5cm, desenvolvida com o intuito de reduzir a mortalidade materna e fetal. Esta técnica de mini-histerotomia não é um procedimento minimamente invasivo, pois é baseada na cirurgia aberta para o tratamento da MMC fetal, como preconiza o estudo *Management of Myelomeningocele Study* (MOMS).

Palavras-chave

- mielomeningocele
- cirurgia fetal
- espinha bífida
- Arnold Chiari II
- hidrocefalia

Introduction

Spina bifida or spinal dysraphism is characterized by a defect in the closure of the neural tube at a certain point in the spine. Spina bifida can be opened when there is exposure of the spinal cord and nerve roots through a skin defect. Spina bifida occulta, or closed spina bifida, however, does not expose the central nervous system, with the defect being covered by intact skin. Myelomeningocele (MMC), or open spina bifida, is the most frequent congenital alteration of the central nervous system compatible with life, occurring due to a defect in the closure of the neural tube, in the first four weeks of pregnancy, during primary neurulation.[1] It is characterized by the presence of a hernial sac, most often in the lumbosacral region, containing the spinal cord, nerve roots and cerebrospinal fluid, and is generally associated with Arnold-Chiari II malformation. Hydrocephalus is always present in MMC and approximately 80% of patients who are treated in the postnatal period require peritoneal ventricle shunt (PVD)[2,3]. This malformation occurs at a rate of approximately 0.7 to 0.8 per 1000 live births in the USA; in Brazil, there is an incidence of 1 to 2 cases per 1000 live births. The neural plate found in the center of the MMC (placode) corresponds to the dysplastic medullary neural tissue that did not close during the embryonic period. A median groove can be viewed longitudinally and corresponds to the central canal of the spinal cord, open dorsally. Associated with protrusion of the meninges and, dorsally, of the placode, the formed hernial sac contains cerebrospinal fluid. The most frequent location of MMC is in the lumbosacral region.[1,4,5]

Most children who are born with MMC have the Arnold-Chiari II malformation concomitantly, which presents a low implantation of the torcula and straight sinus, associated with a lower displacement of the IV ventricle, bulb, and lower portion of the cerebellum. This malformation is commonly associated with hydrocephalus.[6] Both the Chiari II malformation and hydrocephalus impose on these children a need for constant follow-up and monitoring for the rest of their lives.

Ultrasonography performed during pregnancy in women with fetuses with MMC has demonstrated a progressive evolution of the Chiari II malformation and hydrocephalus in these fetuses. Another detail observed during the serial performance of the ultrasounds is a progressive worsening the fetuses affected by MMC have in relation to the motor function in the lower limbs. This worsening could be attributed to the exposure of nervous tissue, placode and roots, to the neurotoxic action of amniotic fluid, as well as the absence of posterior vertebral elements as a result of the neural plate closure defect, between the 19th and 25th day of gestation during primary neurulation (two-hit hypothesis).[7–9]

After conducting the prospective, randomized, controlled, multicenter MOMS trial,[4] it became evident that the prenatal surgical treatment for the repair of MMC would significantly improve the quality of life of these children, with important regression of the Chiari II malformation, reduced need for

placement of PVD, and improvement of motor sensory parameters in all the fetuses.[4,5,7,10–13] Regarding the functions of the urinary tract, the neurogenic bladder continues to be present, but the occurrence of urinary tract infections in patients treated in the prenatal period is lower than in children who received postnatal treatment.[14] Another very important observation was seen in Toronto where, after the beginning of fetal treatment for repair of MMC, combined with the good postoperative results evidenced in these children, there has been a reduction in the optional termination of pregnancy in fetuses with MMC, considering that in Canada the termination of pregnancies in the face of congenital malformations is allowed by law.[15]

Methods

This study was approved by the IRB with the number 32112920.2.00008110 version 3.

Descriptive study of 26 cases with intrauterine MMC repair by mini-hysterotomy or the Peralta technique performed at the Instituto Estadual do Cérebro Paulo Niemeyer (IECPN) from December 2017 to February 2020.

Epidemiology / Etiology

Epidemiological studies have revealed a wide variation in the prevalence of MMC based on ethnicity, race, temporal and geographical trends. Spinal dysraphism occurs at approximately 0.7 to 0.8 per 1000 live births in the USA; in Brazil there is an incidence of 1 to 2 cases per 1000 live births, and underdeveloped countries have a slightly higher incidence.[1,8,16,17]

It is recognized that MMC has a complex etiologic basis with genetic and environmental predisposing factors. The genetic influence is evidenced by the presence of recurrence within families (5% for the second child, 10% for the third child, and 25% for a fourth child of the same couple)[18], ethnic groups, and an increased risk in genes involving the folate metabolism and other cellular processes.[19] Other maternal conditions implicated as risk factors are obesity and diabetes.[15] A body mass index (BMI) greater than 30 seems to double the risk of conceiving children with dysraphism,[4] as well as the presence of febrile illness in the early stages of pregnancy. The mean BMI of our series was 27.8 (►**Table 1**). Maternal intake of anticonvulsants, such as valproate and carbamazepine, during the pre-conception period is also a widely recognized risk factor. Folic acid supplementation is recommended for women of childbearing age at least 3 months before conception, as it is known that women with a diet low in folic acid (vitamin B9) have a greater chance of having children affected by the disease.[1,4,20] In our series, it was observed that the majority of pregnant women with a lower level of education did not use folic acid supplements, while patients with a higher level of education used this medication more (►**Chart 1**).

Inclusion Criteria for Fetal Surgery

Inclusion criteria are: single pregnancy, gestational age between 19 and 27 weeks and 6 days, MMC level between T1 and S1, evidence of Arnold-Chiari II malformation, absence of fetal chromosomal alteration, absence of other fetal malformations, absence of fetal scoliosis greater than 30%, absence of a previous history of prematurity or cervix smaller than 25 mm during pregnancy, absence of serious maternal disease that may increase surgical risk, and absence of positive maternal serology for HIV or hepatitis B and C.[2,4,13,21,22]

Table 1 Data from patients operated on at IECPN compared to data chosen from the MOMS study.

Characteristics	IECPN Fetal Surgery	MOMS Fetal Surgery
Fetal gender: female – %	56%	45%
GA – weeks	26.5	23.6
Maternal age – years	29.8	29.3
Married – %	39.1%	94%
BMI	27.8	25.9
Smoker – %	*29%*	6%
Nulliparous	14.6%	42%
Previous uterine surgery – %	16%	14%
GUS injury level – % Thoracic	0%	4%
L1–L2	13%	27%
L3–L4	53.5%	38%
L5–S1	34.1%	19%

Abbreviations: BMI, body mass index; GA, gestational age. IECPN, Instituto Estadual do Cerebro Paulo Niemeyer; MOMS, management of myelomeningocele study. **Source:** Data from patients of the IECPN and MOMS study; GUS, gestational ultrasound.

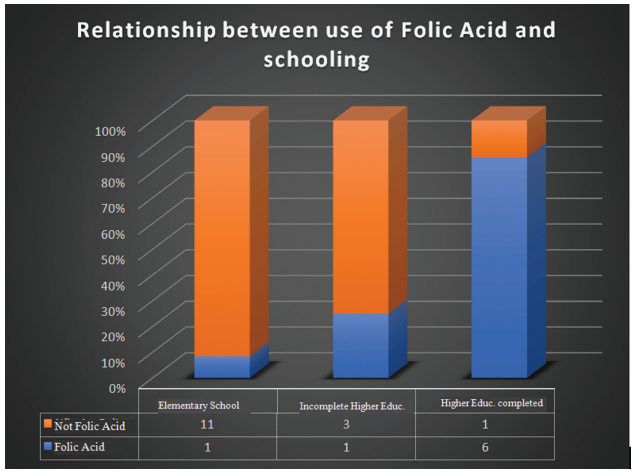

Chart 1 Correlation between patients who used folic acid and schooling. We evidenced that among the mothers with complete higher education, 6 used folic acid and 1 did not use it. Regarding those with incomplete higher education, 1 used folic acid and 3 did not. Eleven patients with elementary education did not use folate and one did. The chart shows how higher levels of education are related to the use of folic acid.

Diagnose

Currently, the diagnosis of MMC is made with ultrasound (2D or 3D) between the 12th and 14th week, which has a sensitivity of 80 to 90%. The diagnosis is made through the presence of indirect signs such as ventriculomegaly, lemon sign (scalloping of the frontal bones), banana sign (inversion of the cerebellum curvature) and obliteration of the cisterna magna (Chiari malformation type II). Direct signs are best detected in the axial plane, where the U- or C-shaped vertebrae can be visualized, due to the absence of the dorsal arches, and the interruption of the skin contour with or without the meningocele. The spinal examination also includes the location of the medullary cone, which varies according to the gestational age; typically, the medullary cone ends at L4 between the 13th and 18th week; in L3 around the 19th and 36th week, and L2 after the 36th week.[22,23] Although the image quality is currently excellent, some characteristics are still difficult to accurately assess, including the size of the placode and the extent of normal skin around the lesion. Ultrasound can also be used to assess the degree of involvement of the lower limbs in the fetus, including the presence of congenital clubfoot. The presence of active movement of the lower limbs indicates a good prognosis, and must be distinguished from involuntary movements, sometimes present in fetuses with open dysraphism.[23]

Ventriculomegaly is present in 70 to 90% of fetuses with MMC. It is assessed at the level of the ventricular atrium of the lateral ventricle in the axial plane of the fetus's head at the level of the thalamus and is considered abnormal if greater than 10 mm. The prevalence of ventriculomegaly increases along with the gestational age. Generally, there is a correlation between the severity of ventriculomegaly, its onset gestational age, and the severity of malformation of the posterior fossa. It is important to note that the ventricles may be asymmetrically dilated.[22] It is in the postnatal period that the need for hydrocephalus treatment is evaluated, either by placing a shunt or performing an endoscopic third ventriculostomy.[19,24]

Prenatal magnetic resonance imaging (MRI) is very useful to evaluate more specific details of the malformation, details that are important, but not essential in the evaluation for fetal surgery. T2 weighted images (T2WI), including single-shot fast spin-echo, or half-fourier acquisition single-shot turbo spin-echo (HASTE) with 2 to 4 mm cuts, are sufficient for diagnosis. There is no need to use gadolinium.[22,25]

Other malformations be associated with MMC are hydrocephalus (80%), Chiari II, disorderly cortical migration (92%), hypoplasia or aplasia of the cranial nerve nuclei (20%), fusion of the thalamus (16%), agenesis of the corpus callosum (12%), complete or partial agenesis of the olfactory tract or bulb (18%), dysplasias or abnormalities of the corpus callosum and heterotopias of the gray matter (19%).[18]

The presence of Chiari malformation type II occurs in almost all children with MMC who received postnatal treatment, according to the theory of Mc Lone and Kepper,[26] due to a cerebrospinal fluid fistula caused by the presence of spinal malformation, which reduces pressure in the ventricle and, consequently, originates a smaller posterior fossa, with the tentacle in a lower position. When the cerebellar primordium begins to grow, herniation occurs through the cervical vertebral canal, below the foramen magnum. Symptoms related to Chiari malformation type II are determined by the degree of descent of the cerebellum into the vertebral canal and include sialorrhea, inspiratory stridor, weak crying, and respiratory failure, among others.[27]

The level of MMC is an important predictive factor in the ability to walk. Patients with lesions at the sacral level are able to walk 100% of the time. However, patients with the lesion at the level of L3 or above will need a wheelchair to move around.[28] Most of the patients in our series had a lesion between levels L3 and L4 (►**Table 1**). Approximately 84% of children with neurogenic bladders have altered bowel control and severe chronic constipation.[18] The quality of their social life will depend on the degree of functional loss (difficulty walking, fecal and urinary incontinence).

Surgical Treatment

Classically, MMC repair is performed shortly after birth with the postnatal repair of the lesion. However, studies show that spinal cord injury in MMC occurs before birth, both due to an abnormality in the development of the neural tube during the embryonic period, and the chronic exposure of this nervous tissue to the intrauterine environment (amniotic fluid, trauma to the wall of the uterus, and hydrodynamic pressure on nervous tissue without the protection of normal skin), which worsen the neurological lesion. This theory is called two-hit hypothesis.[12] Some studies on the histological evaluation of these spinal closure defects show that the nervous tissue exposed directly to the amniotic fluid (spinal cord, meninges, and nerve roots) presents different degrees of loss of neural tissue, at the same time as the less exposed portions (ventral and dorsal horns, especially of the proximal portions of the lesion) have a normal histological aspect. Additionally, several observational studies have shown that most fetuses with MMC with movements in the lower limbs in ultrasound exams do not present the same motor function soon after birth. This theory (two-hit hypothesis) led to the initiation of studies for intrauterine treatment of MMC, in order to improve the prognosis by reducing environmental factors.[4,10,16,22,29,30]

The first experimental studies on intrauterine closure of MMC were carried out in the mid-1980s, in primates. Initial animal studies showed that coverage of lesions similar to dysraphism in the intrauterine period preserved neurological function and reversed cerebellar herniation to varying degrees.[24,31,32] The repair of the defect in human fetuses started in 1997 with Bruner et al.,[31] and the initial studies corroborated with the previous results, and still reported the reduction of the need to use shunts for hydrocephalus. Since then, several techniques have been developed, and since 2004 the intrauterine repair of MMC has been recommended. Before then, there was no standardization as to the indications and techniques used. In 2011, a randomized clinical trial was conducted in the USA, called MOMS (Management of Myelomeningocele Study),[3,7,30] the

results of which were published in the New England Journal of Medicine in 2011. In this study, 183 pregnant women whose fetuses had MMC were randomized for intrauterine treatment (MMC repair through hysterotomy) or for postnatal treatment (control group). The main criteria for inclusion of patients in this study were: gestational age between 19 and 27 weeks, MMC with a higher level of injury between T1 (first thoracic vertebra) and S1 (first sacral vertebra), absence of other serious fetal malformations or chromosomal abnormalities, presence of Chiari II, and absence of severe tortuosity in the fetal spine. The repair of the defect in the fetus was done through a body hysterotomy of 6 to 10 cm in length, in order to allow adequate exposure of the fetal lesion so that the neurosurgeon could perform the classical MMC layered closure surgery. The results were extremely promising. There was a significant reduction in the need to install ventriculoperitoneal shunts in the fetal surgery group (40%) in relation to children operated after birth (82%), and it improves global neurological and motor scores of infants. In the 30th month follow-up of these children, there was a significant increase in the chance of walking without using orthoses and a significant improvement in intellectual development, when compared to the group of children who were operated after birth.[3,6,7]

Despite the favorable results for the child, fetal surgery was accompanied by some controllable, but not negligible, maternal complications. The most frequently observed were premature rupture of ovular membranes (PTROM, 46%), premature labor (PTL, 38%), complete or partial dehiscence of the hysterotomy observed at the time of pregnancy resolution (30%), chorioamniotic separation (26%), need for maternal blood transfusion at delivery (9%), acute pulmonary edema (6%) after fetal surgery, and placental abruption (6%) during fetal surgery. These complications ended up somewhat limiting the spread of fetal surgery for MMC worldwide.[3–5,30]

In order to minimize the access necessary for the repair of fetal dysraphism and, therefore, to reduce maternal morbidity, some groups have tested the endoscopic approach. However, the neurological results after these apparently less invasive procedures are still not well known, and the rates of PTROM, PTL and fetal/neonatal scar dehiscence requiring postnatal reoperation are still high.[13,33,34]

Considering that adverse maternal results are the biggest concerns regarding the intrauterine approach to fetal repair of spinal dysraphism, a technical innovation was described in 2016 in order to minimize these complications. This new technique is described as mini-hysterotomy, or the Peralta technique,[20] and consists of a modification of the classical open surgery for the treatment of fetal MMC, in which the same multilayer repair of the spinal defect is performed through a 2.5 to 3.5 cm hysterotomy. This technique is the one we have been using at the IECPN, since December 2017.

The Peralta Mini-Hysterotomy

The surgery is performed with the pregnant woman in the supine position, under general anesthesia; an enlarged Pfannestiel incision is made with subsequent exteriorization

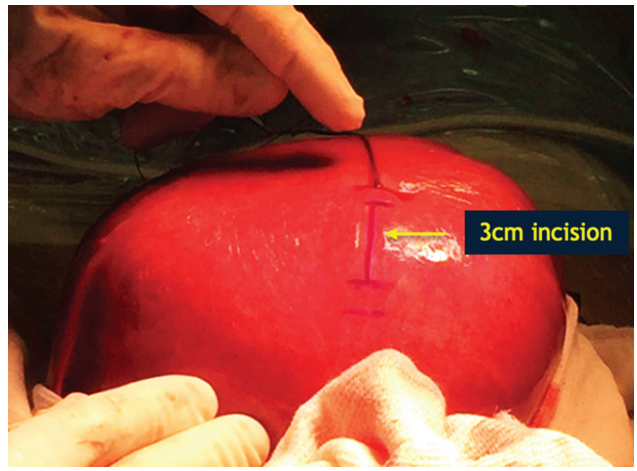

Fig. 1 Mini-hysterotomy (Peralta technique).

of the uterus from the abdominal cavity. The fetus is gently moved by ultrasound-guided external manipulation, so that the spinal defect is located against the uterine wall in the region where the placenta is not located. Thereafter, a 2.5 to 3.5 cm hysterotomy is performed, at least 2 cm from the placental edge (►**Fig. 1**). The amniotic membrane is sutured in the inner layer of the myometrium and then the neonatal Ankeney retractor is introduced, which is fixed with the help of the Leyla retraction system, in order to keep the uterine walls separate and expose the malformation (►**Fig. 2**). Then, the repair of MMC is performed by the neurosurgery team. During this part, the fetus is monitored by the obstetric team.[20]

From the neurosurgical point of view, the goal of the treatment of MMC is to remove the malformed hernial sac, protect the exposed nervous system by creating a barrier between the spinal canal and the outside, preventing trauma and protecting the central nervous system against the aggressive action of the amniotic fluid, in addition to restoring

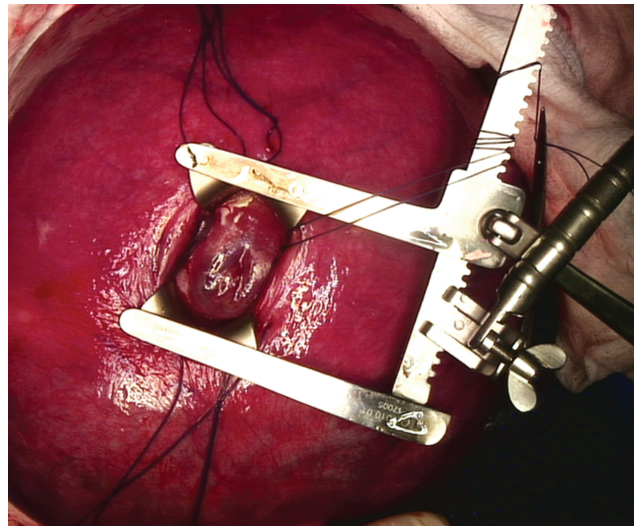

Fig. 2 The neonatal Ankeney retractor is introduced, which is fixed with the help of the Leyla retraction system, in order to keep the uterine walls separate and expose the malformation.

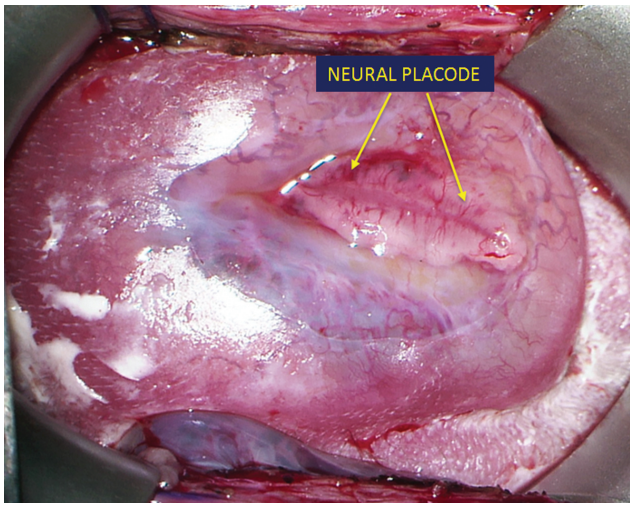

Fig. 3 The placode is identified after the Ankeney retractor has been introduced.

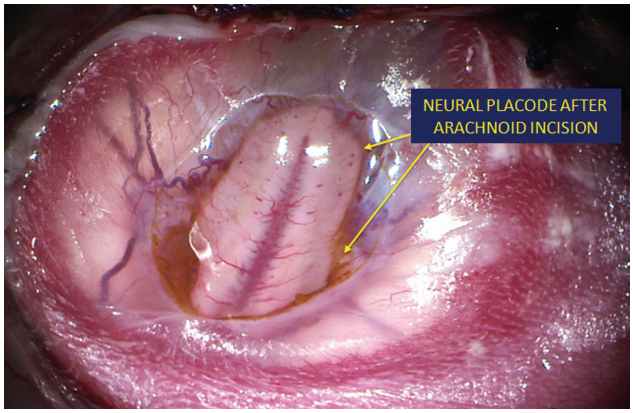

Fig. 4 The neural placode is circumferentially dissected. The neural groove can be seen, which would represent the central canal of the spinal cord.

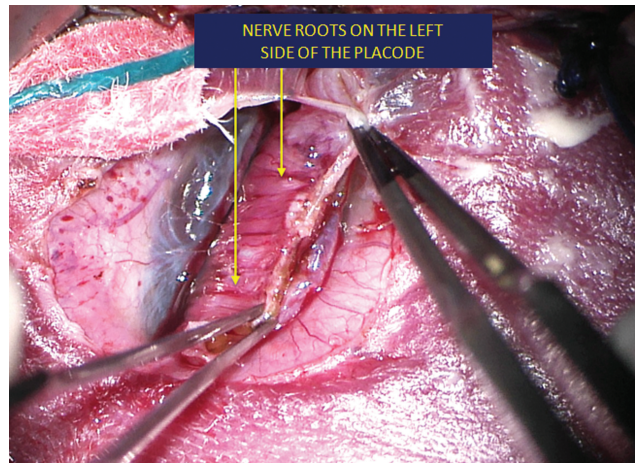

Fig. 5 The dorsal roots can be seen after arachnoid incision.

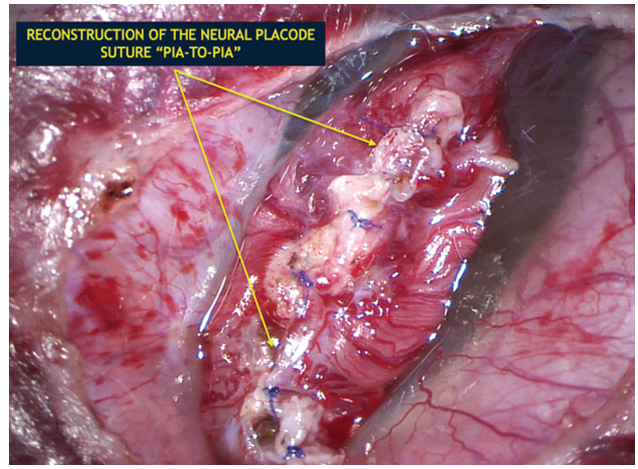

Fig. 6 Reconstruction of the spinal cord with micro sutures (pia-to-pia) with PDS 7.0.

the cerebrospinal fluid medium around the malformed spinal cord, thereby preserving motor and sensory functions.

In fetal surgery, neurosurgical steps are similar to those of postnatal surgery. With the aid of the surgical microscope, the placode is identified (►**Fig. 3**), then separated from the surrounding epithelium (►**Fig. 4** and ►**Fig. 5**). The junction between the placode and the skin is variable, usually a translucent tissue extends from each side of the placode to the medial side of the skin, and this is the entry point for the surgical repair. This layer represents the primitive arachnoid pia and should be incised close to the skin, as the placode is very fragile; thereafter, the circumferential incision is continued, allowing complete mobilization of the placode, which is closed with PDS 7.0 sutures, bringing the edges together (pia-to-pia) (►**Fig. 6**). The dura mater is often transparent and has characteristics of the arachnoid of older children. It is present along the vertebral canal and extends laterally beyond the vertebral canal, being lost in the subcutaneous tissue. The junction between the dura and the dermis can be seen by slightly elevating the skin. At this point, a small incision is made and the dura mater is dissected in a circumferential manner, separating the dorsal fascia. After the 22nd week, the dura mater becomes more substantial and easier to handle. After its complete dissection, it is sutured with a continuous stitch with PDS 6.0 (►**Fig.7A**, ►**Fig.7B**, ►**Fig.7C**). When the dural closure is completed, the fetal skin is closed in a single plane, also with continuous stitch with PDS 5.0 (►**Fig. 8**). The dissection of the muscular plane and fascia is not performed due to bleeding and reduced surgical time. The elevation of the skin and separation of the adjacent subcutaneous tissue does not present any major difficulties. Once the primary closure is performed, the postnatal result is very good. Finally, it should be taken into account that the fetuses' skin can break with a harsher movement, despite its great elasticity.

After the injury is closed, the obstetrics team continues to close the uterus and abdominal wall. A Nelaton probe is then inserted into the amniotic cavity in the opposite direction to the location of the placenta, then the uterine wall is closed in layers, bringing the edges of the hysterotomy closer together. During this closure, warm saline is instilled in the amniotic cavity, in an amount sufficient to involve the entire fetus (monitored by ultrasound), always giving fetal vitality. Right

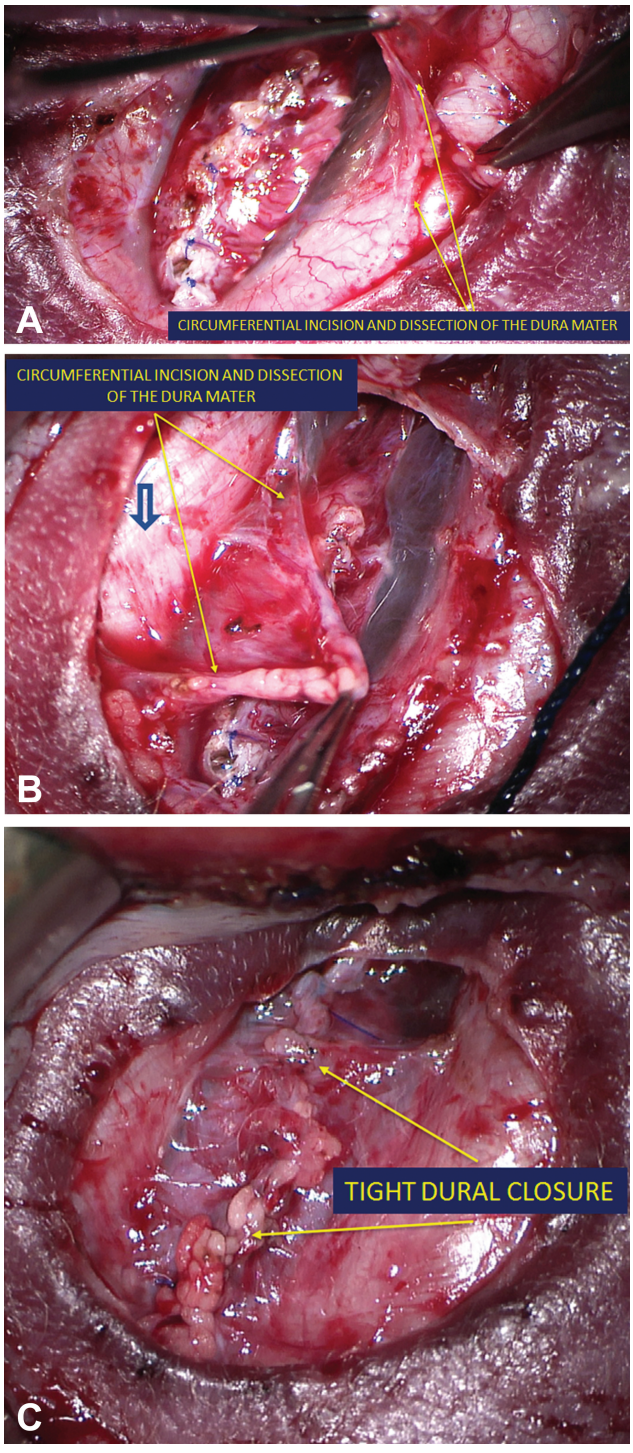

Fig. 7 (A) Circumferential dissection of the dura. (B) After complete circumferential dissection of the dura, we can see the muscle fascia (open arrow). (C) Tight dural closure with PDS 6.0 (running sutures).

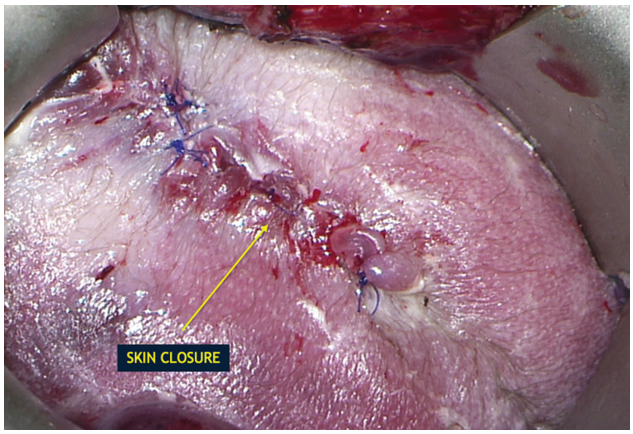

Fig. 8 The fetal skin is closed in a single plane, also with continuous stitch with PDS 5.0.

Table 2 Observed results of skeletal muscle characteristics. And exam evaluating the reflexes presented in the first month of life, performed by a neonatologist.

Skeletal muscle characteristics no. (%)	Yes	No
Anatomical defect of the lower limbs	10 (43)	13 (56.5)
Unilateral clubfoot	2 (8.6)	20 (86.9)
Bilateral clubfoot	8 (35)	13 (56)
Neonatal neurological examination: Normal +	15 (65.2)	8 (34.7)
Abolished tendon bone reflexes	2 (8.6)	21 (91.3)
Active movements of the lower limbs	20 (86.9)	3 (13)

Note: The most common anatomical defect was clubfoot. Most patients had a normal motor neurological exam for their age.

after the hysterotomy is closed and the Nelaton tube is removed, the peritoneal cavity is cleaned, and the hemostasis and pelvic viscera are reviewed. Then, the uterus is hydrated with saline inside the peritoneal cavity and the overlying layers of the abdominal wall are closed.

The follow-up of these babies in the postnatal period includes an initial observation of the MMC scar, being necessary to reoperate in cases of cerebrospinal fluid fistula; monitoring of ventriculomegaly, assessing the need or not for surgical treatment, and monitoring of bladder dysfunction with assessment of the possible need for vesical catheterization. These children subsequently require the monitoring of a multidisciplinary team: pediatrician, neurosurgeon, neurologist, geneticist, orthopedist, urologist, physiotherapist, and psychological support (►**Table 2**).

Regarding maternal complications,[35] we observed two cases of placental abruption, two cases of preeclampsia and one case of uterine rupture. Regarding fetal complications, we had two deliveries under 30 weeks and one perinatal death (►**Table 3**).

Of the 23 children in our series, aged 12 months, only 5 needed treatment for hydrocephalus, and 12 of the 23 children aged 12 months did not have Chiari II malformation (►**Table 4**).

Table 3 Results showing maternal complications, comparing the two groups, MOMS / IECPN.

Maternal – fetal complications (%)	IECPN	MOMS
Oligo amnio	1 (4)	16 (21)
DPP	2 (8.6)	36 (46)
Chorioamnionitis	1 (4)	2(3)
Placenta previa	1 (4)	5 (6)
Gestational diabetes	2 (8.6)	4 (5)
Pre-eclampsia	2 (8.6)	3(4)
Uterine rupture	1 (4)	1 (1)
Fetal complications		
Repair dehiscence	1 (4)	10 (13)
Gestational age at birth (weeks)		
< 30	2 (8)	10 (13)
30–34	11 (47)	26 (33)
35–36	6 (26)	26 (33)
> 37	5 (22)	16 (21)
Mean birth weight (grams)	2,096	2,383
Perinatal death	1 (4)	2 (3)

Abbreviations: DPP, premature placental abruption; IECPN, Instituto Estadual do Cerebro Paulo Niemeyer; MOMS, management of myelomeningocele study. **Notes:** Perinatal death at the IECPN was related primarily to intrauterine infection, and secondarily to premature birth evolving to the newborn's respiratory distress syndrome. Low birth weight and premature birth are risk factors for fetal complications. At IECPN, the uterine opening is 2.5 to 3.0 cm in diameter, which is one of the causes of different values between the variables of DPP and oligo amnio.

Table 4 Comparative data of the results in the first 12 months of life of patients operated on fetal myelomeningocele, between IECPN and MOMS study.

Primary results of children at 12 months of age		
Results	**IECP patients (n = 23)**	**MOMS patients (n = 73)**
Placement of PVD / TVE – no. (%)	5 (26.5)	31 (40)
No evidence of FP herniation – no. (%)	12 (63)	25 (36)
Decompression FP for Chiari II – no. (%)	0	1 (1)
PVD infection – no. (%)	2 (10)	5 (6)

Abbreviations: FP, posterior fossa; IECPN, Instituto Estadual do Cerebro Paulo Niemeyer; MOMS, management of myelomeningocele study; PVD, peritoneal ventricle shunt; TVE, third ventriculostomy endoscopy.

Discussion

Surgical treatment for fetal MMC has been widely indicated regarding the postnatal treatment.[13] Fetal surgery, whether made by microscopy or endoscopically, requires a coordinated effort of several specialists, including from the nursing staff, neonatologists, obstetricians, pediatric surgeons, anesthesiologists with maternal-fetal experience, neurosurgeons, radiologists, geneticists, and psychologists, which makes the IECPN a qualified and complete hospital to perform this type of procedure in Rio de Janeiro, Brazil.

The resources necessary to start a program dedicated to fetal surgery need to be known and no details should be ignored. A multidisciplinary team with experience to carry out patient evaluation is essential to perform procedures, as well as appropriate postoperative follow-up. Hospitals where fetal surgeries are performed most often generate very high costs, but it is essential that they have multidisciplinary and qualified teams to perform fetal surgery.

The main trial conducted in 2011, MOMS, started in a developed country, with more favorable technology and physical means to carry out the study, yet Brazil already performed this type of surgery with excellent and favorable results, being one of the countries with a high number of surgeries and positive outcomes.[22,36,37]

Lunet et al.,[38] suggest that the non-use of folic acid is dependent on some demographic and socioeconomical factors, especially in cases of women with less education, single mothers, without prenatal monitoring, becoming more vulnerable to malformations of the neural tube.[39] Barbosa et al. showed that the level of education and higher number of prenatal consultations are directly linked to the use of folate, and a higher education level corresponds to a higher use of folic acid and lower incidence of children with neural tube defects. [40] In our series, we have noted that patients with more education were the ones who used folic acid the most during prenatal care; this shows that the socioeconomic and educational parameter is directly linked with one of the main factors of closure of the neural tube.

Not only does the fetus present potential risks from intrauterine fetal surgery, but the mother's health can also be threatened. The mother undergoes two laparotomy surgeries, one for MMCf correction and another to perform the c-section at the appropriate moment to interrupt the pregnancy. In our study, we noted that we were able to perform the procedure in several patients with more than one pregnancy and previous C-section without causing maternal complications for this group of pregnant women. It is not necessary to exclude women with previous c-sections. Our school adopts the Peralta mini-hysterotomy (uterine opening of 2.5–3.5 cm)[20], with more maternal favorable outcomes compared to the MOMS study.

In our series we have noted a total of 16% of women with previous uterine surgeries, which is similar to the results in the MOMS study (14%). Nulliparity between the 2 centers had a difference of almost 30%, IECPN (14.6%) vs MOMS.[35,41] Placental abruption occurred in 8% of our patients, while at MOMS placental abruption occurred in 42% of pregnant women; we believe that this great difference is due to the use of the Peralta technique, which is related to less postoperative maternal complications.

Within the expected outcomes for patients who need shunt, only 26% of our patients, all of which were over

11 months old, underwent internal ventricular shunt or third ventriculostomy endoscopy (TVE). A surgery performed with gestational age within the stipulated time (19–25.6 weeks) minimizes the risk of reduced posterior fossa and descent of the brain stem by the foramen magnum (Chiari II), which is one of the physical mechanisms that favor hydrocephalus when surgery is performed in the postnatal period.[33]

Hydrocephalus tends to progress in patients with MMC during pregnancy, which is why operating earlier in pregnancy, when hydrocephalus is less evident, reduces the possible need for postnatal procedure for ventriculoperitoneal shunt placement. This was suggested by Bruner et al., who showed that the intrauterine repair after 26 weeks of age conferred much less benefit than the surgery performed between 20 and 24 weeks.[17,33]

McLone (1983) commented that up to 32% of patients with MMC observed and corrected in the postnatal period presented the Arnold-Chiari II malformation.[41,42] It is currently known that this malformation is seen in 80 to 100% of patients with MMC who are operated in the postnatal period.[43] Stevenson (2004) observed that patients with Arnold-Chiari II, sometimes had such prominent deformities and bony angulations posterior fossa decompression was required in patients up to 2 years old to decompress the bulb and release cerebral spinal fluid (CSF) flow,[44] a situation not observed in our study of cases at the IECPN.

Conclusion

Microsurgery provides better results when compared to patients treated after birth. We have observed that prenatal surgery for the treatment of MMC provides a decreased occurrence of hydrocephalus, resulting in a decrease in the need to place a peritoneal ventricular shunt. We also proved an important reduction in the occurrence of Chiari II, which was proved through gestational ultrasound and, in some cases, fetal MRI. Finally, we have also proved that the use of the Peralta technique results in more independent children, due to a better motor sensory function, when compared to the newborns submitted to traditional postnatal closure.

Conflict of Interests

The authors have no conflict of interests to declare.

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Educational Status of Minimally Invasive Spine Surgery

Situação educacional da cirurgia minimamente invasiva da coluna

Bernardo de Andrada Pereira[1] Kanwaljeet Garg[2] James Mamaril-Davis[1] Bipin Chaurasia[3] Alfredo Guiroy[4] Jahangir Asghar[4] Jay D. Turner[5] R. John Hurlbert[1]

[1] Department of Neurosurgery, Banner University Medical Center, University of Arizona, Tucson, Arizona, United States
[2] Department of Neurosurgery, All India Institute of Medical Sciences, New Delhi, India
[3] Department of Neurosurgery, Bhawani Hospital and Research Center, Birguni, Nepal
[4] Spine Department, Elite Spine Health and Wellness Center, Fort Lauderdale, Florida, United States
[5] Department of Neurosurgery, Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona, United States

Address for correspondence Bernardo de Andrada Pereira, MD, University of Arizona, Banner University Medical Center, Tucson, Arizona, United States (e-mail: bernardoandradamd@gmail.com).

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Abstract

Introduction The objective of this study was to understand how spine surgeons learn minimally invasive spine surgery (MISS) and how the COVID-19 pandemic impacted the educational experience of MISS. Potential solutions for increasing the spine surgeon's access to MISS educational resources were also discussed.

Methods An internet survey was distributed to neurosurgical and orthopedic spine surgeons across multiple online platforms from April to June 2021, asking specific questions about education and training for MISS. Online survey tools were used to contact spine surgeons in the five geographical continents.

Results A total of 303 spine surgeons responded to the survey: 272 (89.7%) neurosurgeons and 31 (10.3%) orthopedic surgeons. The six countries with the greatest number of participants were: Argentina ($n = 70$; 23.1%), India ($n = 47$; 15.5%), Brazil ($n = 34$; 11.2%), Pakistan ($n = 10$; 3.3%), Mexico ($n = 9$; 3.0%), and Chile ($n = 8$; 2.6%).

Conclusion Most spine surgeons were able to attend virtual learning events during the pandemic, but cadaveric study was still considered the gold standard for learning MISS. Multidisciplinary effort is needed to develop structured curriculums for teaching MISS that include a variety of educational tools such as cadaver laboratory, guidance from experienced surgeons, and virtual demonstrations.

Keywords
- MISS
- spine surgery
- minimally invasive surgery
- cadaver-laboratory
- online education
- COVID-19

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Resumo

Introdução O objetivo desse estudo foi entender como os cirurgiões de coluna aprendem técnicas minimamente invasivas e como a pandemia de COVID-19 impactou essa atividade. Soluções em potencial para aumentar o acesso a ferramentas educacionais de cirurgia minimamente invasiva são discutidas.

Métodos Uma pesquisa realizada na internet para neurocirurgiões e ortopedistas em múltiplas plataformas on-line de abril a junho de 2021, perguntando especificamente questões sobre o estado educacional e de treinamento em cirurgia minimamente invasiva de coluna. Plataformas online específicas foram utilizadas para alcançar cirurgiões de coluna nos cinco continentes geográficos.

Resultados Um total de 303 cirurgiões de coluna responderam à pesquisa: 272 (89,7%) neurocirurgiões e 31 (10,3%) ortopedistas. Os seis países com os maiores números de respostas foram: Argentina ($n = 70$; 23,1%); Índia ($n = 47$; 15,5%); Brasil ($n = 34$; 11,2%), Paquistão ($n = 10$, 3,3%), México ($n = 9$; 3,0%) e Chile ($n = 8$; 2,6%).

Conclusão A maioria dos respondentes foi capaz de frequentar cursos online durante a pandemia, porém cursos cadavéricos ainda são considerados o padrão-ouro para o aprendizado de técnicas minimamente invasivas. Um esforço multidisciplinar será necessário para desenvolver um currículo estruturado que inclua uma variedade de ferramentas educacionais como laboratório cadáver, tutoria por pares mais experientes e demonstrações virtuais.

Palavras-chave

- cirurgia de coluna minimamente invasiva
- treinamento online
- COVID-19
- pandemia
- cadáver

Introduction

Minimally invasive spine surgery (MISS) is attracting interest as a feasible alternative to open surgery, with benefits such as decreased blood loss, less soft tissue and muscle injury, lower rates of surgical site infections, and reduced length of hospital stay.[1,2,3] Interest in MISS is increasing steadily not only among spine surgeons but also among patients. In a prospective survey, up to 80% of the patients reported a preference for MISS should the need of a spine surgery arise at a later date.[4] Recently, there has been substantial advancements in MISS technology including specific retractor systems (portals), coupled with illumination, microscopes and endoscopes for magnification, and 3D navigation imaging techniques. These improvements in technology, along with increased learning opportunities—such as cadaver courses and laboratories—have equipped spine surgeons with tools to develop their skills and become more familiar with the philosophy and approaches of MISS. This technique has also been touted as less costly, with more economic value than open techniques, especially in developed countries.[5,6,7] However, there is still ambiguity as to whether this is true for all spine procedures.[8] Given the high cost and steep learning curve for implementing MISS into routine spine surgery practices, we sought to better understand its current status. Therefore, we presented an internet survey to both neurosurgical and orthopedic spine surgeons across various online platforms to examine their practice regarding the use of MISS surgical techniques, as well as access to educational resources and availability of instruments for learning. We also aimed to identify potential bottlenecks for the worldwide adoption and patient access to it.

The detailed objective of this study was to understand how spine surgeons learn and practice MISS, as well as how the COVID-19 pandemic impacted this activity. We also discussed potential solutions to increase the spine surgeons' access to educational resources.

Materials and Methods

This cross-sectional study was performed using an online survey consisting of 23 questions via Google Forms (Google LLC., Alphabet Inc., Mountain View, CA, USA). The Google form was accessible through a hyperlink from April 21 to June 8, 2021. The questionnaire was designed in the English language and distributed to neurosurgical and orthopedic spine surgeons. Four social media platforms were used to contact spine surgeons in six geographical continents (North and South America, Europe, Africa, Asia, and Oceania): Facebook (Facebook Inc; Menlo Park, CA, USA), LinkedIn (Microsoft Corp., Sunnyvale, CA, USA), WhatsApp (Facebook Inc., Menlo Park, CA, USA), and Telegram (Telegram Messenger LLP., London, United Kingdom). The survey was posted in various forums that were created exclusively for topics related to neurosurgery and spine surgery (i.e., clinical cases) in the prior listed platforms.

Survey

Questions in the survey were related to spine surgeon demographics (country and city of practice), age, years of practice, features of their respective institutional features (number of members on team), specialty, types of surgeries more frequently performed (decompression vs. fusion), as well as specific questions regarding MISS, such as surgery experience, access to technology, access to educational training, types of approaches learned and comfortably performed, opinion about preferred educational strategies for

Table 1 List of 23 questions included in the online questionnaire

Questions	
1	Do you provide consent for this survey? The responses collected here can be used for statistical analysis, research purposes, and to guide actions toward a better learning environment?
2	What is your specialty?
3	Please select the country that you work in:
4	Please mention the city where you work:
5	What is your age?
6	What is the current duration of your experience in neurosurgery (in completed years)?
7	What kind of set up are you working in?
8	How many neurosurgeons are there in your team?
9	What percentage of your total practice is related to spinal disorders?
10	What percentage of your total spine practice is via MISS approach?
11	How much of your spine practice involves fusion?
12	How much of your fusions are via MISS approach?
13	Are minimally invasive spine surgery (MISS) instruments, tools and apparatus being usually available to you?
14	Did you ever had an opportunity to be trained in a MISS spine case? You can check more than one box.
15	How often do you attend cadaver-lab?
16	Before the COVID-19 pandemic, how often did you use to travel to other countries with the objective of attending MISS spine course or cadaver-lab?
17	Have you ever attended virtual MISS teaching?
18	What do you think is the gold standard for MISS learning?
19	Who funded your MISS teaching? Can check more than one option.
20	Do you think practice in cadaver is important before doing a real case?
21	Which all of these procedures are you trained at?
22	Which all of these procedures do you perform independently?
23	How do you think the COVID-19 pandemic affected your ability to learn MISS?

Abbreviation: COVID-19, coronavirus disease 2019; MISS, minimally invasive spine surgery.

learning the related techniques, and opinion about how COVID-19 impacted access to education. ►**Table 1** shows the survey questionnaire.

Analysis

The answers from the survey were analyzed based on different aspects: neurosurgical versus orthopedic spine surgeons; geographical location of the practicing surgeon; institutional setup (government vs. private); and age of the surgeon. Countries located in Central America (Caribbean Islands and Continental countries) were all considered in the North American analyses. Responses from participants who did not provide consent for use of their data in the present manuscript were excluded from analysis. The statistical analysis was performed using R language v 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).[9] Categorical data were expressed as percentages, while continuous data were expressed as means with standard deviation (SD). Categorical data were analyzed using the Chi-Square test or the Fisher exact test, wherever indicated. If the continuous data met the condition of normality, then the Student *t*-test or analysis of variance (ANOVA) was implemented; otherwise, nonparametric counterparts were used. A *p*-value < 0.05 was considered statistically significant.

Results

A total of 308 spine surgeons answered the survey during the aforementioned time period. Of those, 5 (1.6%) did not give their consent to utilize their answers for research purposes, so they were excluded from the analysis. Hence, the responses of 303 participants were included in the present study.

Demographics

Out of the 303 respondents included in this study, 272 (89.7%) were neurosurgeons and 31 (10.3%) were orthopedic spine surgeons. Age of the respondents ranged from 23 to 70 years old (mean: 40.83 ± 8.75). The six countries with greatest number of participants were Argentina ($n = 70$; 23.1%), India ($n = 47$; 15.5%), Brazil ($n = 34$; 11.2%), Pakistan ($n = 10$; 3.3%), Mexico ($n = 9$; 3.0%) and Chile ($n = 8$; 2.6%). All countries included in the survey, with their respective number of participants, are summarized in ►**Table 2** and ►**Fig. 1**.

Table 2 Countries from which survey respondents originate

Africa	*n* = 17 (5.6%)	Asia	*n* = 104 (34.3%)	Europe	n = 29 (9.6%)	North America	n = 23 (7.6%)	Oceania	n = 1 (0.3%)	South America	n = 129 (42.6%)
Botswana	1 (0.3%)	Afghanistan	1 (0.3%)	Austria	1 (0.3%)	Dominican Republic	2 (0.6%)	Australia	1 (0.3%)	Argentina	70 (23.1%)
Egypt	5 (1.6%)	Bangladesh	6 (2.0%)	France	1 (0.3%)	Guatemala	3 (1.0%)			Bolivia	3 (1.0%)
Ethiopia	1 (0.3%)	India	47 (15.5%)	Germany	5 (1.6%)	Honduras	1 (0.3%)			Brazil	34 (11.2%)
Mauritius	1 (0.3%)	Indonesia	1 (0.3%)	Italy	5 (1.6%)	Mexico	9 (3.0%)			Chile	8 (2.6%)
Nigeria	3 (1.0%)	Iraq	2 (0.6%)	Poland	1 (0.3%)	Panama	2 (0.6%)			Colombia	4 (1.3%)
South Africa	1 (0.3%)	Jordan	4 (1.3%)	Portugal	1 (0.3%)	Trinidad & Tobago	1 (0.3%)			Ecuador	1 (0.3%)
Sudan	2 (0.6%)	South Korea	2 (0.6%)	Romania	2 (0.6%)	United States	5 (1.6%)			Peru	5 (1.6%)
Zambia	3 (1.0%)	Lebanon	1 (0.3%)	Russia	7 (2.3%)					Uruguay	1 (0.3%)
		Nepal	2 (0.6%)	Spain	1 (0.3%)					Venezuela	3 (1.0%)
		Pakistan	10 (3.3%)	Switzerland	1 (0.3%)						
		Philippines	2 (0.6%)	Ukraine	2 (0.6%)						
		Qatar	1 (0.3%)	United Kingdom	2 (0.6%)						
		Saudi Arabia	7 (2.3%)								
		Syria	4 (1.3%)								
		Taiwan	2 (0.6%)								
		Thailand	2 (0.6%)								
		Turkey	6 (2.0%)								
		United Arab Emirates	1 (0.3%)								
		Uzbekistan	2 (0.6%)								
		Vietnam	1 (0.3%)								

Abbreviation: n, number of respondents (%).

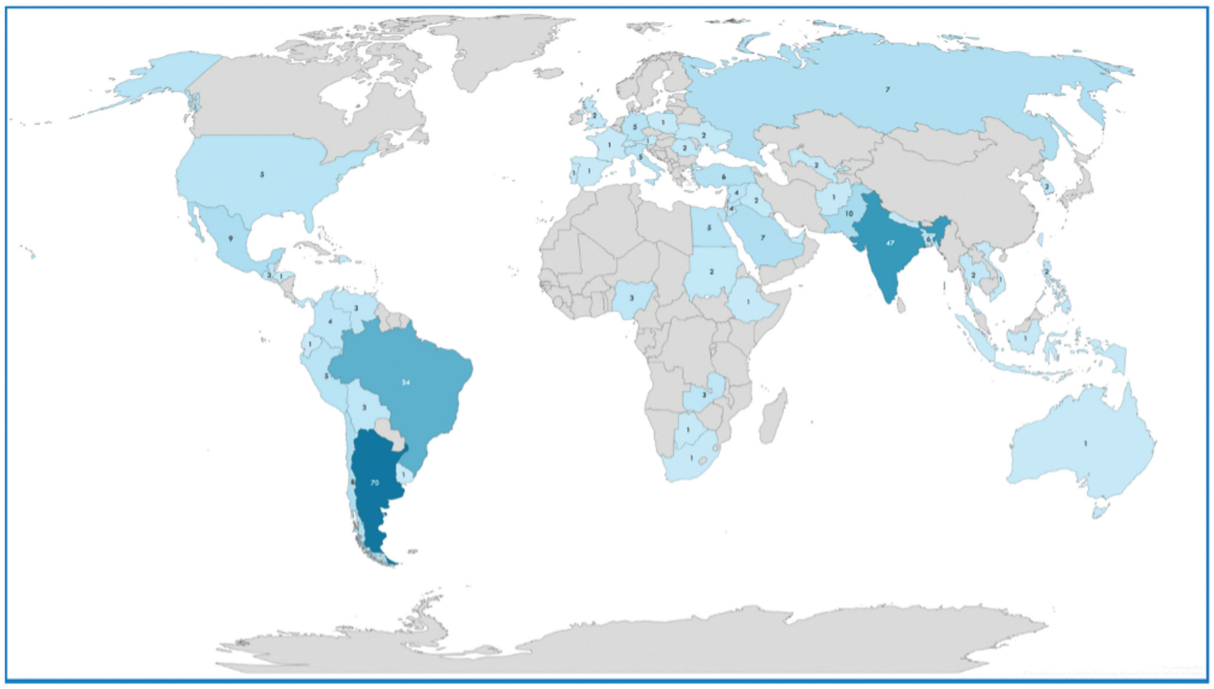

Fig. 1 World map of countries from which survey respondents originate.

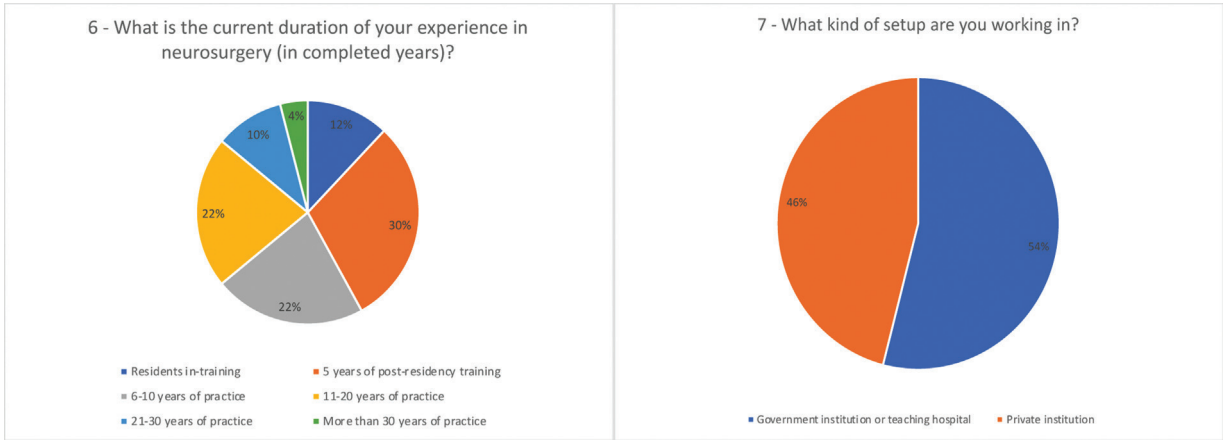

Fig. 2 2D pie charts showing distribution of answers to questions 6 and 7 about demographics.

It is important to highlight that 34 (11.5%) of the respondents were residents in-training, 91 (30.0%) had up to 5 years of post-residency practice, 67 (22.1%) had 6 to 10 years of practice, 67 (22.1%) had 11 to 20 years of practice, 31 (10.2%) had 21 to 30 years of practice, and 13 (4.2%) had more than 30 years of practice (►**Fig. 2**). Furthermore, 165 (54.4%) of the contributors worked at a government institution or teaching hospital, while 138 (45.5%) of respondents worked at private institutions (►**Fig. 2**). A significantly larger number of participants affiliated with government institutions was observed in Africa ($n = 16$, 94.1% vs. $n = 1$, 5.88%) and Europe ($n = 24$, 82.7% vs. $n = 5$, 17.2%) compared with those working in private institutions ($p < 0.0001$). The mean and SD of members in the surgical team was 11.7 ± 17.9 in Africa, 6.1 ± 6.2 in Asia, 12 ± 8.4 in Europe, 4.4 ± 5.9 in North America, and 6.0 ± 6.9 in South America. The mean and SD of members in the surgical team was 9.2 ± 9.7 for government institutions, and 3.9 ± 3.4 for private institutions ($p = 0.0002$).

Spine Practice

Regarding medical practice, 30 respondents (10%) reported 100% of their total practice relating to spine disease; 64 (21%) reported 76% to 99%; 97 (32%) reported 51% to 75%; 79 (26%) reported 26% to 50%; and 33 (11%) reported less than 25% (►**Fig. 3**). Furthermore, 6 respondents (2%) reported 100% of their spine-related procedures involving a MISS approach; 30 (10%) reported 76% to 99%; 37 (12%) reported 51% to 75%; 64 (21%) reported 26% to 50%; and 167 (55%) reported less than 25% of spine-related procedures involving MISS (►**Fig. 3**). As for spine-related procedures involving fusion, 3 respondents (1%) reported 100%; 12 (4%) reported 76% to 99%; 70 (23%)

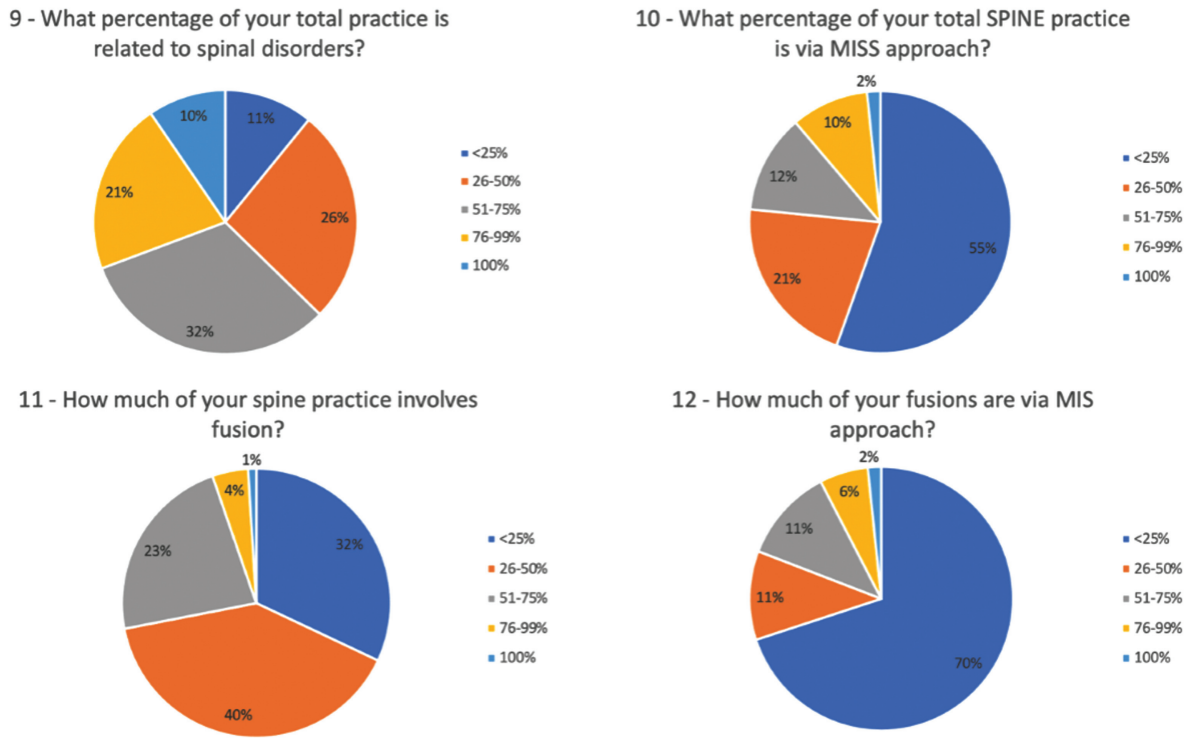

Fig. 3 2D pie charts showing distribution of answers to questions 9, 10, 11, and 12 about spine surgery practice.

reported 51% to 75%; 121 (40%) reported 26% to 50%; and 97 (32%) reported less than 25% (►**Fig. 3**). Finally, 6 respondents (2%) reported 100% of their spine fusions being performed via MISS; 18 (6%) reported 76% to 99%; 33 (11%) reported 51% to 75%; 33 (11%) reported 26% to 50%; and 212 (70%) reported less than 25% of spine fusions being performed via MISS (►**Fig. 3**).

MISS Training

When surgeons were asked about availability of MISS instruments, tools, and apparatuses in their practices, 28.9% had easy access, 25.6% experienced minor obstacles that did not dramatically impair access, 23.7% faced major obstacles, and 21.8% reported rare or no access at all. Whereas 58.6% of spine surgeons in Europe reported easy access to MISS instruments, only 5.9% of spine surgeons in Africa reported easy accessibility ($p = 0.0003$). Among the respondents who used MISS for less than 25% of their spine cases, only 14.9% ($n = 25$) had easy access to a related apparatus. On the other hand, among the respondents who used MISS for 76% to 99% of their spine cases, 62% ($n = 18$) had easy access to the necessary apparatus ($p < 0.0001$).

When asked about opportunities for training in MISS spine cases, 146 spine surgeons (48.1%) attended a cadaver laboratory, 83 (27.3%) attended a spine bony model demonstration, 105 (34.6%) attended an instrument workshop, 77 (25.4%) attended an online virtual demonstration, 95 (31.3%) learned while assisting a more experienced surgeon during a live case, 63 (20.7%) learned during residency, 39 (12.8%) learned during fellowship, and 66 (22.1%) never had an opportunity to train in MISS.

Regarding frequency of attending cadaver laboratory for learning MISS techniques, 15 participants (4.9%) reported attending every 6 months, 89 (29.3%) at least once a year, 123 (40.5%) at least once in the last 5 years, 28 (9.2%) at least once in the past 10 years, and 16 (5.2%) reported no attendance at a cadaver laboratory in the last 10 years.

When asked how often participants traveled to other counties for educational purposes of learning MISS techniques (cadaver laboratory and/or specialized course) before the COVID-19 pandemic, 39 (12.8%) answered every 6 months, 81 (26.7%) at least once a year, 91 (30.0%) at least once in the last 5 years, 23 (7.5%) at least once in the past 10 years, and 69 (22.7%) had not traveled in the past 10 years. Only 11.7% of participants from Africa used to travel every year compared with 34.4% and 37.7% in Europe and South America, respectively ($p < 0.0001$). Only 7.7% of participants from South America had not traveled to other countries in the past 10 years for the purposes of learning MISS techniques, compared with 64.7% from Africa ($p < 0.0001$).

Respondents were also asked if they ever attended a virtual MISS teaching event, as well as their opinion about the event's utility: 83 spine surgeons (27.3%) reported prior attendance and perceived them as useful, 95 (31.3%) reported prior attendance and perceived them as somewhat useful, 10 (3.3%) reported prior attended but did not perceive them as useful, 69 (22.7%) reported no prior attendance but perceived them as useful, 34 (11.2%) reported no prior attendance and perceived them as somewhat useful, and 12 (4.0%) reported no prior attendance and perceived them as not useful.

Fig. 4 Radar plot showing distribution of learning opportunities for training in MISS.

When asked about what educational platform should be the gold standard for learning MISS techniques, 155 spine surgeons (51.1%) preferred the cadaver laboratory, 134 (44.2%) preferred ongoing live cases with patients and more experienced surgeons, 7 (2.3%) preferred bony model demonstrations, 6 (1.9%) preferred workshop demonstrations, and only 1 (0.3%) preferred virtual demonstrations (►**Fig. 4**).

The question "Who funded your MISS teaching?" allowed respondents to select more than one option. Here, the answers were: 208 (68.6%) self-funded, 55 (18.1%) institution-funded, 33 (10.8%) government-funded, 67 (22.1%) partially industry-funded, and 16 (5.2%) fully-industry funded.

When asked about the importance of practicing in cadaver laboratory before performing a live case, 186 spine surgeons (61.4%) thought this was an essential part of MISS learning, 95 (31.3%) thought that this was important but not essential, 16 (5.2%) felt comfortable performing MISS without practicing in cadaver laboratory, and 6 (2.0%) thought that this was not important.

Participants were also asked about training experiences for different MISS procedures: 77 spine surgeons (25.4%) reported prior training for transpsoas lateral lumbar interbody fusion (LLIF); 59 (19.5%) for prepsoas oblique lumbar interbody fusion (OLIF); 167 (55.1%) for transforaminal lumbar interbody fusion (TLIF); 202 (66.6%) for decompressive procedures such as laminectomy, foraminotomy, and diskectomy; 114 (37.6%) for endoscopic procedures; 70 (23.1%) for cervical procedures such as tubular foraminotomies or facet cages; 170 (56.1%) for percutaneous pedicle screw and rod fixation; 24 (7.9%) for deformity correction techniques; 47 (15.5%) for image-guided navigated procedures or robotic systems; and 166 (54.7%) for other procedures such as vertebroplasty, kyphoplasty, and pain procedures. The spine surgeons reported independent operation for the following MISS procedures: 52 (17.1%) for LLIF; 29 (9.5%) for OLIF; 123 (40.6%) for TLIF; 159 (52.5%) for decompressive procedures such as laminectomy, foraminotomy, and diskectomy; 81 (26.7%) for endoscopic procedures; 65 (21.4%) for cervical procedures such as tubular foraminotomies or facet cages; 132 (43.5%) for percutaneous pedicle screw and rod fixation; 19 (6.2%) for deformity correction techniques; 41 (19.8%) for image-guided navigated procedures or robotic systems; and 156 (51.5%) for other procedures such as vertebroplasty, kyphoplasty, and pain procedures.

Pandemic Impact

Regarding how the COVID-19 pandemic impacted the respondents' ability to learn MISS techniques, 125 spine surgeons (41.2%) reported a significant effect in terms of an

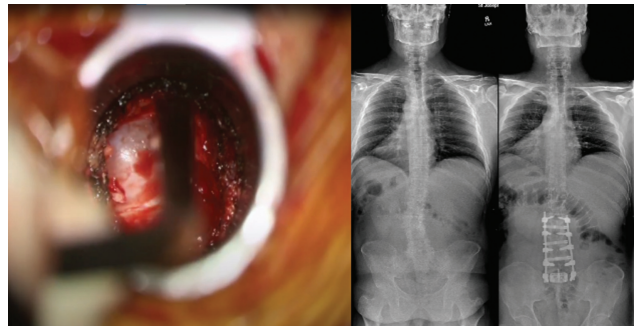

Fig. 5 (A) Minimally-invasive decompressive procedure (foraminolaminectomy) performed through a tubular retractor (access portal) ensures satisfactory neural decompression and radicular pain relief. (B) Minimally-invasive circumferential multi-stage fusion procedure utilized for degenerative deformity correction: preoperative image on left shows lumbar degenerative scoliosis; postoperative image on right shows 3-levels lateral lumbar interbody fusion from L2 to L5 associated with 4-levels posterior percutaneous pedicle screw and rod fixation from L2 to S1. Note that, in this particular case, the patient had an anterolumbar interbody fusion at L5 to S1, which was performed via opened traditional exposure.

inability to experience useful learning activities, 117 (38.6%) reported a moderate effect in that prepandemic normalcy has not returned, 29 (9.6%) reported a mild effect in that prepandemic normalcy has returned, and 32 (10.5%) reported no effect at all. Therefore, 79.8% of spine surgeons were affected by the COVID-19 pandemic in that access to MISS education was either completely or significantly limited (41.2% completely limited and 38.6% significantly limited).

Discussion

The MISS technique treats spinal disease via minimal alteration of natural anatomy, while simultaneously delivering clinical outcomes to a similar degree as open surgery (►**Fig. 5**).[1,2,3,8] There are a few advantages of MISS over open surgery, such as shorter hospital stays and less postoperative pain for most procedures.[10,11]

The philosophy of MISS is echoed by Luis Tumialan: "Opened traditional exposure is more a consequence of the midline incision than of an actual need to expose the requisite anatomy to accomplish the operation, while MISS is the opposite, almost every millimeter of exposure is granted by an access port."[12]

Although a promising alternative to traditional open surgery, MISS is not without its challenges. It is associated with a high cost for implementation in most countries, as well as a steep learning curve that involves understanding anatomical landmarks through narrow surgical ports and limited visualization of the surgical cavity, all without tactile sensation.[13,14] It is difficult to precisely estimate the learning curve for MISS, as there is a high variability between different types of procedures: whereas previous reports indicated a minimum of 39 cases to become 90% proficient in MISS TLIF, other reports indicated 72 as the minimum to become 90% proficient in MISS lumbar discectomy.[15,16,17] With this complex learning curve, it is therefore essential for the community to develop standard educational programs to minimize learning curve-induced complications. Combined with the COVID-19 pandemic, the challenge of learning from early 2020 to mid-2021 was even steeper, as residents across various surgical specialties reported a significant decline in cases and a shift to online didactics.[18] This internet survey attempted to understand the gaps in the learning process for this technique, as well as how COVID-19 impacted access to education.

The present study found significant differences in MISS tool availability between social media-using spine surgeons in Africa and Europe, despite both regions reporting spine surgeon practice predominantly in government or academic institutions. The low access to MISS tools in Africa found in this study is not surprising considering a recent global survey reported an acceptance-to-performance lag gap to be highest in Africa and the Middle East compared with lower rates in Europe, Asia, and South and North America.[19] This gap was defined as the percentage of spine surgeons who perceived MISS as part of mainstream spine surgery to the percentage of spine surgeons who actually performed it in their practices. The higher gap between perceived MISS acceptance into mainstream spine surgery and physical deployment of the techniques in Africa and the Middle East suggests that both regions have possibly delayed access to the necessary tools.[19] Furthermore, in the present study, access to MISS tools was a major determinant of MISS practice regardless of region. There were significantly more spine surgeons who reported it as representing 76% to 99% of their overall caseload with easy access to the necessary tools than those spine surgeons who reported it as representing less than 25%. Although outside the scope of this study, this may be due to a lack of support from national societies endorsing MISS in formal treatment guidelines, as there is a paucity of recommendation sheets in the current literature. Future studies could focus on examining whether access to this technique is associated with higher rates of implementation in practice.

Most of the spine surgeons who responded to this survey reported a prior opportunity to learn MISS techniques via attending cadaver laboratory. At the same time, 69.9% of spine surgeons included in this study attended cadaver laboratory either every 6 months, at least once a year, or at least once in the last 5 years. This suggests that the main educational tool for learning MISS in the pre-pandemic era was via cadaveric study. It seems clear that development of a structured curriculum will need to include training on cadavers. This suggestion is further supported by Sharif et al., who determined that cadaveric study, access to appropriate tools, and the guidance of experienced surgeons were associated with shorter learning curves for attaining MISS proficiency.[16] Although, outside the scope of this study, Sharif et al. further determined that as the spine surgeon's experience with this technique increases, the operative time and length of hospital stay improve.[16] In summary, we recognize the importance of routine practice, especially with cadaveric study, as MISS requires learning spine surgery without the traditional aspect of tactile sensation.

We also sought to understand how spine surgeons learned MISS during the COVID-19 pandemic era. Whereas 62% of spine surgeons in this study reported attendance to at least one virtual event, 38% of them reported no virtual attendance. Furthermore, 50.1% found virtual learning useful, 42.5% found it somewhat useful (not sufficient), and 7.2% did not consider it useful. When comparing opinions about the gold standard for learning MISS, 51.1% of spine surgeons considered cadaveric study, 44.2% considered guidance from an experienced, and only 0.3% considered virtual demonstration. Even though we found cadaveric study as the most appreciable method of learning MISS, virtual demonstration played a vital role with learning surgical techniques, especially during the COVID-19 pandemic. This is supported by Aziz et al., who found that resident education for online didactics transitioned to completely online platforms in 80.6% of their resident respondents across the United States in 2020.[18] Although virtual learning does not replace hands-on training with cadavers or in the operating room, it appears to be a useful supplement when access to in-person events becomes hampered by extreme circumstances. It remains to be seen, however, how purely online didactics during the COVID-19 pandemic will adequately prepare

graduating residents for fellowships and independent practice.

In the present study, 79.8% of spine surgeons were affected by the COVID-19 pandemic in that educational access for learning MISS was either completely or significantly limited, and have not presently returned to prepandemic levels. From these professionals, 41.2% reported a complete inability to experience a useful MISS learning event since the start of the pandemic. Considering that resident didactic training in the United States shifted to online platforms for 80.6% of surgical residents due to COVID-19, the lack of return to normal educational access for MISS is not surprising.[18] Moreover, nearly 45% of the respondents in this survey originated from South America. When combining the COVID-19 pandemic with international travel restrictions, spine surgeons from certain regions of the world are limited from accessing MISS technology, more commonly spine surgeons from South America. Guiroy et al. previously found that this group of spine surgeons is significantly limited from accessing the necessary resources, as only 43% had access to microscopy; 34% had access to cages such as those for ALIF, LLIF, or TLIF; only 26% had access to percutaneous screws; and an additional 71% reported never having access to navigation.[20] The authors further determined that the predominant constraints for learning MISS were related to implementation costs and lack of face-to-face educational activities.[20]

Access to MISS educational resources is essential for acquiring proficiency. As such, based on the findings presented from this survey, we propose potential solutions for increasing the neurosurgical or orthopedic spine surgeon's access to education: investment from governments, academic institutions, or surgical societies in fellowship programs; creation of organized leadership in the subject; standardization of virtual didactics; simulations including augmented reality or 3D printed models; and restoration of on-site cadaver laboratories.

Limitations

The present study has some limitations. Considering that the study design was based on a population survey, there was an inherent weakness of self-selection bias. There was also a significant response rate from South America when compared with other regions of the world, thereby limiting generalizability. Out of the 303 respondents in this survey, only one originated from Australia or Oceania, so this geographic territory was essentially removed from analysis. The United States and China were also misrepresented here, since a vast majority of spine surgeons who employ MISS are from these territories. Our attempts to reach surgeons in both territories were unsuccessful, thereby lending to an incomplete comparison to these geographic regions. The sample presented in this study, therefore, does not reflect the current state of worldwide MISS practice. Future studies may implement a more expansive protocol that includes participation from spine surgeons in the United States and China. Additionally, there may be interregional differences between surgical practices and training that were not considered. For example, not every neurosurgical or orthopedic spine surgeon in every region would be reluctant or interested in changing their practices to include MISS. Lastly, we did not utilize any form of two-factor authentication for verification of spine surgeon identity. It is therefore possible that a respondent included in the analysis was not a spine surgeon, despite only social media forums consisting of spine surgeons were accessed when sending the questionnaire online.

Conclusion

This survey reached 303 neurosurgical and orthopedic spine surgeons from April 2021 to June 2021 with most responses originating from South America. Even though most of the spine surgeons who responded to this survey were able to attend virtual MISS learning events during the COVID-19 pandemic, they still considered cadaveric study as the gold standard for learning MISS. Among other tools, spine surgeons found that guidance from an experienced surgeon was an invaluable learning experience, with nearly similar rates as that of cadaveric study. Therefore, a multidisciplinary effort is needed to develop structured training programs for teaching MISS, including cadaver laboratory, guidance from experienced surgeons, and virtual demonstrations for spine surgeons, particularly those from South America.

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Conflict of Interests
Jahangir Asghar is a consultant for NuVasive, Medtronic, and Immertec. Jay D. Turner is a consultant for NuVasive, SeaSpine, and AlphaTec. The other authors report no conflicts of interest regarding presented methods or findings. No external research grants were received to support this work.

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Decompressive Craniectomy in Extensive Ischemic Stroke. An Experience in a Single Institution

Craniectomia descompressiva no acidente vascular cerebral isquêmico extenso. Uma experiência em uma única instituição

Diego Alejandro Echenique-Fajardo[1] Edenys Lourdes Izaguirre-González[1]
María Lucy De Gouveia Rodríguez[1] Nafxiel Jesús Brito-Núñez[1]

[1] Department of Neurosurgery, Hospital Universitario de Caracas, Caracas, Venezuela

Address for correspondence Nafxiel Brito, MD, Department of Neurosurgery, Hospital Universitario de Caracas, Caracas, Venezuela (e-mail: nafxiel@gmail.com).

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Abstract

Introduction Decompressive craniectomy (DC) is a valuable treatment for reducing early lethality in malignant intracranial hypertension (IH); however, it has been shown that the decision to implement DC in patients with extensive ischemic stroke should not be based solely on the detection of IH with the use of intracranial pressure (ICP) devices.

Objective To establish the usefulness of DC in patients with extensive ischemic stroke who came to the emergency room during the period between May 2018 and March 2019.

Methods This was an analytical, prospective, and longitudinal study whose population corresponded to all patients with a diagnosis of extensive ischemic stroke.

Results The sample consisted of 5 patients, of which 3 were female and 2 males, the average age was 62.2 years old (minimum 49 years old, maximum 77 years old). Of all the patients who underwent DC, it was found that 80% of the patients did not present an increase in intracranial pressure. Decompressive craniectomy was not performed in a case that responded adequately to medical treatment. The mean values of ICP were 25 mmHg with a minimum value of 20 mmHg and a maximum value of 25 mmHg; in patients with a moderate value, the ICP averages were < 20 mmHg. The mortality was of 40% (RANKIN of 6 points).

Conclusions Decompressive craniectomy is useful in extensive ischemic stroke. The decision to implement DC in patients with extensive stroke rests on clinicoradiological parameters. The monitoring of the IPC was not particularly useful in the early detection of the neurological deterioration of the patients studied.

Keywords
- decompressive craniectomy
- intracranial hypertension
- intracranial pressure
- ischemic stroke

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Resumo

Fundamento A craniectomia descompressiva (CD) é um tratamento valioso para reduzir a letalidade precoce na hipertensão intracraniana (HI) maligna; no entanto, foi demonstrado que a decisão de implementar a CD em pacientes com acidente vascular cerebral (AVC) isquêmico extenso não deve ser baseada apenas na detecção de HI com o uso de dispositivos de pressão intracraniana (PIC).

Objetivo Estabelecer a utilidade da CD em pacientes com AVC isquêmico extenso que chegaram ao pronto-socorro no período entre maio de 2018 e março de 2019.

Métodos Foi realizado um estudo analítico, prospectivo e longitudinal cuja população correspondeu a todos os pacientes com diagnóstico de AVC isquêmico extenso.

Resultados A amostra foi composta por 5 pacientes, sendo 3 do sexo feminino e 2 do sexo masculino, com média de idade de 62,2 anos (mínimo 49 anos, máximo 77 anos). De todos os pacientes que realizaram CD, verificou-se que 80% dos pacientes não apresentaram aumento da pressão intracraniana. Não foi realizada uma CD que tenha respondido adequadamente ao tratamento médico. Os valores médios de pressão intracraniana foram de 25 mmHg, com o valor mínimo de 20 mmHg e o valor máximo de 25 mmHg; em pacientes com escala moderada, as médias de PIC foram < 20 mm Hg. A mortalidade foi de 40% (RANKIN de 6 pontos).

Conclusões A DC é útil no AVC isquêmico extenso. A decisão de implementar uma CD em pacientes com AVC extenso depende de parâmetros clínico-radiológicos. O monitoramento do PCI não foi muito útil na detecção precoce da deterioração neurológica dos pacientes estudados.

Palavras-chave

- craniectomia descompressiva
- hipertensão intracraniana
- pressão intracraniana
- acidente vascular cerebral isquêmico

Introduction

Ischemic stroke constitutes the second cause of death worldwide, with 15.2 million deaths in 2016; it is the most expensive pathology that exists, consuming 2 to 4% of health resources worldwide, being the leading cause of disability in the world, with an estimated incidence of 345 cases per 100,000 inhabitants per year.[1,2,3] In Venezuela, it constitutes the fourth cause of death.[2] The number of strokes is expected to increase in the future (from 16 to 23 million cases from 2005 to 2030, with a mortality that will rise from 5.7 to 7.8 million annually).[3]

The presence of a large hemispheric ischemic stroke associated with intracranial hypertension (IH) can be defined as a malignant cerebral infarction due to rapid neurological deterioration and high associated mortality (close to 80%), despite the use of adequate diagnostic and therapeutic methods.[4] Numerous studies have consistently revealed that higher intracranial pressure (ICP) (to levels $\sim$ 20 to 25 mmHg) is independently associated with a high risk of mortality. The mortality rate has also been shown to be further increased in patients with prolonged refractory elevated ICP.[4,5,6]

Extensive experimental and clinical data indicate that DC is a valuable treatment for reducing early lethality in malignant IH. This type of surgery has been performed in patients with extensive ischemic stroke, in whom, due to the development of cerebral edema, increased ICP, and consequent cerebral herniation, there is a high mortality rate. Considering that nonsurgical treatment to reduce ICP has been shown to be mostly ineffective, the release of the cranial vault and of the dura mater allows the edematous brain tissue to expand outwards, thus offering a clear survival advantage, decreasing the mortality rate from 80% to $\sim$ 20%, which appears to be related to changes in the pressure gradients that develop within the skull, provided by surgical decompression.[7,8,9,10]

There are currently no well-defined levels for the treatment of elevated ICP caused by clinical conditions other than traumatic brain injury. However, in different medical centers, therapy is started when ICP is $>$ 20 to 25 mmHg. The key to surgical treatment of ischemic stroke lies in the early detection of patients who will progress to extensive ischemia. Candidate selection is based primarily on clinical and neuroradiological data.[8,11,12,13,14,15,16,17,18,19,20,21]

The purpose of the present study was to establish the usefulness of DC in patients with extensive ischemic stroke.

Methods

An analytical, prospective, and longitudinal study was performed. The population corresponded to all patients with a diagnosis of extensive ischemic stroke who entered the emergency room during the period between May 2018 and March 2019. The sampling technique was of an intentional nonprobabilistic type and it was made up of those patients who met the inclusion criteria, which were: Patients with a diagnosis of extensive ischemic stroke, presence of malignant cerebral edema, deterioration of the neurological state according to the National Institute of Health Stroke Scale (NIHSS)[22,23] and to the Glasgow scale,[24] patients $>$ 18

years old, and patients or family members who have signed the informed consent. Patients with thrombocytopenia and/or altered clotting times and Glasgow scale < 4 points were excluded. The present case series has been reported in line with the Preferred Reporting of Case Series in Surgery (PROCESS) guideline.

Procedures

Patients with ischemic stroke were received and were indicated, based on the clinical examination (taking into account the NIHSS scale, the Glasgow scale, and pupillary diameter) to undergo an imaging study (computed tomography [CT] or magnetic resonance imaging [MRI]), which confirmed the diagnosis of ischemic stroke. The device (Codman microsensor Metal Bolt kit manufactured in Raynham MA USA) used to measure ICP was placed at the Kocher point. After the device with continuous ICP measurement was placed, clinical follow-up was performed to define the surgical time; the definition of the surgical time was determined by the deterioration of the clinical state of the patient, with an NIHSS > 25 points, Glasgow < 8 points, pupillary anisocoric and an ICP $\geq$ 20 mmHg refractory to antiedema medical treatment. Once the surgical time was defined, it was decided to perform a DC (see surgical technique), with the two-month postoperative follow-up of the patients being performed using the modified RANKIN scale.[25]

Placement of the intracranial pressure-measuring catheter[26]

The patient was positioned in dorsal decubitus; after asepsis and antisepsis, sterile bonnets were placed, a 2-cm long linear incision was made on the affected cerebral hemisphere at the Kocher point, and an automatic separator was used to separate the edges of the skin. The 2.7 mm drill bit was placed into the hand drill bit holder and a hole was made through the bone. The cranial screw was placed and manually screwed in by turning it clockwise until it was properly seated. The dura mater obturator/perforator was used to open the passage through the screw and the durotomy was performed. The canal was irrigated with sterile saline. The fiber was connected to the monitor and calibrated to 0. The CODMAN device fiber was then guided through the 15 to 20 mm screw into the white matter.[27] The compression cap was rotated firmly clockwise to fix the transducer. The skin incision was closed in a single plane, with separate stitches.

Surgical technique to perform decompressive craniectomy[16,28]

The patient was positioned in dorsal decubitus; after asepsis and antisepsis, sterile bonnets were placed, and a Rasmussen incision was made. The incision should be extended through the subcutaneous tissue, including the temporalis muscle, down to the cranium. The resulting myocutaneous flap was challenged anteriorly and secured with scalp hooks. A trepan hole was made just above the posterior root of the zygomatic arch and another one behind the frontal insertion of the lower zygomatic arch to the superior temporal line, a frontal-temporo-parieto-occipital craniectomy of 12 cm by 16 cm was performed. Hemostasis was performed with bone wax and Dural suspension stitches, respectively. Durotomy was performed leaving 1 centimeter from the edge of the craniectomy. Duroplasty with autologous graft was performed. In a second surgical period, the bone flap was placed subdermally in the abdominal wall.

Statistical Analysis

A database was made IBM SPSS Statistics for Windows, Version 19 (IBM Corp., Armonk, NY, USA). The data were analyzed using descriptive statistics such as median, mean, absolute (n) and relative frequencies (%). The Fisher test, the chi-squared test, and the Kendall Taub C test were performed. A p-value < 0.05 was considered statistically significant.

Results

The sample consisted of 5 patients who met the selection criteria, of which 3 were female and 2 males, the average age was 62.2 years old (minimum 49 years old, maximum 77 years old). ►**Table 1** shows the clinical characteristics of the patients and ►**Table 2** shows the surgical characteristics. It was found that the time between the onset of symptoms and surgery was 48 hours in 2 cases, 72 hours in 1 case and >72 hours in 1 case, additionally it was observed that one of the cases did not need surgery due to responding to medical treatment.

At admission, 60.0% ($n = 3$) of the patients had a mild score in the NIHSS scale, whereas at the time of surgery all patients had severe NIHSS ($p = 0.05$). Regarding the Glasgow scale, there was a statistically significant difference between admission (moderate Glasgow [80%]) and at the time of surgery (severe Glasgow [100%]) ($p = 0.02$). Regarding the pupillary diameter, a significant difference was found ($p = 0.003$); on admission, all patients had isochoric pupils and, at the time of surgery, they were anisocoric. More than 70% of the cases had an ICP $\leq$ 20 mmHg both at admission and at the time of surgery. ►**Table 3**.

Regarding the frequency of the decompressive craniectomies performed, it was found that 80% of the patients did not present an increase in ICP; the incidence of ICP frequency > 20 mmHg with DC was of 20% ($n = 1$), observing that 60% of the patients presented an ICP < 20 mmHg. In one case, no DC was performed due to a clinical response to medical treatment.

Of the 5 patients evaluated, 1 had a severe score in the NIHSS scale, with an average intracranial pressure of 25 mmHg with a minimum value of 20 mmHg and a maximum value of 25 mmHg. In patients with a moderate score in the NIHSS scale, the mean ICP was < 20 mm Hg. ►**Table 4**.

Three patients were found to have an ICP $\leq$ 20 mm Hg and a moderate score in the NIHSS scale (►**Fig. 1**). The association between the modified RANKIN scale at admission and at 2 months is shown in ►**Fig. 2**.

A total of 40% of the patients with a moderate score in the NIHSS scale were associated with 40% of the patients with a moderate Glasgow scale; 20% of the patients with a moderate score in the NIHSS scale were associated with 20% of the patients with a moderate score in the Glasgow; and 20% of

Table 1 Clinical status at admission of patients with ischemic stroke with intracranial pressure monitoring

Patient	Clinical picture upon admission	Clinical picture at the time of surgery	Finding on brain CT
1	NIHSS scale 23 pts	NIHSS scale 26 pts	Hypodensity in the right frontotemporoparietal area with displacement of the midline of 2 cm
	Glasgow scale 8 pts	Glasgow scale 6 pts	
	Isochoric pupils	Anisocoric pupils	
	Left hemiplegia	Left hemiplegia	
2	NIHSS scale 28 pts	NIHSS scale 31 pts	Hypodensity in the right frontotemporoparietal area with displacement of the midline of 2 cm
	Glasgow scale 9 pts	Glasgow scale 5 pts	
	Isochoric pupils	Anisocoric pupils	
	Left hemiplegia	Left hemiplegia	
3	NIHSS scale 14 pts	NIHSS scale 23 pts	Hypodensity in the left frontotemporoparietal area with displacement of the midline of 2 cm
	Glasgow scale 1 pt	Glasgow scale 7 pts	
	Isochoric pupils	Anisocoric pupils	
	Right hemiplegia	Right hemiplegia	
4	NIHSS scale 8 pts	No surgery was performed	Hypodensity in the right frontotemporal area with 1 cm displacement of the midline
	Glasgow scale 13 pts		
	Isochoric pupils		
	Left hemiplegia		
5	NIHSS scale 13 pts	NIHSS 28 pts	Hypodensity in the right frontotemporoparietal area with 2 cm displacement of the midline
	Glasgow scale 10 pts	Glasgow 5 pts	
	Isochoric pupils	Anisocoric pupils	
	Left hemiplegia	Left hemiplegia	

Abbreviations: CT, computed tomography; NIHSS, National institute of Health Stroke Scale; pt, point.

Table 2 Surgical characteristics of patients with ischemic stroke with intracranial pressure monitoring

Patient	Age (years old)	Gender	Time between onset of symptoms and surgery	ICP (mmHg)	Craniectomy location
1	71	M	48 hours	12	Right
2	49	F	72 hours	25	Right
3	77	F	4 days	8	Left
4	74	M	———	10	———
5	40	F	48 hours	15	Right

Abbreviation: ICP, intracranial pressure.

the patients with a severe score in the NIHSS scale were associated with 20% of the patients who presented a severe Glasgow scale, with a statistically significant linear association ($p = 0.025$). ►**Table 5**.

It was observed that, on average, the ICP at admission was 14 ± 6.7 mmHg; in the postoperative period, the ICP was 11.6 ± 5.9 mmHg, with a mean difference of 2.4 mmHg (95% confidence interval [CI]: 0.5–4.3 mmHg), which was statistically significant ($p = 0.02$). ►**Table 6**.

In this series of patients, it was observed that females with an injury to the left hemisphere presented a 3-fold greater risk than the rest of the patients (95%CI: 0.61 -14.86). The risk of NIHSS $>$ 60 years was 2 (95% CI, 0.75 -5.33) the risk was two times higher in the left hemisphere than in the right. The same was observed in the deviation from the midline of 20mm over 10mm which was 2 (95% CI 0.05 -78.25) and mortalitywas higher in patients older than 60 years (relative risk [RR] 1.33; 95% CI 0.27 -6.61) ►**Table 7**.

The probability of survival of the patients who were monitored for ICP lowered as the hours of evolution passed. ►**Fig. 3**.

Discussion

The sample of patients who met the inclusion criteria in the present study has similarities with those of other studies conducted in the same period.[3,8] It is important to note that extensive ischemic stroke represents $\sim$ 10 to 15% of all

Table 3 Clinical characteristics at admission and at the time of surgery of patients with ischemic stroke with intracranial pressure monitoring

NIHSS scale	Admission ($n = 5$)		At the time of surgery ($n = 4$)		*p-value*[*]
	n	%	*n*	%	
Mild	3	60.0	0	0.0	0.05
Moderate	0	0.0	0	0.0	
Serious	2	40.0	4	100.0	
Glasgow scale					0.02
Mild	0	0.0	0	0.0	
Moderate	4	80.0	0	0.0	
Severe	1	20.0	4	100.0	
Pupillary diameter					0.003
Anisocoric	0	0.0	4	100.0	
Isochoric	5	100.0	0	0.0	
Intracranial Pressure		0.0			0.85
$\leq$ 20 mmHg	4	80.0	3	75.0	
$>$ 20 mmHg	1	20.0	1	25.0	

Abbreviation: NIHSS, National institute of Health Stroke Scale.
[*]Chi-squared test

Table 4 Frequency of the functional disability severity scale according to the averages of intracranial pressure in patients with ischemic stroke

Patient	NIHSS scale	Intracranial pressure		
		Mean	Maximum	Mininum
1	Moderate	12	12	9
2	Serious	25	25	20
3	Moderate	8	8	6
4	Mild	10	10	8
5	Moderate	15	15	13

Abbreviation: NIHSS, National institute of Health Stroke Scale.

supratentorial infarcts. Mortality rates of up to 80% have been reported and can leave people surviving with severe disabilities. On the other hand, even with the technological advances in medicine, the treatment of malignant cerebral edema is difficult. Nonetheless, the role of DC in such infarcts has been reported to be lifesaving and to even help improving functional outcomes.[20,29]

In addition, investigations have been performed to evaluate the specific prognostic factors that lead to the favorable course of DC in extensive ischemic stroke. In these studies, it can be seen that younger patients ($<$ 60 years old) with a higher score on the Glasgow scale who are operated on in the first 24 hours after the ischemic stroke, before presenting neurological deterioration, show a more favorable result.[7,29]

However, considering that patients with extensive ischemic stroke have a poor prognosis, the use of ICP monitoring has been more useful in different units that opt for more aggressive therapies, such as DC; despite this, we can find in other studies that these new therapeutic measures are beneficial only when applied early.[19,30]

That being said, ICP monitoring in patients with extensive ischemic stroke would aim to guide therapeutic decision-making, to assess the efficacy of applied therapeutic maneuvers, and to detect unexpected complications, such as hemorrhagic transformation of ischemic stroke.[30] However, in our study, we found that a considerable percentage of patients (80%) had normal ICP values despite the marked displacement of the midline. In addition, 3 patients presented anisocoric while their ICP was below the accepted threshold of 20 mm Hg.

It has been found that, in patients with extensive ischemic stroke who present neurological impairment, the ischemic stroke is not accompanied by significant increases in ICP.[26,30] Our findings suggest that despite normal ICP values, severe brain herniation with brainstem compression can be found.

These findings do not imply that ICP monitoring is of no value in these patients because hemorrhagic transformation, a sudden increase in midline displacement, or new lesions, can be detected based on an increase in ICP values.[30]

Additional monitoring methods are necessary despite patients presenting with normal ICP values in order to avoid sudden neurological deterioration. Sequential CT and, above all, strict monitoring of their clinical evolution are the most useful elements in evaluating the evolution of these patients.

Various elements could justify the presence of normal ICP in patients with extensive ischemic stroke with cerebral herniation. Probably, one of these elements is the sudden reduction in cerebral blood flow and, therefore, in cerebral blood volume in the ischemic hemisphere at the beginning of the event and later in the nonrecovered brain. However, in

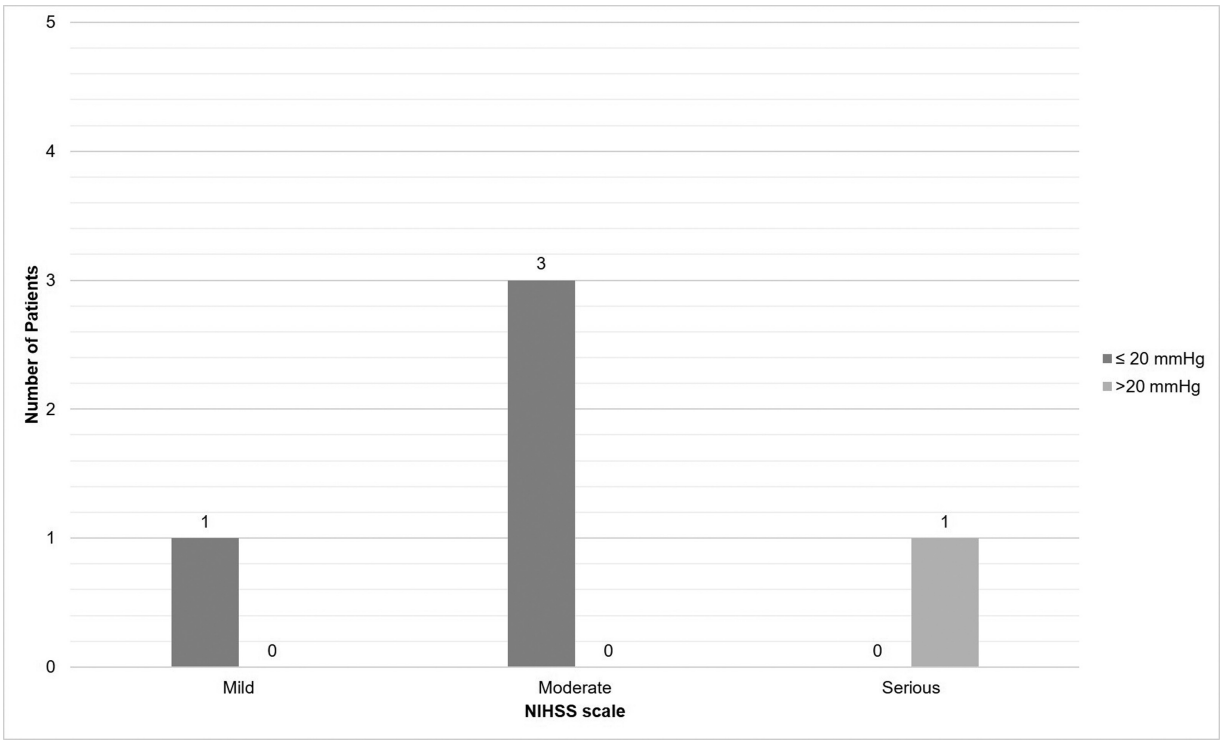

Fig. 1 Relationship between ICP and the NIHSS scale in patients with ischemic stroke.

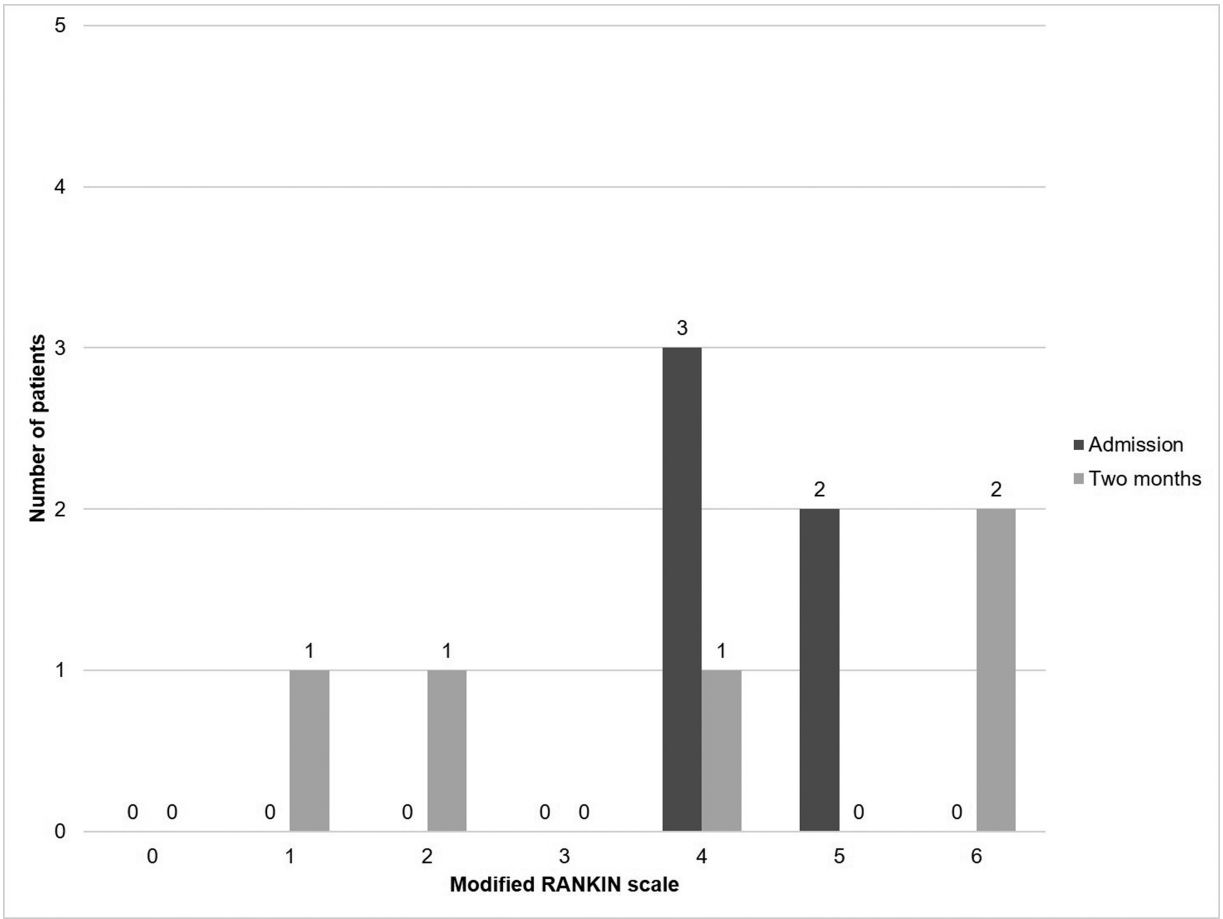

Fig. 2 Comparison of the frequency of the modified RANKIN scale at admission and at 2 months in patients with ischemic stroke.

Table 5 Association between NIHSS severity and the Glasgow scale in patients with ischemic stroke

NIHSS Scale	Glasgow scale						Total	
	Mild		Moderate		Severe			
	n	%	*n*	%	*n*	%	*n*	%
Mild	0	0.0	0	0.0	0	0.0	0	0.0
Moderate	1	20.0	2	40.0	1	20.0	4	80.0
Severe	0	0.0	0	0.0	1	20.0	1	20.0
Total	**1**	**20.0**	**2**	**40.0**	**2**	**40.0**	**5**	**100.0**

Abbreviation: NIHSS, National institute of Health Stroke Scale.
Tau c Kendall = 0.64; $p = 0.025$ (significant)

Table 6 Variation of intracranial pressure at admission and postoperatively in patients with ischemic stroke

Intracranial pressure (mmHg)	Mean	Standard deviation	Mean difference	Standard deviation	95%CI for the difference		*p-value**
					Inferior	Superior	
Admission	14.0	6.7	2.4	1.5	0.5	4.3	**0.02**
Postsurgery	11.6	5.9					

Abbreviation: CI, confidence interval.
*t student

Table 7 Relative risk in patients with ischemic stroke with intracranial pressure monitoring

Association	Relative risk	95%CI	
		Inferior	Superior
Female / left hemisphere	3.00	0.61	14.86
NIHSS severe / age > 60 years old	2.00	0.75	5.33
Hemisphere (left / right)	2.00	0.05	78.25
Midline deviation 20mm / 10mm	2.00	0.05	78.25
Mortality /> 60 years old	1.33	0.27	6.61

Abbreviation: CI, confidence interval.

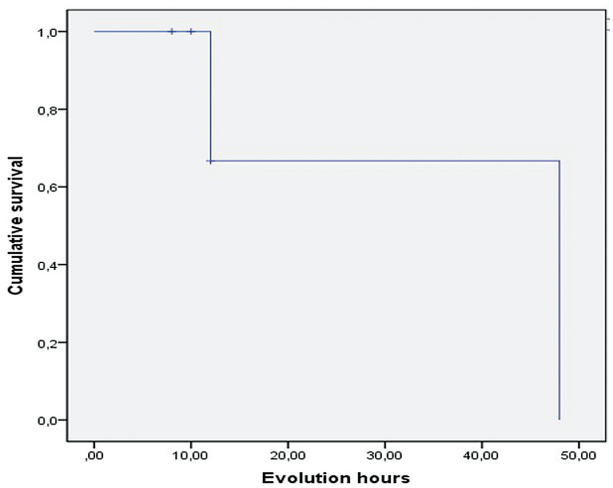

Fig. 3 Kaplan-Meier survival curve according to hours of evolution in patients with ischemic stroke.

a second stage, this reduction in blood volume in the affected hemisphere is compensated by the formation of edema (cytotoxic and vasogenic).[30]

Another factor that could have caused the maintenance of normal ICP in these patients is that the brain volume remains partially compensated at the time the patient begins the course of the disease; therefore, the patient is still in the initial period of the pressure-volume curve, when changes in brain volume are easily compensated for.[26,30]

Pupillary changes before ICP rises may occur from compression of the third nerve and the brainstem due to primary temporal lobe injury.[30]

Another explanation for this phenomenon is that the appearance of a hernia requires a pressure delta between 2 compartments and not an absolute value; thus, a pressure of 12 mmHg in 1 hemisphere can cause uncus herniation if the contralateral hemisphere presents a pressure of 3 mmHg.[31]

On the other hand, it must be taken into account that DC reduces the mortality rate, but increases morbidity, mainly in patients > 60 years of age, with a longer survival, but adjusted for quality of life. Therefore, the decision to perform DC must be individualized.[32] Knowing this, we purpose a therapeutic algorithm for the management of the extensive ischemic stroke. (►**Fig. 4**)

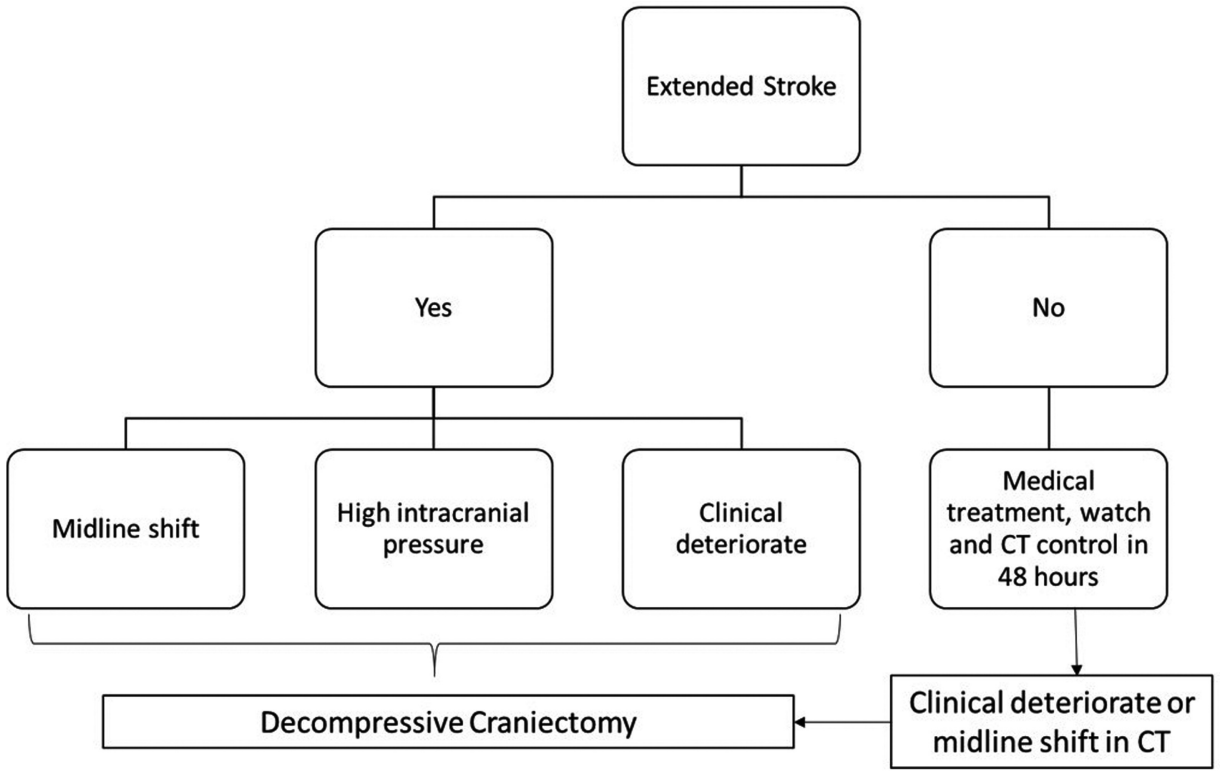

Fig. 4 Proposed algorithm for the management of extensive ischemic stroke.

Conclusion

The female gender was the most affected. The average age was 62.2 years old. In patients < 60 years old with extensive stroke with 48-hour deterioration despite medical therapy, DC reduced mortality by $\sim 50\%$, and 100% of the survivors of the surgery achieved moderate disability or 2-month modified RANKIN score of 2 points. In those > 60 years old, a DC can be considered since it reduced mortality by $\sim 30\%$, and 30% of the surgical survivors have a moderate disability. A total of 80% of the patients presented with neurological deterioration without elevation of ICP. The probability of survival of the patients lowered as the hours of evolution passed. In the present series, the mortality was of 40%.

The decision to implement DC in patients with extensive ischemic stroke should not be based solely on the detection of IH with the use of ICP devices. Currently, the decision to perform DC in patients with extensive stroke rests on clinicoradiological parameters.

Conflict of Interests

The authors have no conflict of interests to declare.

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Compressive Myelopathy Caused by Arachnoid Cyst and Extramedullary Hematopoietic Tissue in a Patient with Thalassemia Major

Mielopatia compressiva por cisto aracnóideo e tecido hematopoiético extramedular em paciente portador de talassemia maior

Leandro Custódio do Amaral[1,2] Hugo Abi-Saber Rodrigues Pedrosa[2,3]

[1] Hospital Metropolitano Odilon Behrens, Fundação Benjamin Guimarães/Hospital da Baleia e da Rede Mater Dei de Saúde, Belo Horizonte, MG, Brazil
[2] Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brasil
[3] Fundação Benjamin Guimarães/Hospital da Baleia e da Rede Mater Dei de Saúde, Belo Horizonte, Minas Gerais, Brazil

Address for correspondence Leandro Custódio do Amaral, Hospital da Baleia e da Rede Mater Dei de Saúde, Rua Cristina, n° 452, apt 1302, Bairro Sion, Belo Horizonte, Minas Gerais 30.310-800, Brazil (e-mail: leandroamaralneurocirurgia@yahoo.com.br).

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Abstract

Thalassemias, inherited diseases of hemoglobin synthesis, are characterized by the presence of deficient hemoglobin chains that deposit in red blood cells, inducing hemolytic anemia. Extramedullary hematopoiesis represents a compensatory picture that usually affects the liver, the spleen, and lymph nodes. The involvement of the epidural space with spinal cord compression is extremely rare. Our objective was to describe the case of RMS, 31 years old, male, β-thalassemia major carrier, admitted with 2-month progressive paraparesis and urinary retention due to medullary compression by extramedullary hematopoietic tissue and thoracic arachnoid cyst, and to discuss therapeutic options. Magnetic resonance imaging (MRI) showed an extensive intraspinal and extramedullary lesion with homogeneous contrast enhancement of T3-T11 in addition to a T1-T3 cystic lesion isointense to cerebrospinal fluid (CSF). After the presumed diagnosis of spinal cord compression by proliferative hematopoietic tissue, a 10-session fractional radiotherapy treatment was immediately performed. After the radiotherapy treatment, the neurological deficits of the patient persisted despite the excellent image response with almost complete disappearance of the intraspinal mass. However, the MRI showed a persistent T1-T3 cystic lesion with significant mass effect on the spinal cord. The patient was submitted to microsurgery for total resection of this cystic lesion. In the postoperative period, the patient improved his sphincter control and motor deficits. Medullary compression by extramedullary epidural hematopoiesis is a rare complication in thalassemic patients and may be treated with surgery and/or

Keywords
- spinal cord compression
- erythropoiesis
- arachnoid cysts

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radiotherapy. There are successful cases with the exclusive use of radiotherapy, especially in extensive lesions.

Resumo

As talassemias, desordens hereditárias da formação de hemoglobina, caracterizam-se pela síntese de cadeias deficientes de hemoglobina que se depositam nas hemácias e induzem a anemia hemolítica. A hematopoiese extramedular representa um quadro compensatório que habitualmente afeta o fígado, o baço e linfonodos, podendo também afetar outros tecidos. O envolvimento do espaço epidural com compressão medular é extremamente raro. No presente trabalho, objetivou-se descrever o caso do paciente RMS, 31 anos, sexo masculino, portador de talassemia β maior, com paraparesia progressiva há 2 meses e retenção urinária devida à compressão medular por tecido hematopoiético extramedular e cisto aracnóideo torácicos, e discutir as opções terapêuticas. Ressonância magnética (RM) evidenciou extensa lesão expansiva intrarraquiana e extramedular com captação homogênea de contraste de T3-T11, além de lesão cística isointensa ao líquor de T1-T3. Devido à extensão da lesão e anemia grave do paciente, foi optado inicialmente pelo tratamento radioterápico fracionado em 10 sessões. Após o tratamento, o paciente manteve os déficits neurológicos apesar da excelente resposta imaginológica, com desaparecimento quase completo da massa intrarraquiana. Contudo, a RM de controle mostrou persistência da lesão cística T1-T3 com efeito de massa importante sobre a medula. O paciente foi submetido a microcirurgia com ressecção completa da lesão cística. No pós-operatório, houve melhora do controle esfincteriano e dos déficits motores. Compressão medular por hematopoiese extramedular epidural é uma complicação rara nos pacientes talassêmicos, e pode ser tratada com cirurgia e/ou radioterapia. Há casos de sucesso com uso de radioterapia exclusiva, especialmente quando as lesões são extensas.

Palavras-chave
- compressão da medula espinhal
- eritropoiese
- cistos aracnóideos

Introduction

Thalassemia is an inherited defect in the formation of hemoglobin, which has effects on various organs and systems in the human body. Normal hemoglobin electrophoresis reveals 97% of hemoglobin A, consisting of 2 α chains and 2 B chains; 2% of hemoglobin B, consisting of 2 α chains and 2 delta chains; and, finally, 1% of fetal hemoglobin, consisting of 2 α chains and 2 gamma chains.[1]

Thalassemia patients do not produce enough hemoglobin A because their cells cannot make the α or β chains. Thus, α thalassemias only affect the production of α chains, and β thalassemia only affects the production of β chains. Clinically, both α and β thalassemias may occur in major (homozygous), intermediate, and minor (heterozygous) forms.[1]

The *HBB* gene, on chromosome 11, is formed by 2 β alleles; however, in major β thalassemia, there is a mutation in this gene, which is formed by the Beta 0/Beta 0 or Beta 0/Beta + alleles. Other mutation combinations may cause the less severe forms of β thalassemia, such as the intermediate or minor subtypes.[2]

In major β thalassemia, there is formation of α chain tetramers that undergo chronic intramedullary and extravascular hemolysis. Patients have hemoglobin levels of 3 and 5 mg/dl, with 98% of fetal hemoglobin.[2]

Extramedullary hematopoiesis is a compensatory phenomenon, most commonly affecting the liver, the spleen and the lymph nodes. In severe cases, hematopoietic tissues may form in the intra-abdominal, paravertebral, pleural, nasopharyngeal, and epidural spaces. In addition to thalassemia, other diseases such as hemolytic anemia, polycythemia vera, and myelofibrosis also have extramedullary erythropoiesis.[3]

Spinal arachnoid cysts also are rare lesions, and represent between 1 and 3% of intrarachian expansive lesions.[4] They result from minor arachnoid membrane defects that induce cerebrospinal fluid (CSF) accumulation, which leads to arachnoid herniation. The mechanism for the formation of arachnoid cysts is not well understood; they increase in size during intense exercise and activity, or due to changes that cause elevations in intracranial pressure.[4] They may be primary, when they are congenital or idiopathic, or secondary, when they are associated with inflammatory reactions related to trauma, meningitis, subarachnoid hemorrhage or iatrogenesis (intradural surgery, postlumbar puncture).[4,5] They are more common in the thoracic spine (54 to 94%), especially in the posterior and posterolateral portions of the spinal canal.[4,5] Regarding their location, they can be classified as intradural or extradural, the latter of which are more common.[4] These lesions are often asymptomatic, causing root symptoms or spinal cord compression.[4,5] Consequently, they are commonly

diagnosed incidentally.[4] In addition, they are underdiagnosed because they are easily missed on standard magnetic resonance images, due to their thin walls and pulsatile CSF motion.[5] Accidental and asymptomatic arachnoid cysts are usually treated conservatively, whereas symptomatic arachnoid cysts require surgical approaches. Thus, surgical interventions on spinal arachnoid cysts are uncommon.[4]

Case Report

RMS, 31 years old, male, with major β thalassemia with the need for biweekly blood transfusions, had been presenting progressive paraparesis for 2 months; evolving with a fall from his own height 1 month prior and since then restricted to a wheelchair; the patient evolved with urinary retention, so he was referred to the Baleia de Belo Horizonte Hospital for propaedeutics and treatment. Physical examination revealed grade 2 paraparesis in the lower limbs, Babinsky and bilateral clonus, as well as hypoesthesia with T2-sensory level.

The propedeutics performed showed an extensive intrarachial and extramedullary expansive lesion with homogeneous contrast uptake of the T3-T11, as well as a T1-T3 CSF cystic lesion. ►**Fig. 1**.

After the diagnosis of the spinal cord compression by proliferative hematopoietic tissue, the patient was immediately submitted to a fractional radiotherapy treatment of 10 sessions, totaling 3,500 Gy, in addition to a hypertransfusion with 600 ml of phenotyped red blood cell concentrate per week, for 3 weeks. The hypothesis was that eliminating the blocking of the subarachnoid space by the proliferative tissue, there would be a reduction of the arachnoid cyst by reducing the high intrarachial pressure that contributed to the expansion of the cystic lesion. In addition, the possibility of massive bleeding in a patient with very low hemoglobin levels made an initial conservative approach more appropriate. However, after the radiotherapy and hypertransfusion, the patient showed no improvement in neurological deficits, despite the excellent radiological response with almost complete disappearance of the intrarachial mass. Nevertheless, there was a persistence of the spinal cord compression by the cystic lesion on T1-T3, located just above the erythropoietic mass, ►**Fig. 2**.

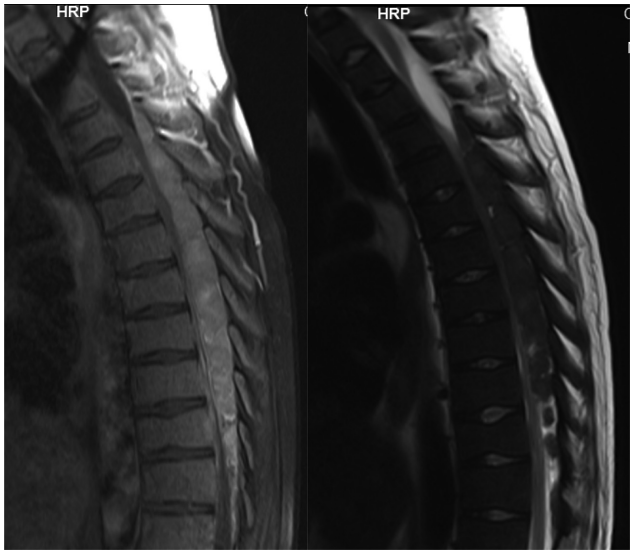

Fig. 1 Ressonância magnética na sequência T1 com contraste e T2 mostrando massa eritropoiética epidural T3-T11 e cisto aracnóideo T1-T3

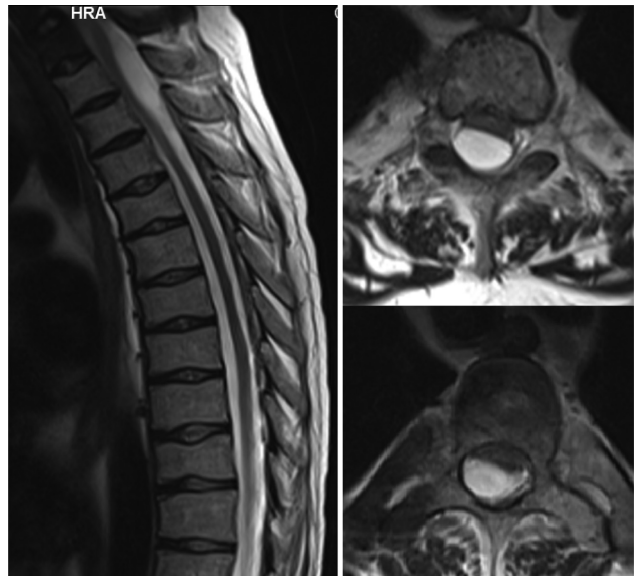

Fig. 2 Ressonância magnética na sequência T2 mostrando regressão importante da massa eritropoiética epidural, mas manutenção do cisto aracnóideo T1-T3 com efeito compressivo sobre a medula espinhal.

The patient underwent hemilaminectomy from T1 to T3 and total microsurgical resection of the arachnoid cyst. Intraoperatively, this cyst was filled with a translucent liquid suggestive of CSF with no signs of blood or inflammatory reactions. After complete surgical resection, the spinal cord had a normal appearance without the previous anterior deviation resulting from the mass effect of the cystic lesion. There were no perioperative complications and the patient was discharged on the 3rd postoperative day, with sphincter control but maintaining grade 2 strength in the inferior limbs. The patient underwent intensive physical therapy and returned within 14 days with significant motor improvement, grade 4 muscle strength in the lower limbs, walking with occasional support but without assistance from others. ►**Fig. 3**.

Arachnoid cyst resection by microsurgery was chosen, with hemilaminectomy of the affected levels. Postoperatively, the patient showed an improved sphincter control and improvement of the motor deficits, with a remarkable functional gain.

Discussion

The first description in the literature of spinal cord compression by an erythropoietic mass was made in 1954 by Gatto et al. The epidural "compartment" is affected in up to 15% of the cases of extramedullary erythropoiesis; however, it is asymptomatic in most cases. When there is spinal cord

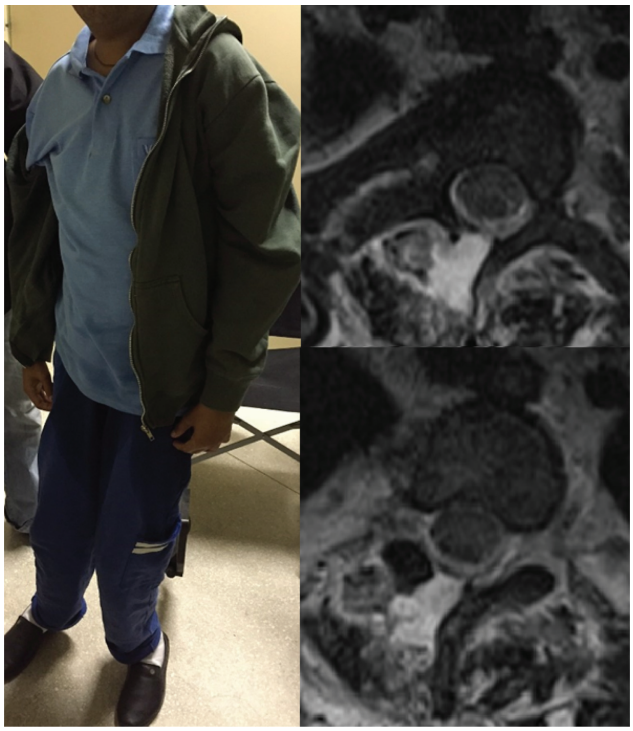

Fig. 3 Paciente RMS no 14° dia de pós-operatório, em ortostatismo sem apoio, em Rankin 3. Ressonância magnética mostrando descompressão satisfatória da medula, ao nível de T1-T3.

compression, the patient presents progressive paraparesis, as well as sphincter and sensory alterations below the level of the lesion.[6]

The diagnosis is made by magnetic resonance imaging (MRI) associated with the clinical history compatible with diseases that cause extramedullary hematopoiesis. An isointense epidural mass at T1 and hyperintense at T2 is visible, homogeneously capturing, mainly in the thoracic spine, associated with paravertebral masses of the same radiological aspect and bone hyperplasia.[7]

Surgical treatment was classically the most used because of its benefit of immediate decompression; however, because these patients are usually at high surgical risk, with very low basal hemoglobin levels, this treatment has been replaced by radiotherapy associated with hypertransfusion, with optimal clinical and radiological results, except when there is already plegia. In cases of intermediate thalassemia, hydroxyurea may also be associated to stimulate fetal hemoglobin production; a strategy that does not benefit patients with major β thalassemia, as they already have ~ 98% fetal hemoglobin.[6,7]

Regarding the surgical treatment of arachnoid cysts, it has two basic objectives: performing spinal decompression and reestablishing the CSF flow.[5] Since arachnoid cysts do not contain proliferative and secretory cells, complete resection is not necessary to achieve these goals, since extensive fenestration or partial resection can cause complete collapse of the cyst.[4,5] These measures aim to avoid injuries, scarring and the formation of adhesions in neural structures, which may cause spinal cord anchorage and obstruction of the CSF flow.[4,5] For these reasons, complete resections of the limbs are restricted to those cases that span up to three vertebral segments, such as the case presented in the present report.[5]

In the literature, alternative treatment methods such as endoscopic fenestration and drainage of cysts with valve devices are pointed out. However, they introduce a foreign body into the subarachnoid space that may lead to adhesion formation and may also be related to the obstruction of the device by cyst collapse, intracranial hypotension syndromes, and slit ventricles. Endoscopic approaches have the risk of damaging medullary blood vessels present in the cyst walls and of performing fenestrations too small to prevent the reclection of cysts.[5] Thus, conventional surgical approaches remain the treatments of choice.

Conclusion

Despite the evidence showing excellent clinical response to the treatment of spinal cord compressions by hematopoietic tissue with radiotherapy and hypertransfusion, the case reported here needed to be individualized, as besides the erythropoietic tissue, there was also the arachnoid cyst causing compressive myelopathy. Thus, the combined treatment was chosen, initially with 3,500 Gy and 1,800 ml of packed red blood cells, both fractionally, followed by surgical decompression with total resection of the arachnoid cyst, with excellent radiological, clinical and functional results.[4,5]

Note

Institution where the study took place: Fundação Benjamin Guimarães – Hospital da Baleia.

Conflict of Interests

The authors have no conflict of interests to declare.

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The Role of Sodium and Glucose in the Prognosis of Patients with Aneurysmal Subarachnoid Hemorrhage: A Literature Review of New Evidence

O papel do sódio e da glicose no prognóstico de pacientes com hemorragia subaracnóidea aneurismática: Uma revisão de literatura das novas evidências

Zeferino Campos Dell'Orto[1] Isadora Valério da Silveira[1] Larissa da Silva Torres França[1] Murillo Sampaio Ferreira Medeiros[1] Talita Cardoso Gomes[1] Bruno Alves Pinto[1] Daniel Gonçalves de Oliveira[1] Gabryell Thiengo Lopes[1] Ivan Magalhães Viana[1]

[1] Medicine Department, Universidade Federal de Juiz de Fora, Campus Governador Valadares, MG, Brazil

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Address for correspondence Zeferino Campos Dell'Orto, Medical Student, Medicine Department, Universidade Federal de Juiz de Fora, Avenida Dr. Raimundo Monteiro Rezende, 330, sala 301, Centro, Governador Valadares, MG, Brazil (e-mail: zeferinocamposdellorto@hotmail.com).

Abstract

The present study aims to review the influence of glycemia and natremia on the propensity to develop complications, worse prognosis, and mortality risk in patients with aneurysmal subarachnoid hemorrhage (aSAH). This is an integrative literature review guided by the guiding question: "Do changes in blood glucose levels or plasma sodium concentration influence in-hospital morbidity and mortality in patients with aneurysmal subarachnoid hemorrhage?". The search for articles was performed on the PubMed platform, limiting the selection to works published in English in the period from 2017 to 2022. The results found demonstrate that the role of sodium ions in changes in the prognosis of patients is complex, with hypernatremia being the main factor described to worse outcomes. In contrast, the part of hyponatremia is controversial and may not have prognostic value, and serum sodium concentration is increasingly an important item to be evaluated in patients with aSAH. As for glucose, the variability of this substrate, both hyperglycemia and hypoglycemia, may be correlated with in-hospital and long-term mortality in patients with aSAH. Thus, the present study concludes that changes in blood glucose values and plasma sodium concentration influence the in-hospital morbidity and mortality of patients with aSAH. However, it is emphasized that the analysis of the independent influence of each of the related predictors must be done with caution due to the heterogeneity of the results found.

Keywords

- neurosurgery
- hemorrhagic stroke
- intracranial aneurysm

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Resumo

O presente estudo tem como objetivo a revisão da influência da glicemia e da natremia na propensão ao desenvolvimento de complicações, no pior prognóstico e no risco de mortalidade em pacientes com hemorragia subaracnóidea aneurismática (HSAa). Trata-se de uma revisão integrativa de literatura guiada pela questão norteadora: "Alterações nos valores da glicemia ou concentração de sódio plasmática influenciam na morbimortalidade intrahospitalar de pacientes com hemorragia subaracnóidea aneurismática?". A busca de artigos foi realizada na plataforma PubMed, limitando a seleção para trabalhos publicados em língua inglesa no período de 2017 a 2022. Os resultados encontrados demonstram que o papel do íon sódio nas alterações no prognóstico dos pacientes é complexo, sendo a hipernatremia o principal fator descrito em relação a piores desfechos, enquanto o papel da hiponatremia é controverso e pode não ter valor prognóstico, e a concentração de sódio sérica apresenta-se cada vez mais como um item importante a ser avaliado no paciente com HSAa. Já quanto à glicose, a variabilidade desse substrato, tanto a hiperglicemia como também a hipoglicemia, pode estar correlacionada com a mortalidade hospitalar e a longo prazo em pacientes com HSAa. Assim, o presente estudo conclui que as alterações nos valores de glicemia e concentração de sódio plasmático têm influência na morbimortalidade intrahospitalar dos pacientes com HSAa. Entretanto, ressalta-se que a análise da influência independente de cada um dos preditores relacionados deve ser feita com cautela devido à heterogeneidade dos resultados encontrados.

Palavras-chave

- neurocirurgia
- acidente vascular cerebral hemorrágico
- aneurisma intracraniano

Introduction

Subarachnoid hemorrhage is a type of hemorrhagic stroke, whose incidence is associated, in ~ 80 to 85% of cases, with the rupture of an intracranial aneurysm, characterized by an aneurysmal subarachnoid hemorrhage (aSAH).[1,2] Aneurysmal subarachnoid hemorrhage has a worldwide incidence of 9 per 100,000 individuals per year, represents 5% of strokes, has high mortality and disability rates, and its general prognosis depends on the volume of initial bleeding, the occurrence of rebleeding, and the degree of delayed cerebral isquemia.[3]

Among the most important risk factors for the development of brain aneurysms are high blood pressure, smoking, alcoholism, family history of the aneurysm in first-degree relatives, and female gender. In addition to these, autosomal dominant polycystic kidney disease is relevantly associated with the formation of aneurysms, and other conditions such as Marfan syndrome, Ehlers-Danlos syndrome type IV, neurofibromatosis, and fibromuscular dysplasia also have a weak association.[3]

As for the rupture, the location, size, and type of aneurysms are relevant to the increased risk. Aneurysms > 1 cm and located in the posterior circulation, especially at the top of the basilar artery, in the posterior cerebral artery, in the vertebrobasilar distribution, and the origin of the posterior communicating artery, were associated with a greater chance of rupture. Furthermore, saccular aneurysms account for 90% of aneurysm morphology and correspond to the most common cause of aSAH.[3]

In addition to the acute effects resulting from aSAH, and the mortality rate of ~ 35%,[2] patients with aSAH may present secondary complications, which result in a worse prognosis and are associated with neurological sequelae such as cognitive alteration, and motor and/or behavioral deficit.[4] The main complications include rebleeding, hydrocephalus, vasospasm, cerebral edema, and late cerebral ischemia.[5,6] Among them, early rebleeding is the most frequent in the first 24 hours, being associated with mortality rates of 50 to 80%.[7]

Factors associated with worse clinical outcomes and incidence of complications after aneurysmal subarachnoid hemorrhage are older age, higher grades on the World Federation of Neurologic Surgeons (WFNS) scale at admission, larger aneurysms located in the posterior circulation, intraventricular hemorrhage, hematoma intracerebral injection and history of arterial hypertension, acute myocardial infarction, liver disease or previous subarachnoid hemorrhage.[8] In addition, biomarkers and electrolytes correlated with an unfavorable evolution in aSAH, such as the glucose-potassium ratio, the glucose-phosphate index, sodium concentration, and plasma glucose, stand out.

Therefore, the present study aims to review the influence of glycemia and natremia on the propensity to develop complications, the worst prognosis, and the risk of mortality in patients with aneurysmal subarachnoid hemorrhage.

Material and Methods

This is an integrative literature review. The present study had as its guiding question: "Do changes in blood glucose values or in plasma sodium concentration influence in-hospital morbidity and mortality of patients with aneurysmal

subarachnoid hemorrhage?" based on the *PECOS* strategy: ***P****atient* – people with aneurysmal subarachnoid hemorrhage; ***E****xposure* – alterations in glycemia (hyper or hypoglycemia or glycemic variations) or plasma sodium concentrations (hyper or hyponatremia); ***C****ontrol* – Normoglycemic and with normal sodium levels; ***O****utcome* – increased mortality; ***S****tudies* – clinical trials, prospective and retrospective cohorts, case-control, and systematic reviews were included.

Inclusion Criteria

As for the inclusion criteria, complete articles were selected for the present work, published between 2017 and 2022, written in English, and belonging to the following types of study: clinical trial, prospective or retrospective cohort, case-control study, or systematic review. In addition, in their methodology, the studies should have performed at least one measurement of blood glucose (in the form of mean glucose per glycated hemoglobin or measurements of daily capillary glucose) or natremia of patients hospitalized for aSAH. Finally, the selected articles should present a statistical correlation between changes in glycemia or natremia with in-hospital mortality; or else demonstrate differences in clinical presentations or prognosis in patients with aSAH and glycemic and natremia alterations in comparison to aSAH patients with normoglycemic and normal sodium levels.

Exclusion Criteria

The established exclusion criteria were duplicate publications on platforms and search; publications inconsistent with the purpose of this research; publications with strong biases that compromise the reliability of the article and publications in languages other than English. In addition, case report studies, narrative reviews, and animal experimentation. Studies that used glycemic monitoring by cerebral microdialysis, whose focus of discussion was the drug treatments of glycemic alterations or natremia, and articles that report on ventriculoperitoneal shunt were also excluded.

Search and Identification of Articles

The search for articles was performed on the PubMed platform, limiting the results to articles published in the last 5 years (2017–2022) in English. To survey the articles, the following descriptors were used: *Glucose; Blood Glucose; Hyperglycemia; Hypoglycemia; Sodium; Hypernatremia; Hyponatremia; Potassium; Hyperkalemia; Hypokalemia* and their respective Entry Terms separated by the Boolean operator OR. Then we used the Boolean AND operator to include the *Aneurysmal Subarachnoid Hemorrhage* descriptor and its Entry Terms.

Results and Discussion

General Description of Results

Based on the described methodology, 106 results were found. After analyzing the titles and abstracts, 40 articles were included for a full reading. Of these, the following were excluded: three because of the impossibility of accessing the complete material, another three because they did not present clear relationships with the objective of the research (glucose and sodium), in addition to three Keywordsget,is of factors for shunt or ventriculoperitoneal shunt. Furthermore, one study for not stratifying hypoglycemia, hypoxia, and hypotension as a cause for worse outcomes or mortality, and another for not using exposure and control groups to assess the risk of hyponatremia.

It was also decided to remove two items that contained their investigations associated with ischemic stroke and nonaneurysmal subarachnoid hemorrhage, which prevented their adequate participation in the present study. Ultimately, one element was removed as it focused on treatment impact. Thus, in the final analysis of the results, 26 articles were considered, 14 referring to sodium (►**Fig. 1**) and 12 to glucose (►**Fig. 2**).

Sodium Change

Primarily, it should be noted that dysnatremia events and fluctuations in serum sodium ion values are extremely prevalent in patients with aSAH. The main event is hyponatremia, present in $\sim$ 30 to $>$ 50%[9] of the patients, followed by hypernatremia found between 31 and 33.6% of the cases and variations in sodium values in $\sim$ 39.3% – considering the value of 12 mmol/L.[10]

Regarding prognosis, the role of such an ion is complex. Studies indicate that both hypernatremia and hyponatremia, or even variation in serum sodium concentration, are more common in patients with unfavorable evolution – including deaths, neurological sequelae, or a higher level of dependence – in-hospital or in later periods of up to 6 months.[10–12]

However, the assessment of independent predictors for patient outcomes is more restrictive. The main factor described is hypernatremia, in which there are correlations of values $>$ 145 mmol/L in the first 2 weeks with higher mortality during hospitalization or with a worse prognosis, in general, when considering the value of 146 mmol/L.[11] Specifically, Sokół et al.,[13] established that values $>$ 155 mmol/L were an independent predictor of mortality, with a specificity of 97.8% and a sensitivity of 47.6%. Furthermore, concentrations $>$ 155 mmol/L were associated with unfavorable outcomes within 3 months.[10] More broadly, a study showed that sodium in the blood, in addition to rebleeding, is an independent risk factor, leading to poor prognosis.[14]

The role of hyponatremia as a predictor is controversial. In most articles, it is demonstrated that it has no prognostic value in the short or long term, especially in terms of mortality.[10,11,15,16] Kieninger et al.[17] even demonstrated that the rate of poor outcome at discharge from the intensive care unit (ICU), 6 months after the bleeding event, was significantly lower in patients with moderate hyponatremia (125–129 mmol/L), allowing only a limited conclusion, as the diagnosis of hyponatremia regularly led to early and elaborate measures to achieve rapid normalization of the sodium level and maintain normonatremia in the later course of ICU treatment. A pathophysiological hypothesis proposed by

Título	Ano	Primeiro Autor	Periodico	Tipo de estudo
The impact of hormonal dynamics and serum sodium fluctuations on symptomatic vasospasm after subarachnoid hemorrhage	2022	Harada, T.	J Clin Neurosci	Prospective cohort
Sodium Variability and Probability of Vasospasm in Patients with Aneurysmal Subarachnoid Hemorrhage	2022	Chua, M.M.J	J Stroke Cerebrovasc Dis	Retrospective observational
Clinical Treatment and Prognostic Analysis of Patients with Aneurysmal Subarachnoid Hemorrhage	2021	Yang, X.	J Healthc Eng.	Comparative analysis
Dysnatremia and 6-Month Functional Outcomes in Critically Ill Patients With Aneurysmal Subarachnoid Hemorrhage: A Prospective Cohort Study	2021	Cohen, J.	Crit Care Explor.	Prospective cohort
Acute hyponatremia after aneurysmal subarachnoid hemorrhage: Frequency, treatment, and outcome	2021	Kieninger, M.	J Clin Neurosci.	Retrospective observational
Risk Factors for Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage: A Population-Based Study of 8346 Patients	2021	Rumalla, K.	World Neurosurg.	Retrospective observational
Long-Term Outcomes of Elderly Patients with Poor-Grade Aneurysmal Subarachnoid Hemorrhage	2020	Yoshikawa, S.	World Neurosur.	Retrospective observational
Temporal Relationship between Hyponatremia and Development of Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage Patients: A Retrospective Observational Study	2020	Escamilla-Ocañas, C.E.	J Stroke Cerebrovasc Dis	Case-control
Prognostic models for neurological functional outcomes in aneurysmal subarachnoid hemorrhage patients with intracranial hematoma	2020	Wang, .Z	Clin Neurol Neurosurg	Retrospective cohort
Impact of Dysnatremia and Dyskalemia on Prognosis in Patients with Aneurysmal Subarachnoid Hemorrhage: A Retrospective Study	2019	Tam, C.W.	Indian J Crit Care Med.	Retrospective cohort
Hyponatremia After Spontaneous Aneurysmal Subarachnoid Hemorrhage-A Prospective Observational Study	2019	Ridwan, S.	World Neurosurg.	Prospective cohort
Predicting mortality in subarachnoid haemorrhage based on first-week routine blood tests	2018	Bartosz, S.	Journal Clinic Neurosci .	Prospective cohort
Electronic Health Data Predict Outcomes After Aneurysmal Subarachnoid Hemorrhage	2018	Zafar, S.F.	Neurocrit Care	Retrospective cohort
Target Serum Sodium Levels During Intensive Care Unit Management of Aneurysmal Subarachnoid Hemorrhage	2017	Okazaki, T.	Shock	Retrospective observational

Fig. 1 Included articles referring to the prognostic value of sodium in aSAH.

Tam et al.[10] would be the ability of brain neurons to adapt to the situation of hyponatremia, in a self-regulation mechanism, managing to reach a state of functional stability in less than 24 hours.

In contrast, Rumalla et al.[18] and Escamilla-Ocañas et al.[9] demonstrated that hyponatremia was significantly associated with cerebral vasospasm, a complication that very often precedes aSAH events.[9,18] Escamilla-Ocañas et al.[9] also reported that poor clinical results and longer hospital stays and ICU were significantly more evident in the hyponatremic group, compared with the normonatremic group. Such data are, in part, supp partlyidwan et al. (2019),[15] who found a correlation between the development of hyponatremia at any time during hospitalization and longer duration of hospital stay; however, with no impact on ICU stay.

Furthermore, some authors, when considering specific periods, such as the decrease in sodium between 14 and 21 days after hospitalization[15] or values below the usual levels, such as 132 mmol/L,[11] found worse outcomes related to hyponatremia within 1 year or at hospital discharge,

Title	Year	First Author	Periodical	Type of Study
Association between hyperglycemia at admission and mortality in aneurysmal subarachnoid hemorrhage	2022	Jia, L.	J Clin Neurosci	Retrospective observational
Elevated Glucose-Potassium Ratio Predicts Preoperative Rebleeding in Patients With Aneurysmal Subarachnoid Hemorrhage	2022	Wang, J.	Front Neurol	Retrospective observational
Association Between Glycemic Gap and In-hospital Outcomes in Aneurysmal Subarachnoid Hemorrhage	2021	Sun, P.Y.	Front Neurol.	Case-control
Association of Plasma Glucose to Potassium Ratio and Mortality After Aneurysmal Subarachnoid Hemorrhage	2021	Jung, H.M.	Neurol Frontal	Prospective cohort
Glycemic indices predict outcomes after aneurysmal subarachnoid hemorrhage: a retrospective single center comparative analysis	2021	McIntyre, M.K.	Sci Rep.	Retrospective cohort
Glucose Variability as Measured by Inter-measurement Percentage Change is Predictive of In-patient Mortality in Aneurysmal Subarachnoid Hemorrhage	2020	Sadan, O.	Neurocritical Care	Retrospective observational
Serum Glucose and Potassium Ratio as Risk Factors for Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage	2019	Matano, F.	Journal of Stroke and Cerebrovascular Diseases	Case-control
Association of Admission Serum Glucose-Phosphate Ratio with Severity and Prognosis of Aneurysmal Subarachnoid Hemorrhage	2019	Dingding, Z.	World Neurosurg.	Case-control
Serum glucose/potassium ratio as a clinical risk factor for aneurysmal subarachnoid hemorrhage	2017	Fujiki, Y.	Journal of Neurosurg	Retrospective cohort
Blood Glucose Variability: A Strong Independent Predictor of Neurological Outcomes in Aneurysmal Subarachnoid Hemorrhage	2018	Okazaki, T.	J Intensive Care Med	Retrospective observational
Elevated glycated hemoglobin level and hyperglycemia after aneurysmal subarachnoid hemorrhage	2017	Beseoglu, K.	Clin Neurol Neurosurg	Prospective cohort
Stress-Induced Hyperglycemia After Spontaneous Subarachnoid Hemorrhage and Its Role in Predicting Cerebrospinal Fluid Diversion	2017	Ray, B.	World Neurosurg	Retrospective observational

Fig. 2 Included articles referring to the prognostic value of glucose in aSAH.

respectively. Another impacting factor that can be considered is the treatment of such hydroelectrolytic conditions, which usually receive a more aggressive treatment of fluid replacement.[10]

Cohen et al.[19] mention that there are several possible explanations for the discrepancy observed in the influence of hyponatremia on morbidity and mortality from aSAH, including the use of variable outcome measures, with only a few studies reporting the long-term neurological status; differences in the definition of hyponatremia (which can be categorized as present or absent or by varying threshold values and a varying number of samples) and reports from analyzes and models that do not take into account duration or severity (for example, temporal changes over an admission).

In turn, the variation in serum sodium concentration is increasingly an important item to be evaluated in patients with aSAH. Increased sodium variability was associated with a longer hospital stay[19] and, between the 1st and 3rd days, it was associated with higher in-hospital mortality.[16] Also, Tam et al.[10] detected that a variation $>$ 12 mmol/L of sodium during hospitalization could be associated with a worse patient outcome, represented by states 1 to 3 of the Glasgow Outcome Scale in the 3 months following aSAH. Furthermore, within[14] days of an aSAH episode andan6 months of hospital discharge, it has been associated with the development of symptomatic vasoespasm[20] and poor neurological outcome,[19] respectively, with progressive decreases in serum sodium being found to precede such complications.

It is speculated that this fluctuation is caused by a response to hormones, such as those related to stress, which begins to show inappropriate secretion after brain damage associated with aSAH.[19,20]

Furthermore, Yoshikawa et al.,[21] when analyzing patients with low-grade aSAH who were $\geq$ 70 years old and who

received treatment, demonstrated that the mean absolute daily difference in the normal plasma sodium level was significantly associated with the modified Rankin Scale scores in 3 and 12 months after aSAH.

Conversely, a study showed that there was no significant difference in serum sodium levels, over the first 14 days post-aSHA, in patients who later developed vasospasm, compared with those who did not, and that, in terms of outcomes neurological, functional, and mortality factors, changes in sodium levels over time were not associated with these outcomes.[22]

Finally, some results support the use of tests referring to natremia more comprehensively, since serum sodium values can be considered as an independent factor for mortality[16] and its variations as predictors of a worse neurological condition at hospital discharge and within 6 months.[10,11]

Glucose Change

At the time of aneurysm rupture, it may result in an increase in glucose within 72 hours after the onset of bleeding.[7] As a result, in addition to hyponatremia events in individuals with aSAH, as already mentioned, we may have some changes in glucose.

In the study by Jia et. al,[23] it was described that 4,804 (70.9%) patients who suffered a spontaneous subarachnoid hemorrhage had hyperglycemia. Of these, a higher in-hospital mortality rate was identified for patients with more severe hyperglycemia in whom the odds of in-hospital mortality were higher, significantly higher in patients with moderate hyperglycemia (odds ratio [OR]: 2.61; 95% confidence interval [CI]: 1,52–3.06) and higher in patients with severe hyperglycemia (OR: 3.18; 95% CI 2.24–4.53; $p < 0.001$). The mortality of these patients may be related to changes in blood glucose.

Reinforcing this analysis, it was also identified in the study by Sun et. al[24] with 119 patients with aSAH who had a high admission glycemic interval (aGG) $\geq$30 mg/dL (66.4%), is associated with markers of disease severity and hospital outcomes, strengthening the concept that is an indicator of physiological response to stress to aSAH. Furthermore, aGG outperformed admission glucose in predicting in-hospital mortality and was equally accurate in the discerning poor composite outcome.

It is also notable that discussions in works regarding glucose variation and its relationship with the occurrence of vasospasm.[25,26] The study by Matano et al[25] including 333 patients, made a statistical correlation between ischemia due to cerebral vasospasm and glucose/potassium ratio ($p < 0.0001$), glucose ($p = 0.016$), and potassium ($p = 0.0017$). The glucose/serum potassium ratio was elevated in cerebral vasospasm (Spearman r = 0.1207; $p = 0.0279$).

Brief-form vasospasm is a common complication after aSAH and is a major contributor to the high morbidity and mortality rate of the disease. The pathophysiology of vasospasm is not well understood and probably involves an interaction between blood products, vasoactive substances, and inflammatory cascades.[27]

In addition to the glucose/potassium ratio, the serum glucose-phosphate index is a potential marker of severity and poor outcomes for patients with aSAH.[28] Higher blood glucose levels were identified in patients with rebleeding, in addition to patients in the group of rebleeding who had a significantly higher glucose/potassium ratio than patients without rebleeding.[12] Furthermore, Zhang et al[29] reported that the glucose-phosphate ratio was significantly correlated with vasospasm (r ¼: 0.581; $p < 0.001$) and DCI (r ¼: 0.523; $p < 0.001$), resulting in an unfavorable prognosis.

As evidenced, high blood glucose levels on admission are associated with aSAH severity and worse evolution. A recent study addressed that cerebral vasospasm exacerbated by hyperglycemia may be a potential mechanism for the poor neurological outcomes observed.[29]

The correlation of hyperglycemia with a poor prognosis has several scientific explanations; some experimental studies indicate that hyperglycemia induces apoptosis, while others claim that hyperglycemia increases the production of superoxide, damaging the blood-brain barrier, causing cerebral edema. Another explanation is that hyperglycemia impairs different components of innate immunity, leading to a systemic anti-inflammatory response.[20] Another explanation would be about cerebral vasospasm exacerbated by hyperglycemia being a potential mechanism for poor neurological outcomes.[29]

On the other hand, the occurrence of hypoglycemia in patients with aSAH is associated with unfavorable neurological outcomes and risk of vasospasm.[30,31] Therefore, glucose variability, both hyper and hypoglycemia, may be correlated with hospital mortality or with a poor prognosis in the long term in patients with aSAH.[32]

Studies identified that previous hyperglycemia (diabetes mellitus [DM]) HAS does not seem to affect the neurological status from admission or the outcome at 6 months. However, hyperglycemia affects these elements, as it is probably a reflection of an acute brain injury.[33,34] Therefore, this information suggests that the unfavorable prognosis is more related to post-aSAH hyperglycemia, but more studies should be performed for the discussion of the relationship between the prognosis of patients who have DM and who have suffered HAS.

Limitations

The present study has several limitations. Primarily, as this is secondary research, the reliability of the information depends on the quality of the primary data. To minimize this bias, the authors tried to stick to the methodology of each work, to include in the results only items with technical quality and scientific rigor. Second, due to the adopted style of integrative and nonsystematic review, certain studies may have escaped the scope of the evaluation. However, it is worth mentioning that the objective is to obtain and synthesize the most recent evidence on the subject and, for this, the recommendations for care in methodological preparation and selection criteria were followed.

In addition, the articles included distinctions in terms of location, sample number, laboratory evaluation method, time of collection, and the scale for analyzing the result – such as the Glasgow Outcome Score and the Modified Rankin

Scale, among others. However, the authors chose not to be very judicious about the complementary test used – provided that at least one measurement of serum sodium or blood glucose was performed – or the assessment scale to allow gathering the largest possible sample size and summarizing the current understanding of the impact of glycemia and natremia in mortality and neurological outcome of patients after aSAH. Thus, the present findings must be evaluated with caution, and systematic reviews and future meta-analyses will be necessary to determine with more precision the correct period to request laboratory evaluation and the values with greater influence on the prognosis.

Conclusion

The present study concludes that alterations in blood glucose values and plasma sodium concentration influence the in-hospital morbidity and mortality of patients with aSAH. However, it is emphasized that the analysis of the independent influence of each of the related predictors must be done with caution due to the heterogeneity of the results found. Sodium alterations, in general, are related to unfavorable consequences. Hypernatremia and fluctuation in serum levels of anxiety are more consistent as an independent risk factor, related to worse outcomes, while hyponatremia shows more controversial results, being more commonly described as having no prognostic value, although other studies describe clinical and negative results. longer ICU stay. As for variations in glucose levels, both hyperglycemia, and hypoglycemia, due to physiological changes, were also associated with poor prognosis and higher in-hospital mortality.

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

Acknowledgments
None to declare.

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Usefulness of Intraoperative Infrared Thermography in Intracranial Surgeries: Past, Present, and Future

Utilidade da termografia infravermelho em cirurgias intracranianas: Passado, presente e futuro

Camila Monteiro Gonçalves da Costa[1] Vinícius Verbicário Botelho da Costa[1] Caio Araujo de Souza[1] Diego Rodrigues Menezes[2] Marcus Andre Acioly[1,2,3]

[1] Division of Neurosurgery, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil
[2] Postgraduation Program in Neurology, Federal University of the State of Rio de Janeiro, Rio de Janeiro, Brazil
[3] Division of Neurosurgery, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Address for correspondence Camila Monteiro Gonçalves da Costa, MS, Marquês do Paraná Av., 303, Centro, Niterói, 24033-900, Rio de Janeiro, Brazil (e-mail: camilamonteiro@id.uff.br).

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Abstract

With the advancement of technology in Neurosurgery, imaging guidance for surgical planning and intraoperative assessment has become relevant. Currently, two major methods of imaging guidance are generally explored in the literature, namely based on imaging and fluorescence. These techniques, however, are not without limitations. Thermal imaging has potentially broad applications in clinical practice, especially for intracranial diseases. Infrared thermography (IT) has been an underestimated tool with few reports on its usefulness during intracranial surgeries. In this article, we aim to provide a brief discussion on the limitations of current intraoperative imaging techniques for intracranial surgeries and to provide an in-depth state-of-the-art review on intraoperative IT (IIT) for intracranial lesions. High-resolution IIT is a non-invasive alternative imaging method that provides real-time estimation of regional cerebral blood flow. For brain tumors, the studies were mostly directed to diagnostic purposes and occasionally for lesion-localization. The use of IIT to address the extent of resection is a potential new application. Clinical data in this issue suggests that IIT might detect residual tumors, occasionally not assessed by other imaging technologies. Thermographic measurements during vascular and epilepsy surgeries comprise an interesting field for future research with potential clinical implications. Further experimental and clinical studies should be addressed to provide technical refinements and verify the usefulness of this noninvasive technology in neurosurgery.

Keywords
- brain tumors
- brain temperature
- imaging
- infrared imaging
- thermography

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Resumo

Com o avanço da tecnologia em neurocirurgia, a orientação do planejamento cirúrgico e da avaliação intraoperatória por métodos de imagem se tornaram extremamente relevantes. Atualmente, dois métodos principais de cirurgia guiada por imagem são geralmente explorados na literatura, ou seja, baseados em imagens e em fluorescência. Essas técnicas, no entanto, apresentam limitações. A termografia infravermelha (TI) tem aplicações potencialmente amplas na prática clínica, especialmente para doenças intracranianas. A TI tem sido uma ferramenta subestimada, com poucos relatos sobre a sua utilidade durante cirurgias intracranianas. Neste artigo, pretendemos fornecer uma breve discussão sobre as limitações das atuais técnicas de imagem intraoperatória para cirurgias intracranianas e fornecer uma revisão aprofundada do estado da arte sobre a TI intraoperatória (TII) para lesões intracranianas. A TII de alta resolução é um método de imagem alternativo não invasivo que fornece estimativa em tempo real do fluxo sanguíneo cerebral regional. Para tumores cerebrais, os estudos foram direcionados principalmente para fins diagnósticos e, ocasionalmente, para localização das lesões. O uso da TII para avaliar a extensão da ressecção é uma nova aplicação em potencial. Os dados clínicos sugerem que a TII pode detectar tumores residuais, ocasionalmente não avaliados por outras tecnologias de imagem. Medidas termográficas durante cirurgias vasculares e de epilepsia constituem um campo interessante para pesquisas futuras com potenciais implicações clínicas. Novos estudos experimentais e clínicos devem ser realizados para fornecer refinamentos técnicos e verificar a utilidade dessa tecnologia não invasiva em neurocirurgia.

Palavras-chave
- termografia
- neurocirurgia
- imagem
- avanços

Introduction

Infrared thermography is a non-invasive real-time imaging technique based on the detection of the emitted electromagnetic radiation coming from an object. Such radiation is converted into temperature color-coded or grayscale images by infrared thermographic cameras, in which different temperatures of body tissues can be interpreted in a localized manner[1] The history of thermal imaging in medical practice started in the 1940s and continued to develop since the 1960s.[2] The detection of cancer was a high priority at that time. The first breast thermography was performed in 1956 by a Canadian surgeon, Dr. Ray Lawson, who observed higher skin temperatures in patients with benign breast tumors and breast cancer (►**Figure 1**).[3,4]

Although thermal imaging has been used in medical practice since the 1950s, its widespread use in the clinical setting is still undetermined and under investigation, except for its application in breast cancer screening.[5] Thermographic profiles have been used to study diverse benign and

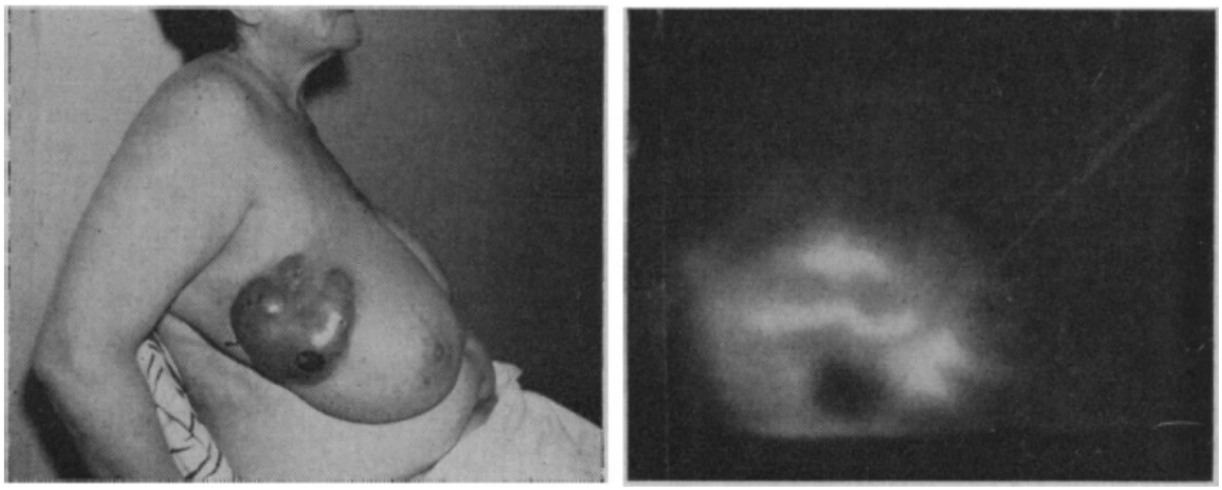

Fig. 1 Patient with advanced breast carcinoma with ulceration (left), demonstrating hyperthermic irregular contours on infrared thermography (right). Adapted from Lawson.[3]

malignant diseases, such as diabetic neuropathy, vascular diseases, thermoregulation, fever monitoring, liver metastatic diseases, and thyroid nodules, among others.[6,7]

Regarding the central nervous system (CNS), thermography has the ability to identify cortical surface temperature as a result of regional cerebral blood flow.[5] In this way, tumor necrosis,[5] low microvascular density,[8,9] vasogenic edema,[10] reduction of cortical metabolism,[11] and the occurrence of cystic lesions[12,13] contribute to lower regional temperature. On the other hand, changes in regional cerebral blood flow after activity-induced tasks during awake surgeries for brain mapping,[14] highly vascularized lesions, namely arteriovenous malformations[9] or some brain metastasis,[5] render thermographic maps of elevated temperature.

Thermal imaging has potentially broad applications in clinical practice, especially for intracranial diseases. Infrared thermography has been an underestimated tool with few reports on its usefulness during intracranial surgeries.[5,9,12,13,15–17] In this article, we aim to provide a brief discussion on the limitations of current intraoperative imaging techniques for intracranial surgeries, especially for brain tumors, and to provide an in-depth state-of-the-art review of intraoperative infrared themography (IIT) for intracranial lesions.

Limitations of Current Intraoperative Imaging Techniques for Intracranial Surgeries

Currently, two major methods of lesion localization and guidance for the extent of resection are generally explored in the literature, namely based on imaging (neuronavigation, intraoperative magnetic resonance imaging [iMRI], and intraoperative ultrasound [iUS]),[18–21] and based on fluorescence (5-ALA, and sodium fluorescein [SF]).[22,23] These techniques, however, are not without limitations.

Neuronavigation loses accuracy intraoperatively over time because of brain deformation, also known as brain shift.[24,25] Cerebrospinal fluid drainage, tissue removal, gravity, tumor localization and size, and brain edema are all well-recognized factors that contribute to intraoperative brain shift.[24,26] Besides brain shift, inaccurate recordings can also limit neuronavigation, especially during surgeries in the lateral or prone positions.[27] In such cases, neuronavigation registration is generally imprecise because of facial distortion and regional deformation on preoperative imaging.[27]

The update of the neuronavigation system with iMRI has been a reliable way to compensate for the effects of brain shift,[24,25] but its use is not widespread worldwide, especially because of the low availability and high costs. Furthermore, infection control, imaging artifacts, and equipment compatibility are always an issue for iMRI.[28–31] iUS has attracted interest for safety, portability, and real-time imaging. Even though iUS has demonstrated high accuracy for lesion location, imaging was deemed suboptimal or of poor quality in up to 8% of the patients.[26] In addition, image quality and the size of the ultrasound transducer are the main limitations of the method.

Regarding fluorescence guidance, tissue overlapping limits the identification of subcortical tumors, since healthy cortex, blood, blood clots, and hemostatic agent's obscure tumor visualization. On the other hand, intraoperative fluorescence enables real-time intraoperative identification of tumor tissue thereby permitting direct visualization of residual tumor.[23,32–34] The seminal paper by Stummer and colleagues in 2006[34] showed a 29% absolute increase in the extent of resection of high-grade gliomas with 5-ALA in comparison to white light. Since then, 5-ALA has been approved in many countries around the world for fluorescence-guided surgery.

SF is the second most used fluorophore, which has recently been given new attention. Even though there is some evidence on the contribution of the extent of resection with fluorescein-guided surgery,[35] its use is still under investigation and not approved for fluorescence guidance brain tumor resection in most countries, because of scanty severe allergic reactions and unspecific staining.[23,32,34] Timing of administration is an essential issue for both 5-ALA and SF. Administering both fluorophores too early might lead to a precocious 5-ALA peak rendering false negative tumor identification or permitting unspecific propagation of SF on edematous brain tissue. Conversely, late administration does not allow effective accumulation of fluorophores. Finally, the low contrast index in low-grade gliomas comprises a crucial limitation of fluorescence.[36]

Usefulness of Infrared Thermography in Intracranial Surgeries

Tumors and Functional Mapping

The first description of the intraoperative application of infrared thermography in brain tumors was made in 1987, in an article in Japanese. Koga et al.[13] studied the thermal microenvironment of six brain tumors (two metastasis and four gliomas). With a low-resolution infrared camera, tumor temperatures were generally cooler than adjacent healthy cortex on thermographic maps, especially for brain metastasis. Cystic and necrotic tumor areas were notably hypothermic, which was confirmed by the help of iUS. In addition, Koga et al.[13] introduced the observation of delayed thermal recovery curves after the cold loading test on those hypothermic areas.

In 2002, Ecker and colleagues expanded the use of infrared imaging for cerebral revascularization surgeries, epilepsy, and cortical brain mapping, in addition to describing thermal characteristics of primary brain tumors by histopathological subtype. Thirty patients were examined with a low-resolution infrared camera (matrix of 256×256 pixels and an accuracy of 0.006°C between pixels). Thus, low- and high-grade gliomas were generally hypothermic in comparison to the adjacent cortex (78% of measurements).[9]

In 2003, Gorbach et al. introduced the identification of cortical functional areas by IIT. The assumption behind this was that thermography was able to identify regional cerebral blood flow changes induced by increased metabolism, because of motor or language tasks during awake mapping.

Twenty-one patients were examined with a low-resolution infrared camera. They concluded that the cortical distribution of the thermographic maps overlaps that obtained with cortical stimulation mapping, thereby comprising a useful tool to study brain function (►**Figure 2**).[14]

In 2004, the same group studied the effects of a brain tumor on the surrounding healthy cortex. Thirty-four tumors comprised their study group. Brain tumors create changes in regional cerebral blood flow, which goes beyond tumoral margins and could be able to improve after tumor resection. Such changes in regional blood flow are made visible by intraoperative infrared thermography rendering temperature differences of about 0.5 to 2.0 °C between the brain tumor margin and the healthy cortex.[15] Tumors of the glial lineage were generally hypothermic, while brain metastasis was consistently hyperthermic. Normalized temperature gradients (the ratio between the coldest and the hottest tumor areas) in brain metastasis were 49% and 40% higher compared to oligodendrogliomas and glioblastomas, respectively. However, the mean temperature gradients may vary depending on the tumor stage, size, location,[15] as well as the occurrence of edema and areas of cystic degeneration or necrosis.

The visualization of these thermal gradients by thermography can be facilitated with the use of isotonic saline solution, at room or cold temperature. With irrigation-induced hypothermia, both the healthy cortex and brain tumor presented temperature reduction, but recovery curves were generally different since brain tumor areas demonstrated a rather delayed curve that lasted 10 to 40 sec longer. Irrigation generated an increase of approximately 10% in the heat gradient, allowing a better visualization of tumor areas.[15]

In 2009, Kateb and colleagues were the first to apply IIT to assess the extent of tumor removal. In a case report, they described a patient with brain metastasis from melanoma. Tumor thermographic maps revealed hyperthermic areas. The resection was deemed complete intraoperatively by the surgical team, however postoperative MRI confirmed subtotal resection (approximately 82%). A retrospective analysis of the three-dimensional thermographic profile indicated the potential location of the residual tumor (►**Figure 3**). It is worth noting that Kateb et al. used a low-resolution thermographic camera (FLIR Systems TCP60 - 320 × 240 pixels and accuracy of 0.06 °C).[5]

Kastek et al. used a high-resolution thermographic camera to report differences in temperature according to diverse regions of interest within the tumor (edema, cyst, and tumor itself) both before and during resection. Six patients were examined with IIT (gliomas, meningiomas, and cystic lung metastasis). Measurements have shown that cystic temperature was 2 °C lower than the surrounding cortex (edema) and 4 °C lower than neoplastic tissue. The magnitude of temperature differences is mainly determined by the histological subtype and degree of metabolic activity. In addition, the authors demonstrated the role of bipolar coagulation and devascularization in reducing tumor temperatures.[12]

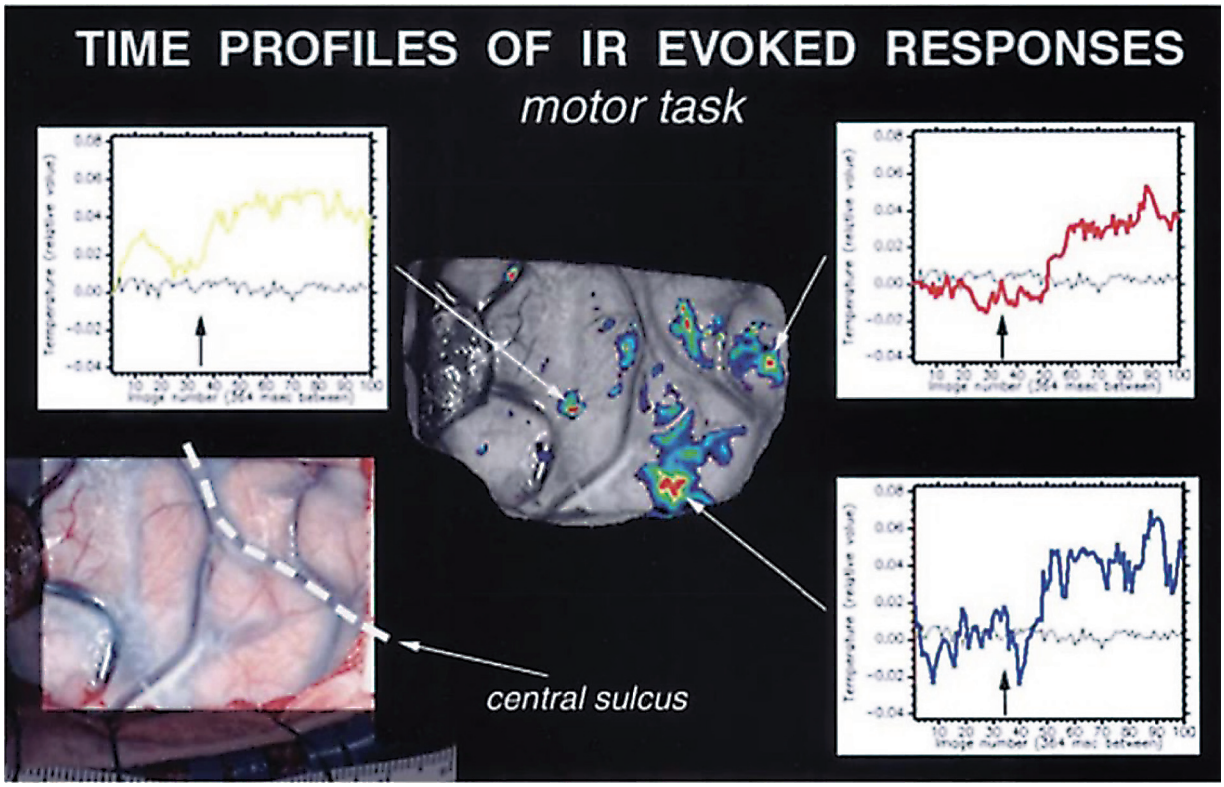

Fig. 2 Surgical microscope (left, bottom) and thermographic (center) images, showing changes in cortical temperature as a function of motor activity. The yellow curve represents the temperature changes during the cold challenge test in the premotor cortex, while the blue graph, is from the primary motor cortex, and the red one, is from the primary sensory cortex. Adapted from Gorbach et al. with permission.[14]

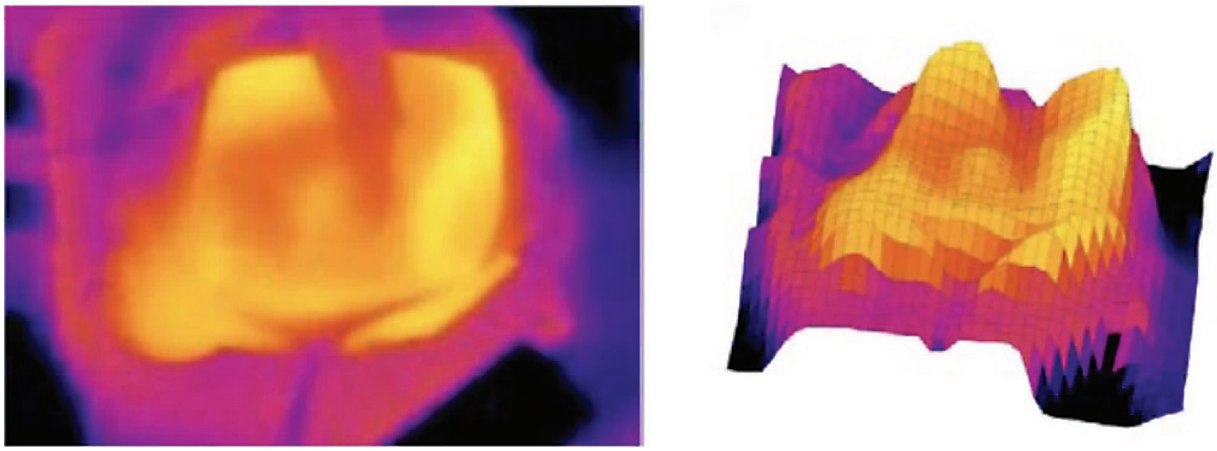

Fig. 3 Intraoperative infrared thermography image (left) of the surgical bed and the three-dimensional thermographic map (right), showing central hypothermia that might suggest the residual tumor detected on postoperative imaging. The black areas might correspond to residual tumors covered by saline or blood clots. Adapted from Kateb et al. with permission (2009).[5]

With these potential applications in mind, we recently started a prospective study in 15 patients with intracranial cortical and subcortical tumors of different histological subtypes to evaluate the usefulness of IIT with a high-resolution thermographic camera for transdural lesion-localization, diagnosis, to assess the extent of resection, and the occurrence of perioperative acute ischemia. Static and dynamic thermographic maps (cold challenge test) were acquired intraoperatively with a high-resolution camera at pre-established time points. Our preliminary results showed that intraoperative thermographic imaging of the exposed dura mater revealed a mixed vascular pattern of meningeal vessels, veins, and cortical arteries. Intra-axial tumors were reliably identified by demonstrating hypothermic areas with high sensitivity and specificity for cortical and subcortical tumors up to 2 cm in depth, which were exacerbated by the cold challenge test.

We also found that dural opening facilitated both the identification of tumors and their neurovascular relations (►**Figure 4**). The analysis of central spot temperatures significantly elucidated histological subtypes. At the end of the surgical resection, there was a consistent rise in the temperature of gliomas and metastasis tumor beds. Residual tumors on imaging were retrospectively evaluated with infrared thermography, presenting a typically delayed temperature recovery curve after the cold challenge test. Acute ischemia was consistently hypothermic, but without clinical deterioration, however (Menezes et al., 2023, submitted).

Vascular Surgery

The application of intraoperative infrared thermography started in 1993 when Okudera and colleagues used a thermographic camera attached to a surgical microscope to study temperature patterns during the resection of an AVM.[37] Thermal imaging permitted real-time noninvasive temperature monitoring of the involved cerebral vessels. At the beginning of the surgical procedure, AVM draining veins was consistently hyperthermic because of arterialization, but progressive occlusion of feeding arteries caused temperature drop to normal levels, especially after the cold loading test (►**Figures 5** and **6**).[37]

Almost ten years have passed since a second study on the field was presented. Watson et al., in 2002, reported their experience using a high-resolution sensitive infrared camera (0.02 °C) to locate cortical function intraoperatively.

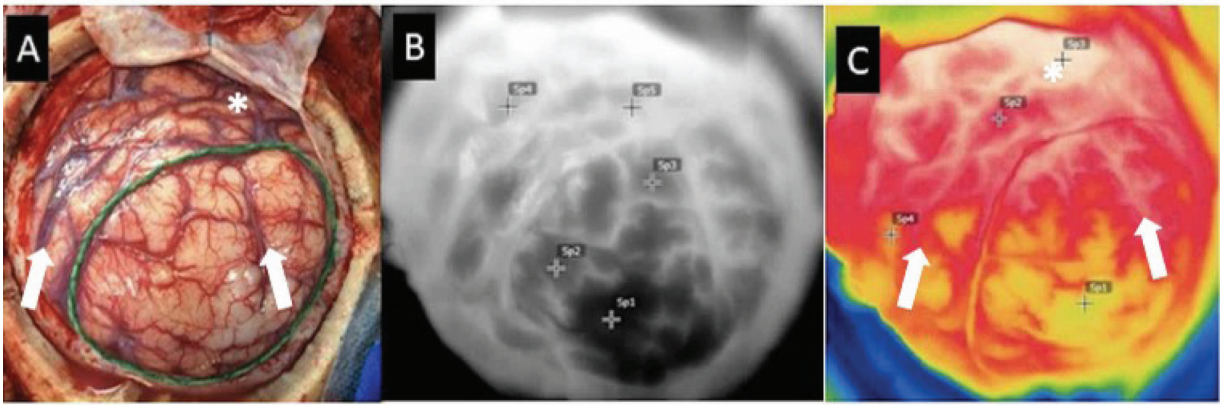

Fig. 4 Intraoperative images during resection of a right temporoparietal tumor (oligodendroglioma WHO grade II). Tumoral area is demarcated with a green cotton thread (**A**). The thermographic maps in black and white (**B**) and color-coded (**C**) reveal higher temperatures in the lateral sulcus (asterisk) and intermediate temperatures in the cortical veins (white arrows). The tumor is consistently hypothermic (yellow area).

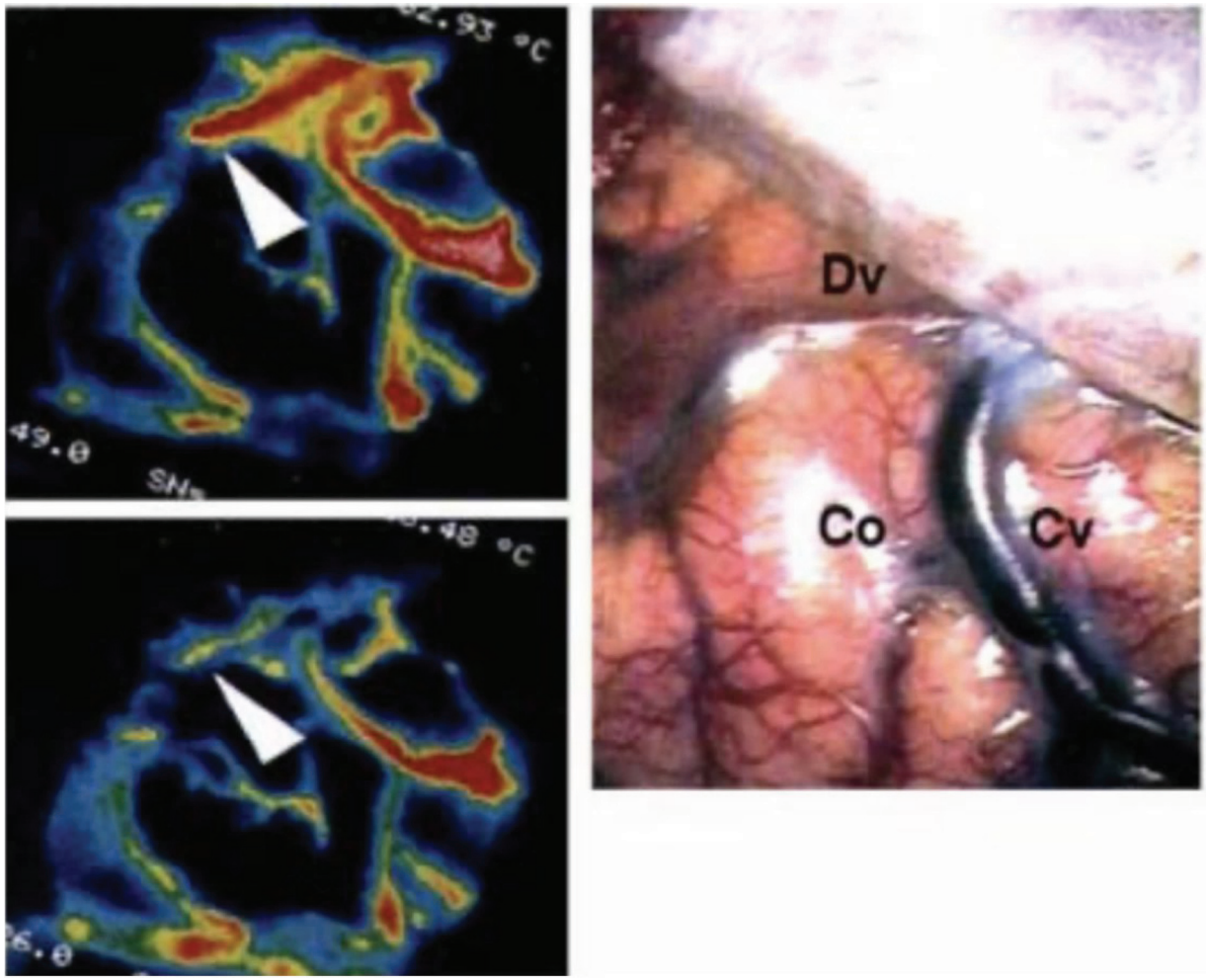

Fig. 5 Intraoperative images of the cortical surface during an arteriovenous malformation resection surgery. The arterialized draining vein (Dv, white arrow) showed a progressive temperature decrease after occlusion of the feeding arteries. Co - cortex; Cv - normal vein. Adapted from Okudera et al. with permission.[37]

They looked at high-resolution images of cerebral vessels and hypothesized that infrared imaging would allow changes in the arterial flow to be seen immediately. Thus, providing a real-time indirect assessment of cerebral perfusion in the vascular territory involved. During surgical procedures that require vascular manipulation, such as brain aneurysms, AVMs, or some tumors, the ability to visualize real-time cerebral blood flow in major vessels and their distribution beds would be beneficial, especially during temporary vascular occlusion.[16]

The next step was provided by Ecker et al., in 2002, showing intraoperative hyperperfusion of the healthy cortex after AVM resection, which was consistent with loss of brain autoregulation. The patency of extra-intracranial bypass for cerebral revascularization was also verified and, additionally, demonstrated an increase in regional cerebral blood flow and indirectly an increase in regional cerebral perfusion. Even though more research is needed to fully define the role of intraoperative infrared imaging for cerebral revascularization, the quantification of increased perfusion can help identify patients who would benefit from a bypass. Such knowledge could have potential implications for detecting cerebral inschemia during brain aneurysm clipping, hemicraniectomy for nondominant stroke, and traumatic brain injury.[9]

Further studies in the field were done by Nakagawa et al.,[38] and Kawamata et al.[39]by using infrared thermography to detect symptomatic cerebral hyperperfusion in patients with moyamoya disease submitted to extra-intracranial bypass for cerebral revascularization. The first study demonstrated that transient neurological symptoms were accompanied by an increase in cerebral blood flow around the anastomosis site, which can be characterized as symptomatic hyperperfusion. Conversely, the results by Kawamata et al. were not optimistic in detecting cerebral hyperperfusion during bypass surgery, since a correlation between intraoperative thermographic changes, and cerebral hyperperfusion was not observed.[39]

Finally, Hwang et al. investigated the role of infrared thermography in studying the steal phenomenon during AVM resection. Through measurements of ocular and perilesional cortical temperatures, the authors demonstrated that ocular temperatures recovered, and perilesional temperature increased. Although such a temperature difference

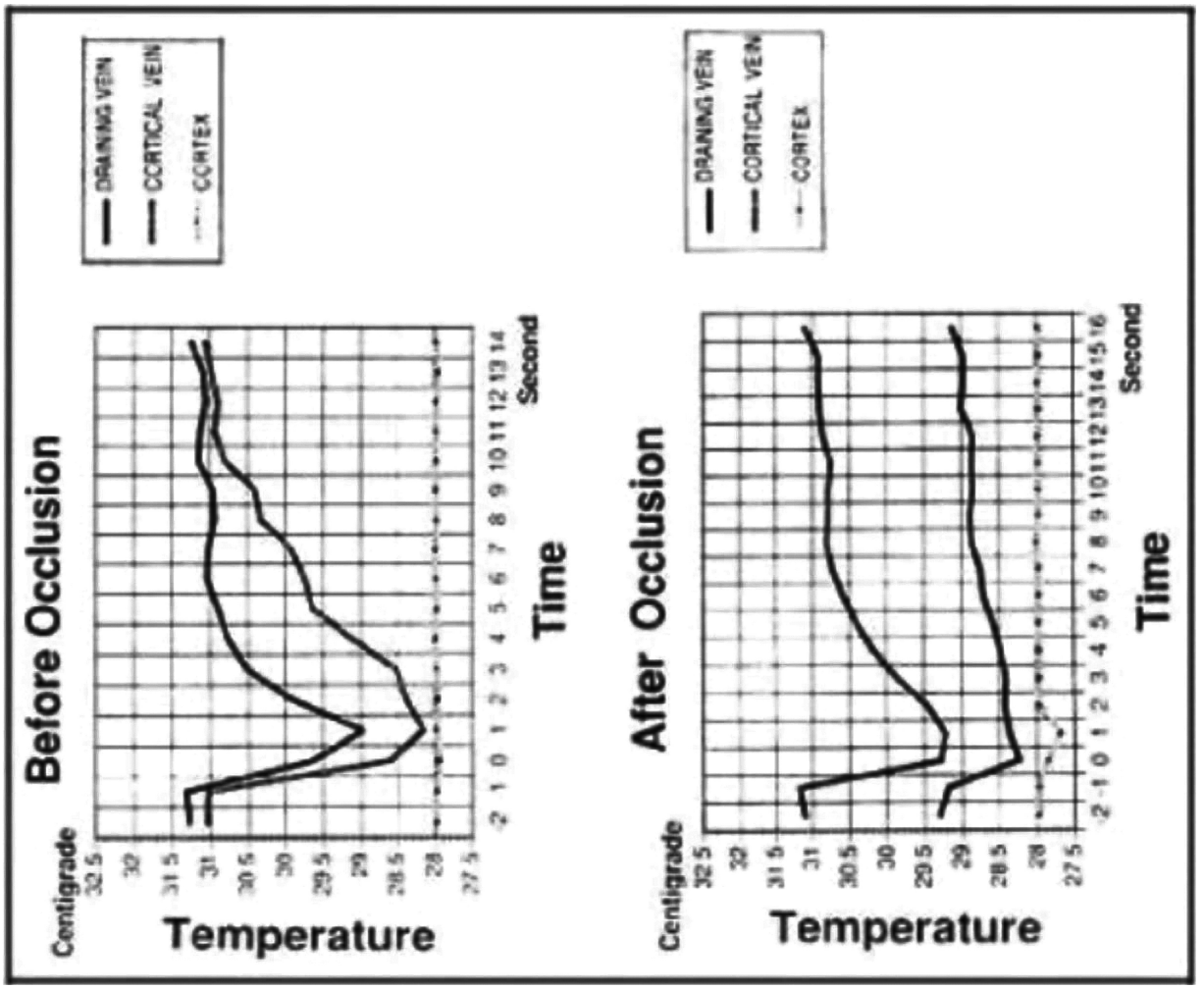

Fig. 6 Temperature recovery curves of the draining and cortical veins, and the exposed cortex obtained after the instillation of cold saline. After occlusion of the feeding arteries (below), the draining vein shows a thermographic recovery profile similar to the cortical vein. Adapted from Okudera et al. with permission.[37]

might be attributed to anesthesia or surgery, the authors deemed thermography to be an efficient tool in identifying the steal phenomenon caused by AVMs (►**Figure 7**).[40]

Epilepsy

The study of seizure foci and their relationship to the adjacent healthy cortex by infrared thermography is sparsely reported in the literature. To the best of our knowledge, only the study by Ecker and colleagues addressed such an issue. In that manuscript, nine patients with intractable extratemporal lobe epilepsy were operated on and had their cortical and lesional thermographic maps measured. Ecker et al. demonstrated highly concordant data between the epileptogenic zone based on preoperative imaging and electrocortigraphic findings and thermal activity. Their results indicated changes in local cortical temperature in the seizure foci, in the way that measurements were generally warmer than the adjacent cortex.[9] No mention is made of absolute thermography values, however. Furthermore, remote, and local hypermetabolic areas caused by seizure activity may not be identified by the method. Therefore, it might not be possible to fully delineate the epileptogenic zones involved in the propagation of seizures.[9]

Conclusion

In the current study, we provided an in-depth overview of infrared thermography for intracranial surgeries. High-resolution intraoperative infrared thermography is a non-invasive alternative imaging method that provides real-time estimation of regional cerebral blood flow. Over the last 30 years, few studies have provided a detailed analysis of thermographic profiles during intracranial surgeries. For brain tumors, the studies were usually directed to diagnostic purposes and occasionally for lesion-localization. Generally speaking, gliomas are consistently hypothermic, both for cortical tumors or the overlying cortex in subcortical tumors, while brain metastases and meningiomas exhibit highly variable thermographic maps that indirectly reveal the grade of tumor vascularization, as well as the presence of edema and cystic degeneration.

For lesion-localization, previous studies and our results demonstrated that infrared thermography allows the

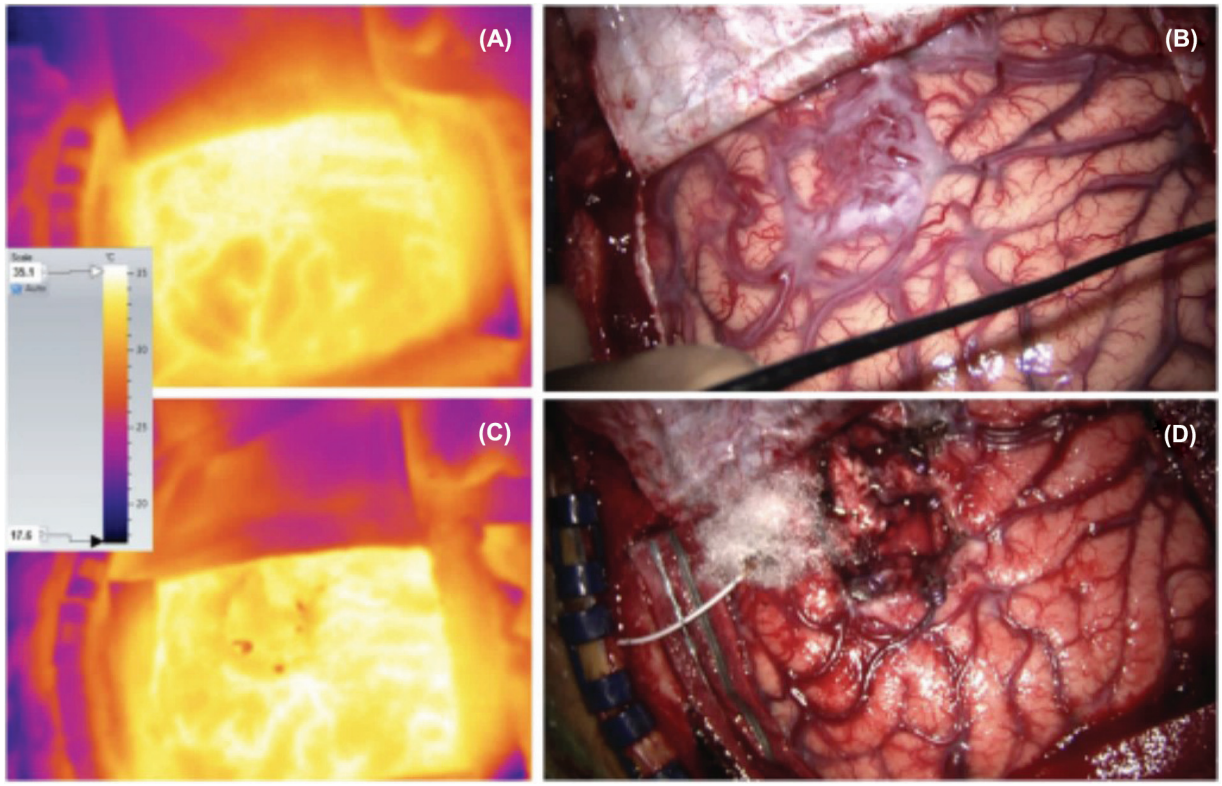

Fig. 7 Thermographic color-coded images (A and C) and intraoperative visual images (B and D) suggest redistribution of blood after AVM resection. Adapted from Hwang et al. with permission.[40]

identification of intracranial tumors of up to 2 cm depth with high sensitivity and specificity. For the assessment of the extent of resection, the literature is scarce. The results obtained by our group suggest a new potential and additional role of infrared thermography since residual tumors revealed nonspecific static and characteristic dynamic thermographic maps. Thermographic measurements during vascular and epilepsy surgeries comprise an interesting field for future research with potential clinical implications. Further experimental and clinical studies should be addressed in order to provide technical refinements and verify the usefulness of this noninvasive technology in neurosurgery.

Conflict of Interest
None declared.

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Aggressive Osteoblastoma of Temporal Bone Causing Facial Palsy in a 9-year-old Child: A Case Report Based on 2020 WHO Classification of Bone Tumors

Osteoblastoma agressivo do osso temporal causando paralisia facial em uma criança de 9 anos: Um relato de caso baseado na classificação da OMS de 2020 de tumores ósseos

Eduardo Cambruzzi[1,2,3,4] Roque Domingos Furian[2] Luiza Gomes Botega[2] Nilo Devigli Júnior[2] Eron Rodrigues Cunha Lopes[2]

[1] Department of Histology and Pathology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil
[2] Pathology Laboratory, Complexo Hospitalar Santa Casa, Porto Alegre, RS, Brazil
[3] Pathology Laboratory, Grupo Hospitalar Conceição, Porto Alegre, RS, Brazil
[4] Hemodynamics Service, Instituto de Cardiologia, Fundação Universitária de Cardiologia, Porto Alegre, RS, Brazil

Address for correspondence Eduardo Cambruzzi, PhD, Department of Pathology, Santa Rita Hospital, Complexo Hospitalar Santa Casa, Rua Sarmento Leite, 187, 2° andar, Porto Alegre, RS, Brazil (e-mail: dudacambruzzi@yahoo.com.br).

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Abstract

Aggressive osteoblastoma (AO) is an uncommon bone tumor that represents a borderline lesion between osteoblastoma and osteosarcoma. The vertebral column, the sacrum, the pelvis, and jaw/craniofacial bones are primarily affected. Aggressive osteoblastoma does not metastasize and is treated by surgical resection. The authors report a case of AO in a 9-year-old female patient presenting with 5th and 7th cranial nerve palsy. Prior pathological history included resection of an expansile nodule in the left temporal bone. Conventional radiological examination and computed tomography (CT) of the skull revealed an osteoblastic lesion arising in the petrous portion of the left temporal bone, measuring 5.2 cm in the largest dimension. The patient was subjected to partial surgical resection of the process. Microscopy revealed a primary neoplastic bone composed of numerous epithelioid round osteoblasts disposed in solid sheets and with mild atypia, large eosinophilic cytoplasm, and an eccentric, ovoid nucleus. The process exhibited loose stroma, low mitotic index, osteoid formation, and a few osteoclast-like multinucleated giant cells. The diagnosis of AO was thus established. After 5 months of clinical follow-up, the patient is asymptomatic, without evidence of tumoral growth on CT scans.

Keywords
- aggressive osteoblastoma
- osteoblastic tumor
- bone tumor
- pathology
- prognosis

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Resumo

O osteoblastoma agressivo (AO) é um tumor ósseo incomum que representa uma lesão limítrofe entre osteoblastoma e osteossarcoma. A coluna vertebral, o sacro, a pelve e os ossos maxilares/craniofaciais são afetados principalmente. O osteoblastoma agressivo não metastatiza sendo tratado por ressecção cirúrgica. Os autores relatam um caso de OA em paciente do sexo feminino, de 9 anos, com paralisia de V e VII pares cranianos. A história patológica prévia incluiu ressecção de nódulo expansivo no osso temporal esquerdo. O exame radiológico convencional e a tomografia computadorizada (TC) de crânio revelaram lesão osteoblástica surgindo na porção petrosa do osso temporal esquerdo, medindo 5,2 cm em sua maior dimensão. O paciente foi submetido à ressecção cirúrgica parcial do processo. A microscopia revelou osso neoplásico primário composto por numerosos osteoblastos epitelióides redondos dispostos em lâminas sólidas e com leve atipia, grande citoplasma eosinofílico e núcleo ovoide excêntrico. O processo exibiu estroma frouxo, baixo índice mitótico, formação de osteóide e algumas células gigantes multinucleadas semelhantes a osteoclastos. O diagnóstico de OA foi assim estabelecido. Após 5 meses de acompanhamento clínico, o paciente encontra-se assintomático, sem evidência de crescimento tumoral na tomografia computadorizada.

Palavras-chave
- osteoblastoma agressivo
- tumor osteoblástico
- tumor ósseo
- patologia
- prognóstico

Introduction

Aggressive osteoblastomas (AOs) are very rare tumors classified as borderline lesions between osteoblastoma and osteosarcoma. Its peak age incidence is in the 2nd and 3rd decades of life.[1–3] Overall distribution patterns are similar to those of conventional osteoblastoma, with a predilection for the axial skeleton. The vertebral column, the sacrum, proximal parts of the appendicular skeleton such as the pelvis and femur, and jaw/craniofacial bones are primarily affected.[2–5] Aggressive osteoblastomas do not metastasize, are likely to recur (in between 20 and 30% of cases) and are characterized by the presence of epithelioid osteoblasts. The lesion is not considered a precursor to osteosarcoma.[1,2,5–7] The present study reports a case of AO compromising the left temporal bone and causing 5th and 7th cranial nerve compression in a pediatric patient and discusses clinical and pathological findings of this rare bone tumor.

Case Report

A female patient, 9 years old, was referred to the neurosurgery service with left 5th and 7th cranial nerve palsy. On physical examination, the patient exhibited good general condition and adequate weight and height development (48.7 kg/1.45 m), without evidence of other focal neurological deficits, optic nerve edema, or alterations in other systems. Her prior pathological history included resection of an expansile nodule in the left temporal bone 2 years earlier at another institution, where the diagnosis of osteofibrous dysplasia was established. Current laboratory tests were within normal values. Conventional radiological examination and computed tomography (CT) of the skull revealed an osteoblastic lesion arising in the petrous portion of the left temporal bone, which measured ~ 5.2 cm in the largest dimension and caused compression of the 5th and 7th cranial nerves (►**Fig. 1**). The patient was subjected to partial surgical

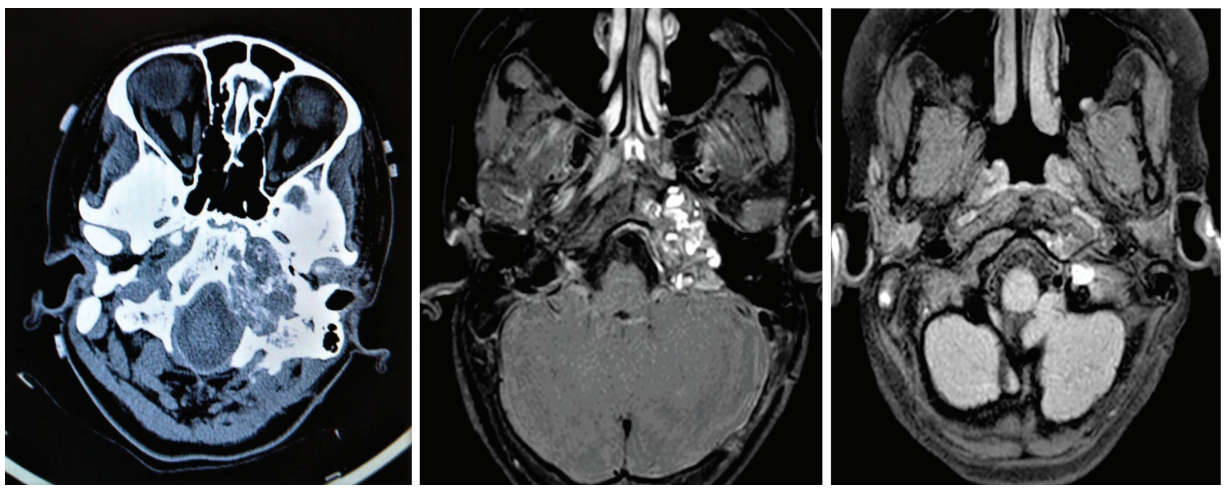

Fig. 1 Aggressive osteoblastoma: Computed tomography of the skull revealing an osteoblastic lesion (5.2 cm in the largest dimension) arising in the petrous portion of the left temporal bone.

resection of the process (~ 80% of the tumoral volume). The patient was placed in right lateral decubitus and underwent a left frontobasal craniotomy. During the surgical procedure, an expansive lesion affecting the temporal bone was identified. The process determined compression of the brainstem and the foramina at the base of the skull. The tumor was resected through the Kawase trigone in its lowest portion and lateral to the Meckel cavum. The VII cranial pair was dissected and preserved during the procedure. On gross examination, the surgical specimen was composed of several irregular, pale gray fragments of bone tissue, the largest of which measured 1.8 × 1.2 × 1.0 cm. On microscopy, a primary neoplastic bone neoplasm was identified. The lesion was characterized by numerous epithelioid round osteoblasts disposed in solid sheets around irregular bone trabeculae and exhibiting mild atypia, large eosinophilic cytoplasm, and an eccentric, ovoid nucleus. The process had loose stroma, numerous small vascular channels, low mitotic index, osteoid formation, and a few osteoclast-like multinucleated giant cells. No chondroid areas were identified (►**Fig. 2**). These findings culminated in a diagnosis of AO. After 8 months of clinical follow-up, the patient is asymptomatic, without cranial nerve palsy or evidence of tumoral growth on CT scans. Previous histological slides were reviewed, and the diagnosis of AO was confirmed.

Discussion

The true incidence and age distribution of AO remain largely unknown because of the rarity of the disease.[1,2,4,5,7] The first case series found in the literature, published in 1984 and 1996, described 15 and 36 cases, respectively.[1,4] Clinical complaints are directly associated with compromised bone, and pain is a common symptom. Radiological findings usually comprise a circumscribed lytic defect sometimes surrounded by a rim of sclerosis.[1,4,6,8,9] The main difference from conventional osteoblastoma is that AO is larger, usually exceeding 4 cm.[2,5,6,9,10] The bone contour may be expanded and have a rim of reactive bone. Eventually, the tumor crosses the joint space, thereby compromising the adjacent bone, a reflection of its aggressive biological behavior. Soft tissues may be involved if the tumor arises in small bones.[1,4,5,8,11,12]

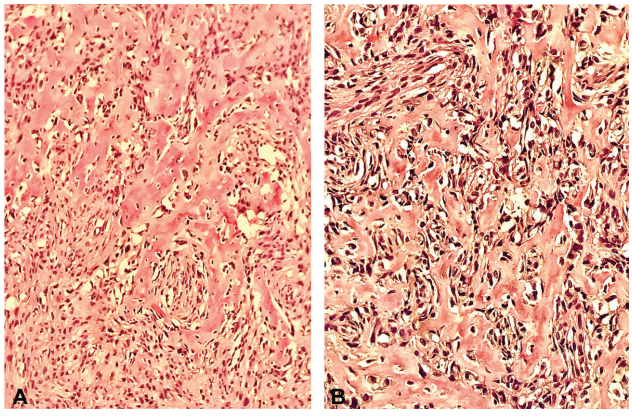

Fig. 2 Aggressive osteoblastoma of the temporal bone: **(A)** Epithelioid osteoblasts occupying intertrabecular spaces (hematoxylin–eosin, 200X); **(B)** Large epithelioid osteoblasts disposed in solid sheets and showing mild atypia. Note osteoid deposition and vascular channels in the tumor stroma (hematoxylin–eosin).

On gross examination, the process is an oval to round, reddish, bright, soft to hard lesion with well-defined margins.[2,4,10,13–15] The bone contour may be markedly expanded and exhibit a thinned, disrupted cortex.[2,4,10,13–16] The tumor stroma is characteristically rich in blood vessels. On microscopy, AO shows many similarities to conventional osteoblastoma. Aggressive osteoblastomas are composed of an irregular network of bone trabeculae distributed in a loose stroma with prominent vasculature.[2,3,7,11,14,16,17] The most important histological finding is the presence of epithelioid osteoblasts that form solid sheets in intertrabecular spaces or rim osteoid trabeculae. Epithelioid osteoblasts are round cells with abundant eosinophilic cytoplasm, an eccentric, oval nucleus with prominent nucleoli, and some degree of atypia.[2,3,7,11,14,16,17] Epithelioid osteoblasts are at least twice the size of normal osteoblasts and, frequently, show a large, clear cytoplasmic area with enlarged Golgi apparatus, which displaces the nucleus.[2,3,7,11,14,16–18] Osteoid can be found around individual tumor cells or in broad zones surrounding epithelioid osteoblasts. The presence of benign osteoclast-like multinucleated giant cells and secondary aneurysmal bone cysts are common features.[2,4,7,10,13,15,17,18] Aggressive osteoblastomas show 1 to 4 typical mitotic figures per 20 high-power fields. Necrosis is uncommon, and chondroid/cartilaginous differentiation has not been described.[7,10,13,15,17–19]

The differential diagnosis includes osteoid osteoma, conventional osteoblastoma, and osteosarcoma.[1,7,10,14,20,21] Osteoid osteoma and osteoblastoma measure < 4 cm in diameter and do not exhibit epithelioid osteoblasts. The main diagnostic problem regarding the entity classified as AO centers around its distinction from osteosarcoma. Classical histological findings of conventional osteosarcoma include moderate to severe cellular atypia, high mitotic index, atypical mitotic figures, prominent osteoid deposition, infiltrative/permeating growth pattern, and presence of neoplastic cartilage.[4,9,10,17,20,22–24] Aggressive osteoblastoma also exhibits a peripheral shell of reactive bone over the soft tissue extension, which is not characteristic of osteosarcoma. Genetic studies are not useful for distinguishing between AO and osteosarcoma or for determining prognosis. There is yet no evidence that AO undergoes spontaneous transformation to osteosarcoma.[1,4,14,21–24] Complete surgical resection, curettage, and/or partial resection is the mainstay of treatment for AO. Skull AO should be treated by wide local excision when technically feasible. Long-term follow-up is necessary to monitor recurrence.[1,4,7,21,23,24] The ►**Table 1** shows a summary of literature reports of aggressive osteoblastoma. Partial resection of skull AO have been accepted when the location of the tumor, such as the temporal bone or the base of the skull, denotes a high risk of vascular or cranial nerve damage or technical limitations.[1,4,7,21,23,24]

Table 1 Summary of literature reports of aggressive osteoblastoma

Reference	Gender, age (years old)	Clinical complaint	Topography	Radiologic findings	Tumor size	Clinical management	Outcome
Morris et al.[5]	Female, 20	Pain	Left scapula	Lytic lesion	8.9 cm	Surgical resection	Disease-free at 3 years after surgery
Lu et al.[6]	Male, 18	Local tenderness	Temporal bone	Lytic lesion	3.3 cm	Surgical resection	No signs of recurrence at 1 year after surgery
Sharma et al.[7]	Male, 18	Progressive swelling	Right parietal bone	Lytic lesion	9.0 cm	Surgical resection	Persistent lesion at 21 months of follow-up
Salmen et al.[8]	Male, 7	Pain	Maxilla	Lytic lesion	2.1 cm	Surgical resection	No signs of recurrence at 1 year after surgery
Al-Ibraheem et al.[9]	Male, 25	Hemimandibular swelling	Mandible	Sclerotic lesion	2.2 cm	Surgical resection	No signs of recurrence at 1 year after surgery
Sharma et al.[10]	Male, 17	Pain in left hip	Acetabulum	Lytic lesion	6.4 cm	Extended curettage	No signs of recurrence at 1 year after surgery
Sonnylal et al.[11]	Male, 21	Painful mass	Left femur	Sclerotic lesion	20.0 cm	Radical resection of the left femur and cryosurgery	No signs of recurrence at 32 months after surgery
Harrington et al.[12]	Male, 25	Enlarging palatal mass	Maxilla	Sclerotic lesion	4.0 cm	Surgical resection	No signs of recurrence at 8 months after surgery
Miyayama et al.[13]	Female, 29	Pain	Left calcaneus	Lytic lesion	3.0 cm	Surgical resection	No signs of recurrence at 10 years after surgery
Ando et al.[14]	Male, 25	Neck pain	6^{th} and 7^{th} cervical vertebrae	Lytic lesion	3.5 cm	Surgical resection	No signs of recurrence at 2 years after surgery
Dixit et al.[15]	Male, 20	Hearing loss and tinnitus in left ear	Left temporal bone	Lytic lesion	6.0 cm	Partial resection	Unknown
Kukwa et al.[16]	Female, 12	Persistent exophthalmia	Sphenoid	Lytic lesion	5.5 cm	Surgical resection	Recurrence at 4 months after surgery
Pontual et al.[17]	Male, 13	Swelling on the left side of the face	Mandible	Lytic lesion	5.7 cm	Surgical resection	No signs of recurrence at 4 years after surgery
Kashikar et al.[18]	Male, 18	Swelling of the oral cavity	Mandible	Lytic lesion	1.2 cm	Extended curettage	No signs of recurrence at 6 months after surgery
Cikojević et al.[19]	Female, 14	Right-sided nasal obstruction and severe headache	Right middle turbinate	Sclerotic lesion	2.2 cm	Surgical resection	No signs of recurrence at 1 year after surgery
Mohanty et al.[20]	Male, 23	Painful swelling	Temporal bone	Sclerotic lesion	3.0 cm	Surgical resection	No signs of recurrence at 8 months after surgery
Baker et al.[21]	Female, 12	Right thigh pain	Right femur	Lytic lesion	5.7 cm	Surgical resection	No signs of recurrence at 9 months after surgery
Chatterjee et al.[22]	Male, 2	Swelling over dorsum of right hand	Third metacarpal shaft	Lytic lesion	3.0 cm	Surgical resection	No signs of recurrence at 2 years after surgery
Srivastava et al.[23]	Male, 24	Painful swelling	Mandible	Lytic lesion	5.3 cm	Surgical resection	No signs of recurrence at 5 months after surgery
Castro et al.[24]	Female, 7	Swelling	Mandible	Sclerotic and lytic lesion	5.6 cm	Extended curettage	No signs of recurrence at 6 years after surgery
Present case	Female, 9	Left 5^{th} and 7^{th} cranial nerve palsy	Left temporal bone	Osteoblastic	5.2 cm	Partial surgical resection	No signs of tumoral growth at 5 months of follow-up

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

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Schwannoma-like Breast Metastasis in the Meckel Cave: Case Report

Metástase de mama semelhante a um schwannoma no cavo de Meckel: Relato de caso

Frederico de Lima Gibbon[1] Antônio Delacy Martini Vial[2] Guilherme Gago[2]
Matheus Prado Magalhães[2] Marcelo Paglioli Ferreira[2]

[1] Universidade Católica de Pelotas, Pelotas, RS, Brazil
[2] Complexo Hospitalar Santa Casa de Misericórdia de Porto Alegre, Porto Alegre, RS, Brazil

Address for correspondence Frederico de Lima Gibbon, Universidade Católica de Pelotas, Avenida Major Carlos Pinto 123, casa 14, Cidade Nova, Rio Grande, RS, 96211-021, Brazil (e-mail: fredericogibbon@gmail.com).

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Abstract

Tumors of the Meckel cave are very rare lesions, especially if they are malignant. We report the case of a patient who presented with a breast metastasis in the Meckel cave and a clinical presentation similar to that of a fifth nerve schwannoma.

Keywords
- Meckel cave
- metastasis
- breast metastasis
- schwannoma
- meningioma
- trigeminal tumors

Resumo

Os tumores do cavo de Meckel são lesões muito raras, especialmente se forem malignos. Relatamos o caso de uma paciente que apresentou metástase mamária no cavo de Meckel e quadro clínico semelhante a schwannoma do quinto nervo.

Palavras-chave
- cavo de Meckel
- metástase
- metástase de mama
- schwannoma
- meningioma
- tumor trigeminal

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Introduction

The Meckel cave is a small dural pouch, filled with liquor, which is located at the petrous apex of the temporal bone and contains the sensitive ganglion of the trigeminal nerve. Tumors in this region are quite rare, and they are usually benign. The most common tumors are fifth-nerve schwannoma and meningioma.[1,2] We report the case of a patient who had breast metastasis in the Meckel cave presenting as a schwannoma of the fifth nerve.

Case Report

A 67-year-old female patient came to our service complaining of facial hypoesthesia and diplopia. The patient reported she had started with hypoesthesia on the right face ~ 1 year before. Initially, there was only a slight numbness, but it progressed to a complete loss of sensation. In addition, the patient reported that in the previous three months she had started to show diplopia mainly when looking to the right side. The patient had no previous comorbidities. Upon the neurological examination, the patient presented tactile and thermoalgesic hypoesthesia in the entire right hemiface, slight atrophy of the masseter muscle, as well as paresis of the VI cranial nerve, identified by a slight convergent strabismus. The direct and consensual corneopalpebral reflex was abolished on the right side. The patient denied any type of facial pain. The rest of the exam was normal.

Apparently, the patient was previously healthy. However, she had treated a breast cancer with chemotherapy in 2017, and had achieved complete remission of the disease.

Initially, a magnetic resonance imaging scan of the skull was requested. This exam showed an expansive lesion in the projection of the right trigeminal cistern, measuring around 2.7 × 1.2 cm, with extension to the tentacle, cavernous sinus and inferiorly to the Gasser ganglion, with homogeneous contrast enhancement (►**Fig. 1**).

Due to the prolonged and insidious clinical scenario and the rarity of metastases in the Meckel cave, our main diagnostic hypothesis was fifth-nerve schwannoma, especially due to its higher prevalence and its clinical manifestations. However, the patient also had another extra-axial lesion, measuring 1 cm, located in the left frontal parasagital region, which captured contrast homogeneously, raising the hypothesis of multiple meningiomas, although there was no dural tail. In addition, the metastasis hypothesis had not been ruled out; however, it was unlikely, since the primary cancer had been controlled for a long time, and the progression of current symptoms occurred quite insidiously. Perineural spread of carcinomas from the infratemporal or pterygopalatine fossae can also invade the cavernous sinus; nonetheless, we consider this type of tumor to be unlikely, since they are extremely rare, and fat obliteration has not been observed in these fossae.

Surgical treatment of the lesion was indicated, with an interdural approach to the Meckel cave. Intraoperatively, we were able to easily resect the entire lesion. In the postoperative period, the patient progressed well and was quickly discharged in good general condition.

In the one-month postoperative follow-up, the patient presented a significant improvement in hypoesthesia in the face, as well as an improvement in strabismus. However, she still persisted with diplopia when looking to the right. On the anatomopathological analysis of the lesion, a breast-cancer metastasiswas identified. Subsequently, the patient was referred to the oncologist, who performed an extensive investigation to search for other metastatic sites, and indicated a complementary treatment with radiotherapy. No other metastic sites were found.

Discussion

Neoplasms of the Meckel cave are extremely rare, and correspond to ~ 0.5% of all intracranial neoplasms.[1] Most lesions in this region are benign, with fifth-nerve schwannoma being the most common lesion by far. In addition, several other benign lesions, such as epidermoid cysts, lipomas, chondromas, among others, have also been described.[1,3] However, malignant neoplasms are not common.

Lesions to the Meckel cave may expand and injure the fifth-nerve ganglion or invade the posterior fossa and injure the fifth nerve in its cisternal portion. When the lesion affects the ganglion, the patients generally have facial pain; however, when there is nerve involvement alone, the complaint of facial pain is not usually important, and hypoesthesia is the most common symptom.[4] Further complaints of diplopia, paresis and

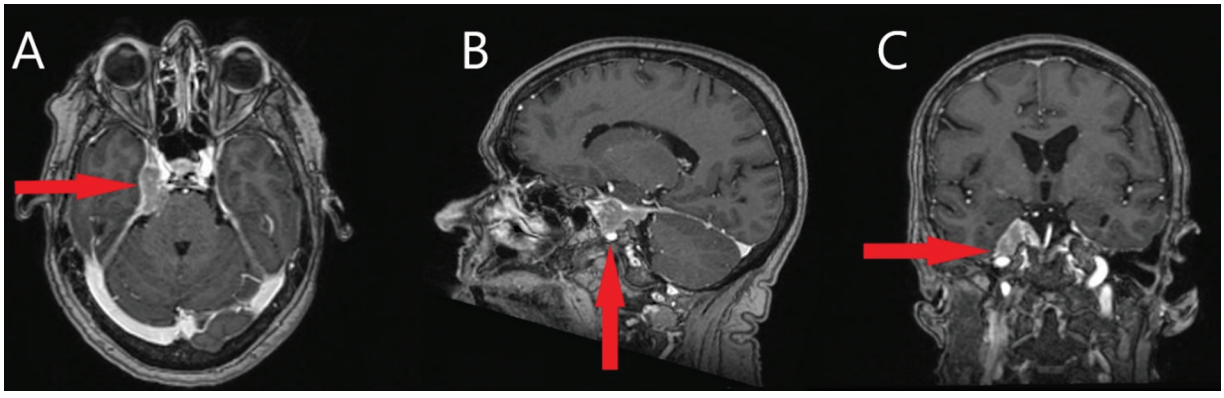

Fig. 1 T1-weighted magnetic resonance image; (**A**) axial, (**B**) sagittal, and (**C**) coronal views showing an expansive lesion in the trigeminal cistern on the right, extending to the tentorium, cavernous sinus, and inferiorly to the Gasser ganglion, with contrast enhancement.

atrophy of the chewing muscles and exophthalmos are also common, especially in benign tumors when there is an anterior extension of the tumor. There may still be facial paralysis, hearing loss, and absence of the corneal-eyelid reflex.

In the case herein reported, the patient had both a lesion in the cavity itself and in a cisternal portion, which ended up manifesting without a painful condition.

Soni et al[5] evaluated 21 cases of metastasis of the Meckel cave and compared them with the case series in the literature on schwannomas and meningiomas, and identified that patients with malignant tumors of the Meckel cave are more likely to develop pain, paraesthesia and motor deficit when compared with patients with schwannomas and cavity meningiomas. In addition, the average time until the development of metastasis is also an important differentiating factor. Soni et al.[5] identified an average of 15 months for the development of metastasis in the Meckel cave, while Delfini et al.[6] identified 33 months for meningiomas, and McCormick et al.,[7] 39 for fifth-nerve schwannomas. Our patient presented metastasis at $\sim$ 12 months, which was already a sign more compatible with metastasis of the Meckel cave. If it were a metastasis in almost any other location of the central nervous system, 12 months of presentation would speak more in favor of a benign neoplasm; however, in the Meckel cave, a duration with this average seems to be more characteristic of malignant neoplasms.

Conclusion

Our case illustrates a case of an elderly patient with a previous history of breast cancer already in remission, who had a single brain metastasis in the Meckel cave presenting as a schwannoma.

In the vast majority of cases, the first hypotheses of neoplasms in the Meckel cave are schwannoma and meningioma, especially if the patient has no history of previous neoplasia. However, although Meckel cave metastases are less likely, they should be considered, and further investigation of a primary site should be performed, especially in the case of older patients with a history of previous neoplasia and faster clinical presentation.

Conflict of Interests

The authors have no conflict of interests to declare.

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Hypotension and Bradycardia Following Papaverine Installation During Intracranial Aneurysm Surgery: A Report of Three Cases

Hipotensão e bradicardia devido à papaverina intracisternal quando instilada durante a cirurgia de aneurisma: Um relato de três casos

Zahraa F. Al-Sharshahi[1] Samer S. Hoz[1] Mustafa E. Almurayati[2] Teeba M. Ghanim[2] Zahraa M. Kareem[2] Zahraa A. Alsubaihawi[2]

[1] Department of Neurosurgery, Neurosurgery Teaching Hospital, Baghdad, Iraq
[2] College of Medicine, University of Baghdad, Baghdad, Iraq

Address for correspondence Zahraa F. Al-Sharshahi, MD, Department of Neurosurgery, Neurosurgery Teaching Hospital, Baghdad, Iraq (e-mail: zahraaalsharshahi@rcsi.com).

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Abstract

Introduction One of the major complications of intracranial aneurysm surgery is vasospasm. Papaverine is an effective vasodilator that can be instilled directly onto the vessels in the operative field with the aim of preventing intraoperative and postoperative vasospasm. Several case reports of hemodynamic instability in general and of hypotension, in particular, were reported after the use of topical papaverine during aneurysm clipping surgery.

Case description Herein, we report three cases of transient profound hypotension and relative bradycardia after intracisternal papaverine usage during ruptured anterior communicating artery aneurysm clipping surgery.

Conclusion Caution should be taken while using papaverine intracisternally during anterior circulation aneurysm clipping, since it may cause several serious complications, including profound hemodynamic instability, particularly when instilling on a fenestrated lamina terminalis.

Keywords
- intracisternal papaverine
- lamina terminalis
- aneurysm surgery
- hypotension

Resumo

Introdução Uma das principais complicações da cirurgia de aneurisma intracraniano é o vasoespasmo. A papaverina é um vasodilatador eficaz que pode ser instilado diretamente nos vasos do campo operatório com o objetivo de prevenir o vasoespasmo intra e pós-operatório. Vários relatos de casos de instabilidade hemodinâmica em geral e de hipotensão, em particular, foram relatados após o uso de papaverina tópica durante cirurgia de clipagem de aneurisma.

Descrição de caso Aqui, relatamos três casos de hipotensão profunda transitória e bradicardia relativa após o uso de papaverina intracisternal durante a cirurgia de clipagem de aneurisma da artéria comunicante anterior rompida.

Palavras-chave
- papaverina intracisternal
- lâmina terminal
- cirurgia de aneurisma
- hipotensão

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Conclusão Deve-se ter cuidado ao usar papaverina intracisternamente durante a clipagem do aneurisma da circulação anterior, uma vez que pode causar várias complicações graves, incluindo profunda instabilidade hemodinâmica, particularmente ao instilar em uma lâmina terminal fenestrada.

Introduction

Vasospasm is one of the major complications of intracranial aneurysm surgery. Papaverine is an effective vasodilator that can be instilled directly on the vessels in the operative field with the aim of preventing both intraoperative and postoperative vasospasm.[1] However, intracisternal papaverine has several reported side effects, including its effects on blood pressure and heart rate. Hemodynamic instability in general and hypotension, in particular, were reported after the use of topical papaverine in aneurysm clipping surgery.[2–4] In the present case report, we report three cases of transient profound hypotension and relative bradycardia after intracisternal papaverine usage during ruptured anterior communicating artery aneurysm clipping surgery. All cases were operated on by the same surgeon and were conducted under cortical somatosensory evoked potentials (SSEPs) and EEG monitoring intraoperatively.

Case One

A 50-year-old female with no history of hypertension presented to the emergency department with a sudden-onset, severe headache with repeated vomiting of 5-hour duration, after attending a party with friends. The patient was diagnosed with subarachnoid hemorrhage (SAH) secondary to a ruptured anterior communicating artery aneurysm, Hunt and Hess (H&H) grade 1 and World Federation of Neurosurgical Societies (WFNS) grade 1. The CT scan also showed ventricular dilatation and small intraventricular hemorrhage. She underwent surgical clipping of the aneurysm on the next morning. She was anesthetized using total intravenous anesthetics (injection fentanyl and propofol infusions). Opening of the Sylvian fissure followed by preparation of the ipsilateral (dominant) A1 for possible temporary clipping was performed, followed by dissection of the aneurysm neck and permanent clip application. There was no intraoperative rupture, and temporary clipping was not used. Both the lamina terminalis and the Liliequist membrane were fenestrated to prevent postoperative hydrocephalus, which is part of our routine technique for aneurysm cases with IVH. Then, 4 ccs of 3% papaverine were instilled intracisternally over the dissected vessels to prevent vasospasm. Twenty minutes after papaverine instillation, the anesthetist reported a decrease in blood pressure (BP) from 115/70 to 85/50 along with a decrease in pulse rate (PR) from 121 to 65. All possible surgical and anesthetic causes were excluded, and 1 L of normal saline was given rapidly, but the vitals were resistant to fluid resuscitation. The brain was relaxed and closure was done. After extubation, the patient was admitted to the neurology intensive care unit (ICU) and she was conscious, obeying commands, and without neurological deficits but the BP and PR were at 85/55 and 68, respectively. The patient was kept under close observation with no added treatment until the vitals normalized 8 hours after the incident. The patient was discharged from hospital after 5 days and she was doing well on subsequent follow-up visits.

Case Two

A 62-year-old female with no history of hypertension presented to the emergency department with severe headache and neck pain along with drowsiness and repeated vomiting over the past 24 hours. A brain computed tomography (CT) scan revealed SAH involving the basal supratentorial cisterns, gyrus rectus hemorrhage, and IVH in the right lateral ventricle and in the third ventricle. A CT angiography showed an 11-mm aneurysm located in the anterior communicating artery. Hunt and Hiss grade 2, WFNS grade 2. Surgical clipping was conducted on the same day. Anesthesia was conducted using the routine protocol. A right pterional craniotomy was done followed by clipping of the aneurysm. Temporary clipping was not used and both the lamina terminalis and the Liliequist membrane were fenestrated. To minimize the possibility of postoperative vasospasm, 4 ccs of 3% papaverine were instilled intracisternally. A few minutes after papaverine instillation, the patient presented with sudden hypotension and bradycardia (BP: from 125/75 to 80/45; and PR: from 110 to 52). All possible surgical and anesthetic causes were excluded and boluses of IV fluids were used, but the vitals were resistant. Inotropes were then employed to control the BP. The rest of the surgery went uneventful. An urgent postoperative brain CT showed no hematoma or hydrocephalus. Postoperatively, the patient was alert, neurologically intact, but she was kept on inotropes boluses in the ICU. Four days after the incident, the vitals were back to normal levels; the patient continued to improve and started to walk normally without any deficit. The patient was discharged home 6 days later and she resumed her normal daily activities.

Case Three

A 39-year-old man presented to the emergency department with an altered level of consciousness, neck stiffness, recurrent bouts of vomiting of 2-day duration. A CT scan of the brain revealed a ruptured anterior communicating artery aneurysm with early hydrocephalus. The SAH was Hunt and Hiss grade 2 and WFNS grade 1. The patient underwent an urgent aneurysm clipping surgery. Anesthesia was conducted using the routine protocol. Right pterional craniotomy was pursued, and the anterior communicating artery

aneurysm was clipped through the trans-Sylvian approach. There was no intraoperative rupture and temporary clipping was not used. Both the lamina terminalis and the Liliequist membrane were fenestrated to release the cerebrospinal fluid from the ventricles and to prevent postoperative hydrocephalus. The surgical field was irrigated by 4 cc of 3% papaverine solution. A few minutes after papaverine instillation, both the BP and PR suddenly dropped; the BP decreased from 130/80 to 80/50 mm Hg, and the PR dropped from 110 to 70 BPM. The possible surgical and anesthetic causes were urgently excluded; however, the patient remained hypotensive with relative bradycardia. Resuscitation with IV saline failed to improve the BP and the PR. We performed the closure rapidly and the patient was sent for an urgent CT scan of the brain and then to the neurology ICU. The brain CT was negative for any hematoma or new findings. The patient remained hypotensive in the ICU, but he was extubated and fully conscious without any neurological deficits. He was kept on IV saline boluses with normal arterial blood gases. Two days postoperatively, the vitals started to improve and then normalized over the next hours. The patient was discharged 9 days later and was stable both neurologically and vitally. The patient achieved a full recovery on subsequent follow-up visits.

Discussion

The use of intracisternal papaverine during anterior communicating artery aneurysm surgery can result in transient hypotension with relative bradycardia, and this effect is amplified if papaverine is instilled after the fenestration of the lamina terminalis.

It is a common practice to use papaverine intracisternally during surgical clipping of intracranial aneurysm with the aim of preventing the possible vasospasm and its disastrous consequences[5,6]

Papaverine is a benzylisoquinoline alkaloid that acts as a potent vasodilator.[7] It inhibits smooth muscle phosphodiesterases (cyclic adenosine monophosphate and cyclic guanosine monophosphate) and inhibits calcium channels, hence causing relaxation of smooth muscle and vasodilation.[8]

Several complications related to intracisternal papaverine instillation have been reported in the literature, including cranial nerve palsies,[9–12] malignant hyperthermia with metabolic acidosis,[13] bradycardia with hypotension,[4,14] tachycardia with hypertension,[15] thrombocytopenia,[16] intracranial pressure changes,[17] transient brainstem depression,[18] and even cardiac arrest.[19]

Although the precise mechanism by which papaverine exerts its circulatory effects is not understood, some reports have suggested that the local vasodilatory effect of papaverine on the hypothalamus or on the brainstem could possibly explain some of these circulatory changes.[4,14,15] Sinha et al. stated that the involvement of the hypothalamus can have several effects on the circulatory system, ranging from hypertension with tachycardia to hypotension with bradycardia[20]; the authors justified this explanation in reference to the fact that the preoptic area of the hypothalamus is responsible for the reduction in the BP and in the PR, while the posterior and lateral hypothalamic areas have the opposite function. The role of the pontine and medullary reticular formation was also suggested by some reports as a possible mechanism for the hemodynamic changes after intracisternal papaverine application.[14] Papaverine can reach the hypothalamus and the brainstem via the basal cisterns and may affect these structures by direct contact; however, this would result in fewer effects, as it would not be in direct contact with the critical internal structures. Based on our experience, papaverine can reach the third ventricle more easily when it is instilled after the fenestration of the lamina terminalis. Thus, a higher dose of less-diluted papaverine can reach the hypothalamus and the brain stem through the fenestrated lamina terminalis and cause a profound effect on the vital centers in the ventricular walls; based on this observation, we changed our intraoperative practice. Therefore, we recommend that papaverine should be instilled on the dissected vessels 10 minutes prior to the opening of the lamina terminalis and to use more diluted papaverine intraoperatively to avoid these complications. Currently, there exists no recommended safe and effective regimen of intracisternal papaverine in intracranial aneurysm surgery. At our institution, 2 cc of 3% papaverine (60 mg) diluted in between 10 and 20 ml of warm 0.9% normal saline or Ringer lactate at room temperature (35–37°C) is the dosing used. The surgical field can then be irrigated and, if required, the lamina terminalis can be fenestrated 10 minutes later, although alternative regimens have been suggested by some reports.[14,15]

Conclusion

Caution should be taken while using papaverine intracisternally during anterior circulation aneurysm clipping, since it may cause some serious complications including profound hemodynamic instability, particularly when instilled on a fenestrated lamina terminalis.

Contributions of the Authors

Hoz S. S.: Case identification, manuscript drafting, literature review

Al-Sharshahi Z. F.: Manuscript review, revision of the original draft

Almurayati M. E.: Revision of the original draft

Ghanim T. M.: Revision of the original draft

Kareem Z. M.: Revision of the original draft

Alsubaihawi Z. A.: Revision of the original draft

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Cobb Syndrome Associated with Spinal Cavernoma – Case Report

Síndrome de Cobb associada a cavernoma medular – Relato de caso

Paulo Moacir Mesquita Filho[1,2] Luan Lucena[1] Leticia Bassani Devens[2] Luana Rossato Dias[2]
Bruno Missio Gregol[2] Nério Dutra Azambuja Jr[1]

[1] Neurosurgery Department, Hospital de Clínicas de Passo Fundo, Passo Fundo, RS, Brazil
[2] Liga Acadêmica do Serviço de Neurologia e Neurocirurgia, Passo Fundo, RS, Brazil

Address for correspondence Luana Dias, Medicine Student, Hospital de Clinicas de Passo Fundo, Passo Fundo, RS, Brazil (e-mail: luana_rossato@hotmail.com).

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Abstract

Cobb syndrome, or cutaneomeningospinal angiomatosis, is a rare condition that affects young adults, and its etiology has not been completely elucidated. It is characterized by a cutaneous sign, or stigma, associated with spinal or intracranial malformations. The symptoms are quite diverse, but, in most cases, the disease presents motor deficit and pain. The present study reports the case of a 48-year-old female patient, who initially sought dermatological medical care for a single skin lesion in the posterior cervical region. During the excision, it was noticed that the lesion had contiguous behavior to the deep anatomical planes, thus requiring the evaluation of the neurosurgical team. The purpose of this report is to describe this rare disease, covering more details about diagnosis and therapy.

Keywords
- arteriovenous malformation
- nevus
- angiomatosis
- Cobb syndrome

Resumo

Síndrome de Cobb, ou angiomatose cutâneo-meningo-espinhal, é uma condição rara que afeta adultos jovens, e sua etiologia não foi completamente elucidada. Caracteriza-se por um sinal cutâneo, ou estigma, associado a malformações espinhais ou intracranianas. Os sintomas são bastante diversos, mas, na maioria dos casos, a doença apresenta déficit motor e dor. O presente estudo relata o caso de uma paciente do sexo feminino de 48 anos, que inicialmente procurou atendimento médico dermatológico para uma única lesão cutânea na região cervical posterior. Durante a excisão, notou-se que a lesão apresentava comportamento contíguo aos planos anatômicos profundos, exigindo assim a avaliação da equipe neurocirúrgica. O objetivo deste relatório é descrever essa doença rara, abrangendo mais detalhes sobre diagnóstico e terapia.

Palavras-chave
- malformação arteriovenosa
- nevo
- angiomatose
- Síndrome de Cobb

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Introduction

Cutaneomeningospinal angiomatosis, a rare pathology that occurs in the spine, is characterized by the association of a vascular malformation affecting the skin, bone, and spinal cord, and it can also reach nerve roots in the same metamer.[1] This syndrome was first described in 1895 and was characterized by Stanley Cobb in 1915,[1] which is why it is also called Cobb syndrome (CS).

To date, only a few cases have been reported, with less than 50 cases in the English language, a series of 61 cases in China, and only one report in South America, all of which report one skin lesion associated with an arteriovenous malformation (AVM) involving the spinal cord.[2] The present study concerns a report of CS associated with a spinal cavernoma. This is the first case reported in Brazil, and no similar cases have been found until the date of this study.

Case Report

A 48-year-old female patient sought dermatological medical attention for the excision of a lesion in the posterior cervical region, which caused sporadic mild pain. During the procedure, the professional noticed that the lesion had visceral contiguity in depth, and requested additional tests for investigation, referring the patient for neurosurgical evaluation.

On physical examination, the lesion accompanied the C1 metamer, causing a bulging in the posterior cervical region (►**Fig 1**). The patient also had monoparesis (grade 4 +/5) in the left upper limb and diffuse hyperreflexia in the same limb. There were no structural changes, flaccidity, or tone abnormalities and no other health issues.

The magnetic resonance imaging (MRI) evidenced an association of the superficial lesion with adjacent tissues, up to the vertebra at the same level (C1), in addition to a vascular lesion, compatible with cavernoma (►**Fig 2**). This association confirmed the criteria for CS. A spinal digital angiography was also performed, and revealed the absence of contrast uptake, corroborating the diagnosis of cavernoma.

The patient was then submitted to neurosurgical treatment, with intraoperative neuromonitoring, and microsurgical technique (►**Fig 3**). Surgical access was performed through a 2-level laminectomy (C1 and C2) to expose the lesion, with subsequent opening of the dura mater and direct visualization of the lesion. The lesion was completely resected, and the patient evolved with improvement in the previous neurological deficit.

Discussion

Currently, the diagnostic criteria accepted for CS, proposed by Kissel and Dureux, are based on the presence of a skin nevus, in the same segment (dermatome/metamer) as the spinal vascular malformation, including or not visceral angioma. The diagnosis can be confirmed by magnetic resonance imaging.[1]

The incidence of this disease is unknown.[1,3] It is known that CS is a disease that affects mostly children and young adults,[3] and it is believed that there is a higher incidence in men.[2] The pathophysiology and vascular subtype of spinal angiomas are still poorly defined. The relationship of familiar genetic factors is not clear, although one study suggested an inherited disposition, when presenting an embryonic connection with ectodermal structures.[4] Although the mechanisms that lead to symptomatic manifestation are unknown, it is believed that the neurological deficit present in CS is a consequence of ischemia, secondary to diversion of the blood flow to the vascular injury, or to mechanical compression of the spinal cord.[2]

The clinical presentation is diverse, ranging from progressive evolution to sudden symptoms. Motor deficit (such as paraplegia), pain, fever, and signs of meningeal irritation may be present.[1] Motor disorders correspond to the earliest and most frequent symptoms.[1,3] The neurological physical examination does not present a characteristic finding, but bilateral patellar and Babinski sign have been described bilaterally.[5] However, there is no specific and determining sign or symptom for the characterization of CS.[5]

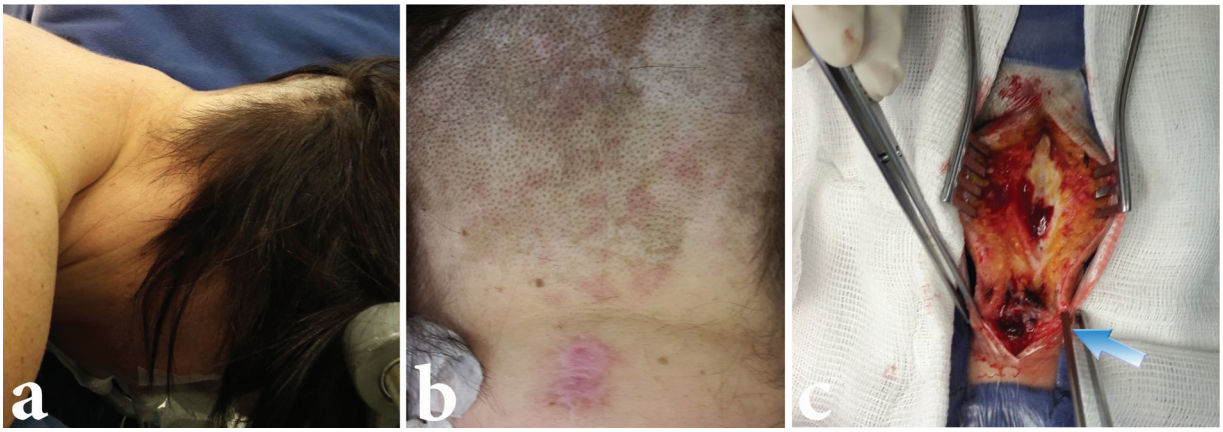

Fig. 1 (**a**) Bulking in the posterior cervical region evidenced after prone positioning of the patient. (**b**) Cutaneous nevus at the skin covering the suboccipital region and upper cervical region, in the C2 dermatome. Below, a scar from previous biopsy. (**c**) Subcutaneous exposure after surgical incision, evidencing contiguity of the lesion, extending from the superficial to deep planes (blue arrow).

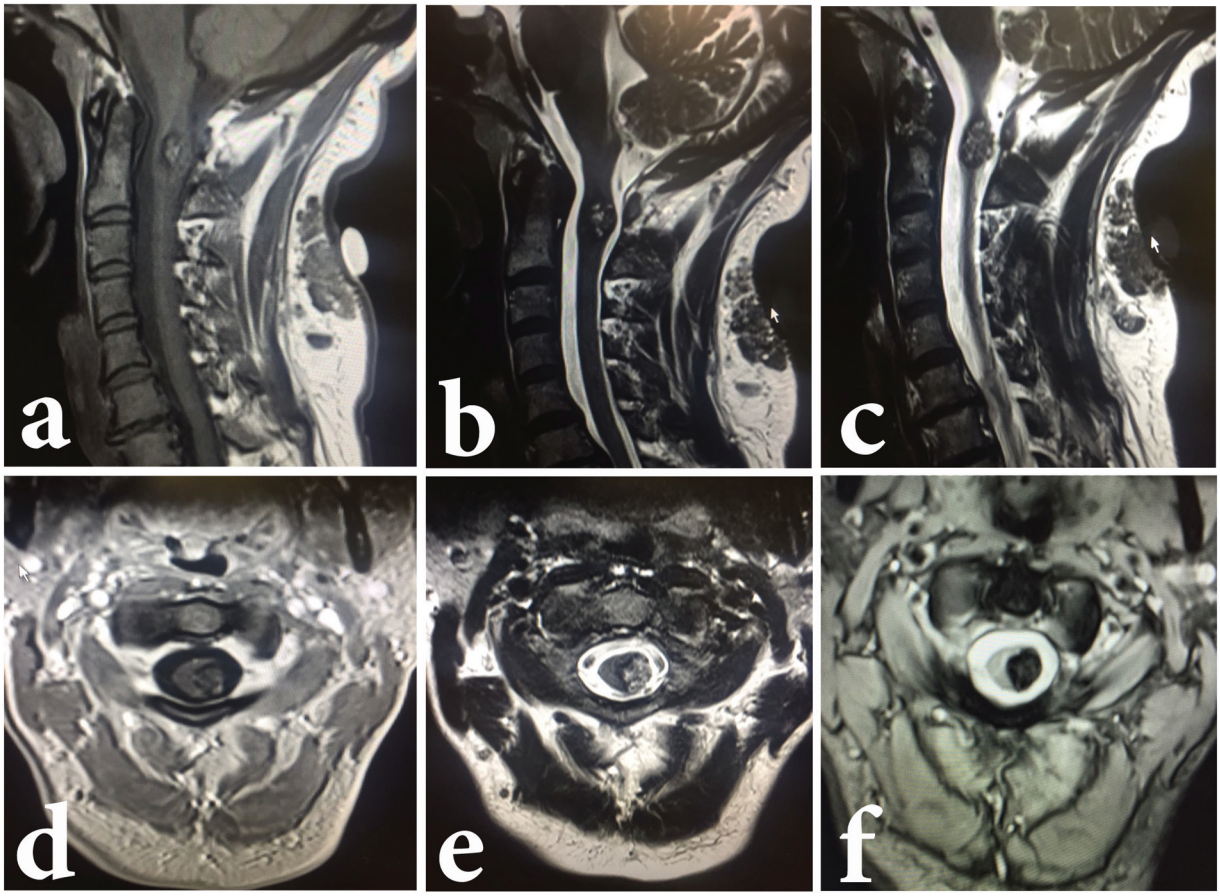

Fig. 2 (**a**) Sagittal T1-weighted magnetic resonance imaging (MRI) of the cervical spine, evidencing a hyperintense lesion, with a hypointense halo at the C1-C2 level. (**b, c**) Sagittal T2-weighted MRI of the cervical spine, evidencing the typical blueberry aspect of cavernomas, with a mixture of hyperintense and hypointense signals at the C1-C2 level. (**d**) Axial T1-weighted MRI of the cervical spine, showing the right lateral aspect of the lesion in relation to the cervical spine. (**e**) Axial T2-weighted MRI of the cervical spine, highlighting the cleavage plane between the lesion and the cervical spine, and the irregular signal. (**f**) Axial T2*-weighted MRI of the cervical spine, evidencing the vascular pattern (hyposignal) of the lesion.

The differential diagnosis should include diseases that present with cutaneous sign and spinal or intracranial malformations, such as Klippel-Trenaunay-Weber syndrome, Sturge-Weber syndrome, Wyburn-Mason syndrome, and Osler-Rendu-Weber syndrome.[4]

There is no consensus regarding a current treatment modality, since the syndrome remains obscure from the genetic point of view, natural history, and even specific diagnostic criteria. The application of the classification of AVMs is made in order to guide the treatment, since the majority of the reports described have been made with spinal AVMs, and not with cavernomas, as in the present case.[3]

In the case presently described, microsurgical treatment was proposed for excision of the spinal cord injury, with intraoperative neuromonitoring. The aim was to remove the mass effect causing spinal compression, and, also, prophylaxis of bleeding, minimizing neurological damage. The treatment modalities described by the literature review include the combination of embolization, neurosurgical intervention, use of corticosteroids, and radiotherapy.[1] It is not possible to infer which treatment leads to the highest clinical improvement, minimizing neurological sequelae, a fact that highlights the importance and the need for further studies about this entity.[1] The report published by Linfante et al.[6] suggest that endovascular therapy, through embolization, can be performed as a preoperative treatment, and possibly as a definitive treatment. In the present case, because the vascular lesion was configured as a cavernoma, endovascular treatment could not be applied.

The present report aims to highlight that CS is remotely suspected; however, it should be kept in mind when patients present with violet skin lesions in the spinal topography. Screening should be encouraged to avoid major surgical complications or neurological sequelae.[3]

Conclusion

Although it is rare, in patients with signs and symptoms of spinal compression, associated with vascular lesions in the skin in the same segment of the motor deficit, CS should be considered as a diagnostic hypothesis for early diagnosis and appropriate treatment.

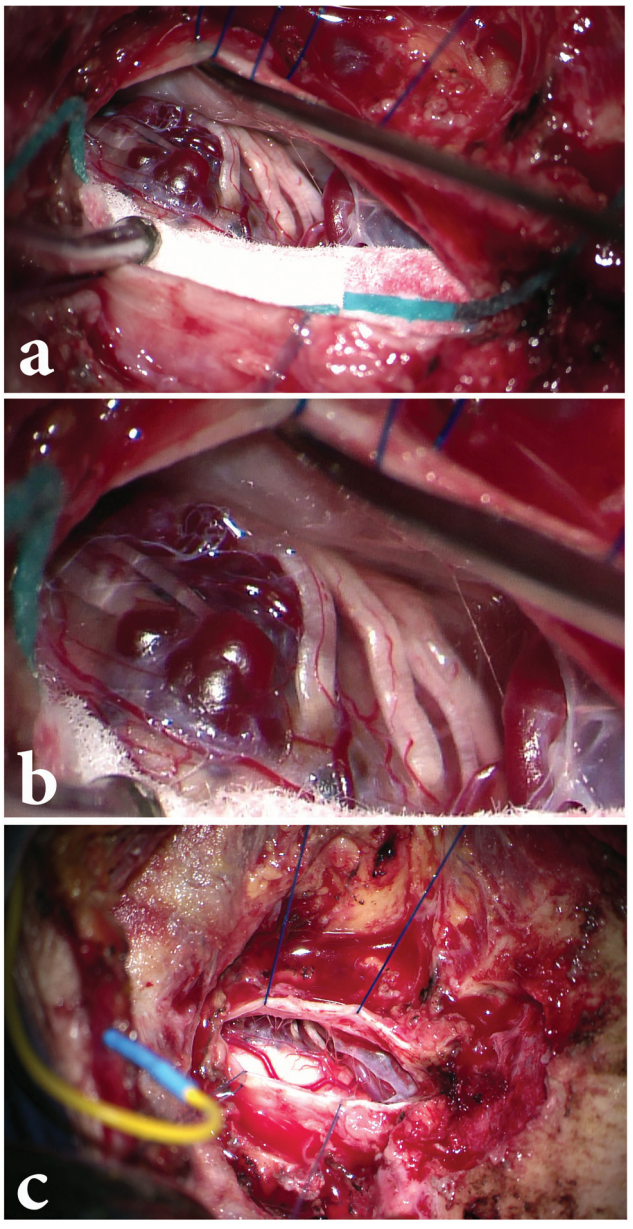

Fig. 3 (**a**) Intraoperative image. Initial exposure, with the cavernoma appearing in the lateral aspect of the cervical spine, in close contact with the C2 roots, on the right side. (**b**) Intraoperative image. After initial dissection, the lesion became more apparent, and the comprised nerve roots, superficial and deep, are highlighted. (**c**) Intraoperative final image. Complete excision of the lesion with preservation of the nerve roots and arterial supply of the cervical spine.

Conflict of Interests

The authors have no conflict of interests to declare.

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Macroprolactinoma in a 14-Year-Old Girl in the Northeast of Iran: A Case Report

Macroprolactinoma em uma garota de 14 anos no nordeste do Irã: Relato de caso

Habibe Sadat Shakeri[1] Samaneh Mollazadeh[1] Alireza Monemi[1]

[1] North Khorasan University of Medical Sciences, Bojnurd, Iran

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Address for correspondence Samaneh Mollazadeh, PhD, North Khorasan University of Medical Sciences, Bojnurd, Iran (e-mail: samanehmollazadeh@yahoo.com).

Abstract

Prolactinoma is frequently found not only in females but also in males with abnormal reproductive and/or sexual function. Patients typically complain about amenorrhea and infertility because of anovulation. Approximately 15% to 20% of cases of secondary amenorrhea are caused by prolactinemia. Galactorrhea may occur simultaneously, before or after menstrual disorders, and sometimes it may not be clinically obvious, or only detected by breast examination. We reported a case of a 14-year-old girl who presented primary amenorrhea accompanied by frequent headaches and blurred vision. Hormonal tests showed severe hyperprolactinemia (prolactin [PRL] concentration: 1,570 ng/ml). Further tests confirmed a mass in the pituitary with an extension to the left parasellar and suprasellar regions. Some parts of the sella turcica tumor were removed by transcranial surgery. During the follow-up, the clinicopathological examinations revealed the patient had hyperprolactinemia. Clinicians should be aware of the diagnostic and therapeutic problems regarding the management of hyperprolactinemia.

Keywords
- macroadenoma
- prolactinoma
- pituitary
- amenorrhea
- sella turcica

Resumo

O prolactinoma é frequentemente encontrado não apenas em mulheres, mas também em homens com funç ão reprodutiva e/ou sexual anormal. Os pacientes geralmente se queixam de amenorreia e infertilidade devido à anovulaç ão. Aproximadamente 15% a 20% dos casos de amenorreia secundária são causados por prolactinoma. A galactorreia pode ocorrer simultaneamente, antes ou depois dos distúrbios menstruais, e às vezes pode não ser clinicamente óbvia ou ser detectada apenas pelo exame das mamas. Relatamos o caso de uma menina de 14 anos que apresentou amenorreia primária acompanhada de dores de cabeça frequentes e visão turva. Os testes hormonais mostraram hiperprolactinemia grave (concentraç ão de prolactina [PRL]: 1.570 ng/ml).Outros exames confirmaram uma massa na hipófise com extensão para as regiões parasselar e suprasselar esquerda. Algumas partes do tumor da sela turca foram removidas por cirurgia transcraniana. Durante o acompanhamento, os exames clinicopatológicos revelaram que o paciente apresentava hiperprolactinemia. Os médicos devem estar cientes dos problemas diagnósticos e terapêuticos relativos ao manejo da hiperprolactinemia.

Palavras-chave
- macroadenoma
- prolactinoma
- hipófise
- amenorreia
- sela turca

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Introduction

Pituitary adenomas are the most common type of tumors of the sella turcica region. Prolactinoma is the most common type of pituitary adenoma, leading to the hyper-/hyposecretion of hormonal syndromes and second amenorrhea.[1] Among the cases of prolactinoma, microprolactinoma and macroprolactinoma are common in female and males respectively.[2] Beyond the reason of prolactinoma, all the patients have similar clinical manifestations. Compared with male patients, who complain about erectile dysfunction, female patients complain about irregular menstrual cycles and infertility. Prolactin (PRL) secretion may be altered by different factors, such as physiological and pathological conditions, and the use of certain drugs.[3] However, the upper threshold for serum PRL in women is 25 ng/ml. The clinical manifestation of amenorrhea-galactorrhea syndrome is influenced by the concentrations of serum PRL. In the classic forms of hyperprolactinemia, the concentrations of serum PRL are $>$ 100 ng/ml.[4] In the current study, we report the case of a girl with prolactinoma who had not been correctly diagnosed in the past to focus more on the clinical manifestations and efficient diagnostic methods.

Case Report

A 14-year-old girl was referred to the endocrinologist at North Khorasan University of Medical Sciences with primary amenorrhea. She also had a positive history of chronic headaches and blurred vision that had started three years before, which was suspected to be related to sinusitis. Physical examinations based on Tanner staging showed the breast and pubic hair area in the second stage without any progress during the three years until she was referred to our institution. Preoperative examinations using a radioimmunoassay and electrochemiluminescence revealed that the levels of serum PRLn and cortisol were of 1,570 ng/ml and 23 Iu/ml respectively. Moreover, the other pituitary and thyroid hormones such as the thyroid-stimulating hormone (TSH), free T4, cortisol and insulin-like growth factor type 1 (IGF-1) were within normal limits. Computed tomography (CT) scans of the pituitary cavity revealed a mass (measuring 32 cm x 24 cm) with an extension to the left parasellar and suprasellar regions. Additionally, magnetic resonance imaging (MRI) scans of the region of the sella turcica revealed the same mass with suprasellar extension and pressure on the cavernous sinus (►**Figure 1**). Basedon these findings, the patient was diagnosed with prolactinoma. A perimetric examination also showed an external visual disorder in the left eye. Although the medical treatment with dopamine agonists is widely established as the first line of treatment for hyperprolactinemia, our case was submitted to the transcranial surgery because of her personal tendency as well as the high size of the tumor. Nevertheless, the mass was not completely eliminated. A pathological examination showed neoplastic tissue involving proliferative and hyperchromic cells, which were a pituitary adenoma with positive CK and synaptophysin, as well as negative GFAP, LCA, EMA, CD99, and S100. Regarding the reduction in the levels of other pituitary hormones after the surgery, the patient was followed up to assess her pituitary function. Postoperative examinations revealed thyroidism, hypogonadism, and a reduction in serum cortisol. Although the concentrations of serum prolactin had a declining trend after the surgery, they were still high enough to show that the tumor mass had not been completely removed. Consequently, 25 radiotherapy sessions were scheduled to completely eliminate the tumor tissue. Currently, the patient is still taking medications regularly and attending check-ups.

Discussion

Prolactinoma is one of the several tumors that can be observed in the pituitary gland, and it can be treated by regular drug therapy.[5] Moreover, the patients may not have any clear clinical manifestations until the progression of the tumor to the local tissues. In such stages, pressure of the tumor on the

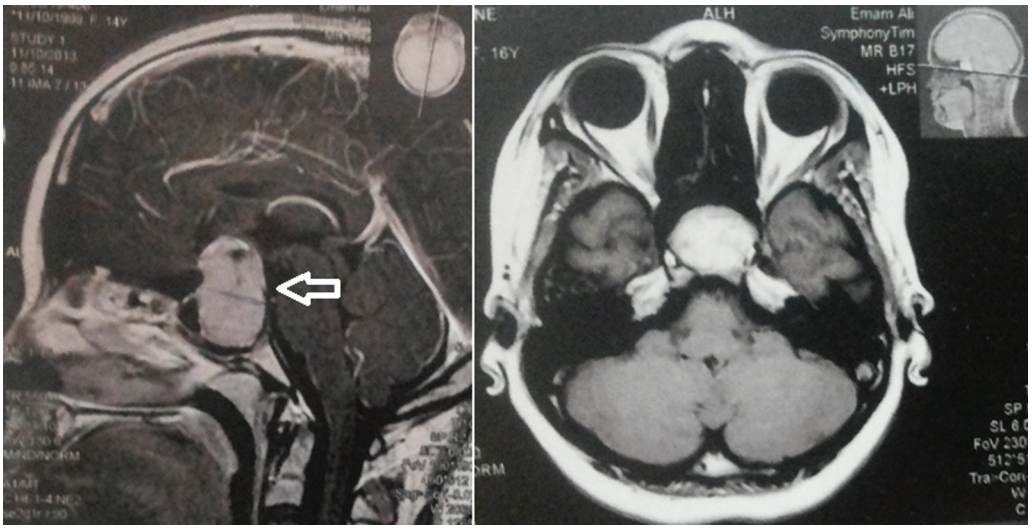

Fig. 1 Magnetic resonance imaging (MRI) scan showing a giant adenoma (white arrow).

local tissues results in chronic headaches, visual impairment, and hypothyroidism.[6] In the current report, we observed primary amenorrhea, blurred vision, and chronic headaches. Nevertheless, clinicians should be aware of the diagnostic errors in the case of high concentrations of PRL, called "high dose hook effect." In this condition, very high concentrations of PRL can lead to abnormal results by saturating all of the immunoglobulin used in the assay.[7]

Fertility and the function of the gonads are reversible in most of the patients with the use of dopamine agonists, bromocriptine, and cabergoline. However, transsphenoidal surgery is required for the cases with blurred vision, neurologic issues, and low drug tolerance. Moreover, if the transsphenoidal surgery is not possible due to the size of the tumor, transcranial surgery should be performed to eliminate the bulk of the tumor. Radiotherapy is also the best treatment option in the case of patients unresponsive to the drug treatment or when complete tumor resection is impossible.[8]

In conclusion, the prepubertal diagnosis of prolactinoma is really important in the cases with delayed puberty. Although in the current case puberty started on time, we haven't observed a normal progress of it in referring time. Therefore, the primary assessment of amenorrhea is required in the cases without secondary sexual features, such as thelarche and adrenarche, to avoid more complications.

Authorship

Habibe Sadat Shakeri and Alireza Monemi participated in the conception, design, and interpretation of data; Samaneh Mollazadeh drafted the manuscript; the final version of the manuscript was approved by all authors.

Ethical Approval

All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate

Informed consent was obtained from the patient included in the study.

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Conflict of Interests

The authors have no conflict of interests to declare.

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Marginal Zone B-cell Lymphoma of the Gasserian Ganglion: Case Report and Review of the Literature

Linfoma de células B da zona marginal do gânglio de Gasser: Relato de caso e revisão da literatura

Ahmed Hegazy[1] Hieder Al-Shami[2] Biswas Arundhatai[3] Mohammed Fathy[1] Ahmed M. Salah[1] Hashem Aboul-Ela[1] Mohamed F.M. Alsawy[1] Amr Mostafa Elkatatny[1]

[1] Department of Neurosurgery, Faculty of Medicine, Kasr Al-Ainy Medical College, Cairo, Egypt
[2] Department of Neurosurgery, Faculty of Medicine, Al-Azhar University, Cairo, Egypt
[3] Department of Neurological Surgery, Albert Einstein College of Medicine of Yeshiva University/Montefiore Medical Center, Bronx, New York, United States

Address for correspondence Hieder Al-Shami, MD, Neurosurgery, Al-Ahly Bank Hospital, Cairo, Egypt (e-mail: Adamhouse73@gmail.com).

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Abstract

Primary central nervous system lymphoma (PCNSL) is a rare subtype of extranodal non-Hodgkin's lymphoma that accounts for 4% of newly diagnosed central nervous system (CNS) tumors. Most primary lymphomas of the central nervous system are of the subtype of diffuse large B-cell lymphomas, which have highly aggressive behavior and may involve the brain, leptomeninges, eyes or spinal cord without evidence of systemic disease. Primary CNS lymphomas are very rare in immunocompetent patients, but their rates are increasing. So far, only 11 primary Gasser ganglion lymphomas have been reported, with an incidence of 2.5 cases per 30,000,000 inhabitants. However, B cell lymphomas of the marginal zone of the Gasserian ganglion have been very rarely reported. We report here a clinical presentation characteristic of B cell lymphoma of the marginal zone of the Gasser ganglion in an immunocompetent patient who was treated with surgery and radiotherapy, evolving with improvement of symptoms and without recurrence in 3 months of follow-up.

Keywords
- facial pain
- primary lymphoma of the central nervous system
- trigeminal neuropathy

Resumo

O linfoma primário do sistema nervoso central (PCNSL, na sigla em inglês) é um subtipo raro de linfoma não-Hodgkin extranodal que representa 4% dos tumores recém-diagnosticados do sistema nervoso central (SNC). A maioria dos linfomas primários do sistema nervoso central é do subtipo dos linfomas difusos de grandes células B, que tem comportamento altamente agressivo e pode envolver cérebro, as leptomeninges, os olhos ou a medula espinhal sem evidências de doença sistêmica. Os linfomas primários do SNC são muito raros em pacientes imunocompetentes, mas suas taxas estão aumentando. Até o momento, apenas 11 linfomas primários do gânglio de

Palavras-chave
- dor facial
- linfoma primário do sistema nervoso central
- neuropatia trigeminal

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Gasser foram relatados, com uma incidência de 2,5 casos por 30.000.000 de habitantes. No entanto, linfomas de células B da zona marginal do gânglio de Gasserian foram muito raramente relatados. Relatamos aqui uma apresentação clínica característica de um linfoma de células B da zona marginal do gânglio de Gasser em um paciente imunocompetente que foi tratado com cirurgia e radioterapia, evoluindo com melhora dos sintomas e sem recorrência em três meses de acompanhamento.

Case Report

A 29-year-old previously healthy male presented with lancinating left facial pain and paresthesia. The pain involved all divisions of the trigeminal nerve and was worse in the mandibular division. He received a daily dose of 1,200 mg of carbamazepine without improvement. The patient was then seen by a dentist and underwent repeated molar extractions; however, his facial pain became worse. He also suffered from severe symptomatic diplopia, which was evident on lateral gaze to the left. Clinical examination revealed an intact corneal reflex with abducent nerve palsy on the left side. There was hypoesthesia to all sensory modalities, involving the maxillary and mandibular divisions; however, there were no trigger points. There was no evidence of weakness of the muscles of mastication on the left side, but the examination showed atrophy of the temporalis muscle.

Brain magnetic resonance imaging (MRI) revealed a globular lesion straddling the posterior and middle fossae, which caused uniform enlargement of the trigeminal nerve from its root at the prepontine cistern unitl the gasserian ganglion at the Meckel cave on the left side, and extending to the left cavernous sinus without encasement of the carotid artery (►**Fig. 1**). It measured $3 \times 1.8 \times 2.8$ cm, showing intermediate T1 and T2 signal intensity, and intense enhancement with gadolinium without a dural tail. The preoperative diagnostic hypothesis was schwannoma, based on the site and imaging characteristics. Routine laboratory investigations were within normal values.

Operative Procedure and Findings

The patient was operated by an anterior petrosal approach. The approach was performed through a frontotemporal osteomuscular craniotomy. The details of anesthesia, positioning and craniotomy, drilling of the apex of the petrous bone, dural opening, and division of the tentorium have been described elsewhere.[1] The tumor was evident after exposure of the gasserian ganglion. However, the posterior fossa part of the tumor was only seen after opening of the dura and division of the tentorium. At this point, the whole trigeminal nerve was evident from the root entry zone and all the way until the division of the gasserian ganglion.

The tumor was greyish-brown in color, quite firm in consistency, and adhesive. It was arising within the plexiform part of the Gasserian ganglion. It was dissected using sharp dissection from within the Gasserian ganglion and, with difficulty, a plane of dissection could be established from the medial aspect of the ganglion. At this point, the sixth nerve became visible and was preserved. We found that the tumor did not encircle the carotid artery. It was completely resected along with the trigeminal nerve root due to its complete infiltration by the tumor. Hemostasis was achieved and the wound was closed in layers.

Postoperatively, the patient was in an excellent condition. The wound was clean and without cerebrospinal fluid (CSF) collection. The sixth cranial nerve started to regain function and the diplopia improved considerably, but did not go back to normal. The trigeminal pain disappeared completely, and the patient stopped taking carbamazepine. However, there was a persistent hypoesthesia involving all division of the trigeminal nerve on the left side, but it was not incapacitating. A follow-up brain MRI with contrast revealed complete excision of the tumor.

Histopathological examination of the excised tumor by light microscopy after hematoxylin and eosin (H&E) staining revealed mildly fibrotic tissue showing moderate lymphoplasmacytic infiltrate with moderate lymphoid hyperplasia.

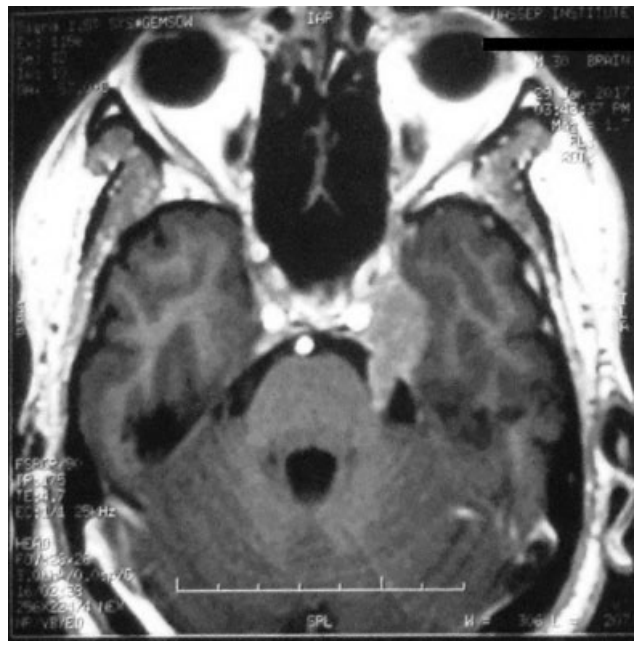

Fig. 1 After discussing the advantages and disadvantages of the available treatment options with the patient, surgery was decided. The other possible treatment was stereotactic radiosurgery (SRS) with serial imaging follow-up.

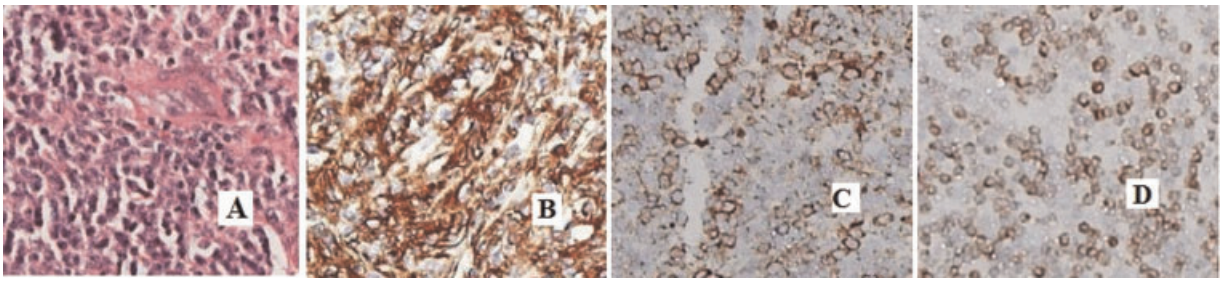

Fig. 2 (A) Histopathology by light microscopy after hematoxylin and eosin (H&E) staining showing moderate lymphoplasmacytic infiltrate with moderate lymphoid hyperplasia. Figure 2 B,C,D: Immunohistochemistry revealed neoplastic cells to be moderately positive for CD20, CD138 and BCL2 in B, C and D, respectively.

The preliminary diagnosis was of an inflammatory process, but immunohistochemistry revealed neoplastic cells that were moderately positive for CD20, CD138 and BCL2, and many scattered non-neoplastic cells positive for CD3. The K_i-67 stain was positive in between 30 and 35% of the neoplastic cells. Accordingly, the findings were compatible with low grade marginal zone B cell lymphoma (►**Fig. 2**).

Systemic involvement was excluded by whole body positron emission tomography (PET) scan, and laboratory investigations including CSF cytology and bone marrow biopsy. The patient received localized intensity modulated radiation therapy (IMRT) on the tumor bed with a dose of 36 Gy divided over 20 sessions in 4 weeks. After a 3-month follow-up interval, there was no recurrence, and the patient was pain-free.

Discussion

The trigeminal nerve is a rare site for primary CNS lymphomas (►**Table 1**).[2–12] The first case was reported in 1996 by Nakatomi et al.[2] The reported cases were in patients with ages ranging from 40 to 77 years old, with a mean age of 56 years old. The male to female ratio was 2.67: 1. Our male patient was 29 years old at the time of presentation. In previous reports, the main presenting symptoms were facial pain followed by diplopia and facial numbness. Our patient also presented with left-sided facial pain that was more severe in the distribution of the mandibular division. This was also associated with numbness and diplopia due to paralysis of the 6th nerve.

As in all the available reports, preoperative diagnosis was not possible. Our proposed preoperative diagnostic hypothesis was schwannoma. Differential diagnosis of lesions involving the trigeminal nerve and extending into the cavernous sinus include: schwannoma of the trigeminal nerve, meningioma, lymphoma, and inflammatory lesions (herpes neuritis of the trigeminal nerve, idiopathic trigeminal neuropathy, and chronic granulomatous neuritis).[11] It is difficult to distinguish these lesions on pure clinical or radiological basis alone, but trigeminal lymphoma may be suggested by the short duration of symptoms.[6] The duration of symptoms in our case was only 3 months. Our patient had rapidly progressing abducens palsy. This is rare in trigeminal schwannomas or meningiomas. As in reported cases, the laboratory investigations were all within the normal parameters.

Eight reported cases involved location in the Meckel cave. In our case, the lesion spanned the whole trigeminal nerve, starting from its root until the Gasserian ganglion at the Meckel cave.

The treatment choices for these cases include surgical excision and stereotactic radiosurgery (SRS). SRS is widely used for lesions of this size. Stereotactic radiosurgery has the advantage of being a noninvasive modality to achieve control or even resolution of the lesion. Nevertheless, pain may not be relieved in cases of trigeminal neuralgia due to tumors.[13] It is risky to perform SRS without definite histopathological diagnosis in trigeminal lymphomas, as in the case reported by Nakatomi et al. Their preliminary diagnosis was meningioma of the cavernous sinus. The patient received Gamma knife radiosurgery leading to improvement of ptosis but not of the facial pain. The imaging obtained 1 year after SRS showed resolution of the cavernous sinus lesion; however, enlargement of the lesion in the prepontine cistern compressing the brain stem was evident, requiring surgical excision.[2] Additionally, early empirical radiotherapy of lymphomas can render biopsies obtained at a later stage non-diagnostic.[9] In our case, after discussing the available options of treatment, we opted to operate on the patient. The pain was unbearable despite receiving maximum carbamazepine dosage, and he already had neurological deficits at presentation. Surgery had several advantages over SRS, including: obtaining a histopathological diagnosis, relieving the diplopia caused by the compression of the 6th nerve and achieving immediate pain relief. Moreover, surgery was a better option in younger patients, and SRS is a better option in elderly patients.

The surgical approaches performed in the reported literature include: lateral suboccipital, subtemporal, transsphenoidal followed by pterional, anterior petrosectomy through frontotemporal craniotomy, and combined lateral suboccipital and subtemporal. The most common approach used was the lateral suboccipital. The surgical approach should be tailored according to the location, to the extent of the lesion, and to the comfort level of the surgeon. The approach used in our case was anterior petrosectomy through a frontotemporal craniotomy. This approach allowed radical excision of the tumor.

The most common histopathological variant of primary lymphoma of the trigeminal nerve reported in the literature is diffuse large B-cell lymphoma. Our case is distinct, as the

Table 1 Reports of Trigeminal Nerve Lymphoma

Authors	Age and gender	Presentation	Site	Preliminary diagnosis	Approach	Histopathology	Fate
Nakatomi 1996(2)	77 Male	Facial hypoesthesia	Lt prepontine cistern-cavernous sinus	Schwannoma or meningioma	Lateral suboccipital	Diffuse large B cell	Death
Abdel Aziz 1999(3)	40 Female	Facial pain, hypoesthesia	Lt Meckel's cave-cavernous sinus	Schwannoma	Frontotemporal craniotomy with orbit zygomatic osteotomy with anterior petrosectomy.	Monocytoid malignant B cell lymphoma	N.A.
Kinoshita 2003(4)	55 Male	Facial pain, diplopia	Lt Meckel's cave-infratemporal fossa	N.A.	Lateral suboccipital	Diffuse large B cell lymphoma Biopsy	Death
Bulsara 2005(5)	52 Female	Facial pain	Lt Meckel's cave-foramen rotundum	N.A.	Subtemporal	Non-Hodgkin lymphoma	N.A.
Iplikcioglu 2006(6)	50 Male	Facial pain, diplopia	Rt prepontine cistern-cavernous sinus	N.A.	Lateral sub occipital	B cell malignant lymphoma	Complete recovery
Akaza 2009(7)	60 Male	Facial pain	Lt prepontine cistern-Meckel's cave	Schwannoma or sarcoidosis	Biopsy from another lesion	Diffuse large B cell lymphoma	Complete recovery
Yamahata 2012(8)	68 Male	Facial pain and numbness	Distal trigeminal root -Lt Meckel's cave	Schwannoma, meningioma, malignant lymphoma, metastasis, or inflammatory disease	Anterior petrosal approach	T cell/histiocyte-rich B cell lymphoma	Complete recovery
Perera 2014(9)	55 Female	Diplopia	Rt cavernous sinus-pterygopalatine fossa	Meningioma	Transsphenoidal and pterional	Non-Hodgkin small B cell lymphoma with plasmacytoid differentiation	N.A.
Jack 2014(10)	57 Male	Facial pain	Lt prepontine cistern-Meckel's cave	N.A.	Lateral suboccipital	Diffuse large B cell lymphoma	Complete recovery
Ogiwara 2015(11)	47 Male	Facial pain, diplopia	Lt prepontine cistern-infratemporal fossa	Schwannoma or neuritis	Lateral suboccipital and subtemporal	Diffuse large B cell lymphomas, nongerminal center B type	Complete recovery
J.W.J 2015(12)	55 Male	Facial pain	Rt cavernous sinus-RtMeckel's cave-infratemporal fossa	Schwannoma or meningioma	Right temporal	Diffuse large B cell lymphoma	Complete recovery
Present case	29 Male	Facial pain	Lt Meckel's Cave - lt cavernous sinus	Schwannoma	Anterior petrosectomy through frontotemporal craniotomy	Low grade marginal zone B cell lymphoma	

pathological type of the lymphoma was marginal zone B-cell lymphoma (MZBL). To our best knowledge, this is the first case of this variant to be reported. Primary marginal zone lymphomas have been reported elsewhere in other intraparenchymal sites only six times in the literature.[14–19] Marginal zone B-cell lymphomas usually give rise to dural based lymphomas. Marginal zone lymphoma is a non-Hodgkin lymphoma that occurs more commonly in the gastrointestinal tract. So, it is sometimes called the "mucosa-associated lymphoid tissue" (MALT) lymphoma. Patients with marginal zone lymphomas have a more promising outcome, with a 5-year overall survival rate exceeding 86%.[20]

Chemotherapy regimens incorporating high-dose methotrexate (HD-MTX) are considered the standard of care as induction therapy for newly-diagnosed PCNSLs.[21] Following introduction of HD-MTX-based chemotherapy, whole brain radiotherapy (36–45Gy) has continued to be employed to consolidate responses and to provide more durable disease control.[22] These data are primarily for treating high grade B cell PCNSLs. But, in this case, our patient had low grade MZBL stage Iea (stage I extra-nodal without B symptoms). Extrapolation of data in treating early stage MZL in solitary extranodal location indicates that local treatment is the preferred treatment and, therefore, we followed surgery with 36Gy of localized irradiation to the tumor bed and, for fear of late toxicity in a young patient with an early stage indolent lymphoma, we used IMRT.

Conclusion

This is a single case report of a known pathological entity found in an unusual location. Lesions in the gasserian ganglion are usually benign tumors such as meningiomas or schwannomas. The message we convey is the importance of clinical correlation. The short duration of symptoms, severe constant pain and involvement of other cranial nerves, for example, the abducens nerve, should raise the suspicion of a different pathology. The administration of SRS in a lymphoma without definite pathological diagnosis would be hazardous, owing to the systemic and malignant nature of lymphomas. Surgery and histopathological examination should be the first option, whenever the primary diagnosis is doubtful.

Conflict of Interests

The authors have no conflict of interests to declare.

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Paraganglioma of the Cauda Equina – Case Report and Literature Review

Paraganglioma de cauda equina – Relato de caso e revisão da Literatura

Arthur Araújo Massoud Salame[1] Bernardo de Andrada Pereira[1] Lygia Sampaio de Arruda Camara[1] Iogo Henrique de Oliveira Araújo[1] Filipe Moreira de Almeida Pinheiro[1] Estevão Cardoso Carvalho[1] Francisco Weldes Brito das Neves[1] José Alvaro Bastos Pinheiro[1]

[1] Departament of Neurosurgery, Hospital Municipal Salgado Filho, Rio de Janeiro, RJ, Brazil

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Address for correspondence Arthur Araújo Massoud Salame, MD, Departament of Neurosurgery, Hospital Municipal Salgado Filho. Rua Arquias Cordeiro, 370, Méier, Rio de Janeiro, RJ, 20770-000, Brazil (e-mail: arthursalame@hotmail.com).

Abstract

Paragangliomas of the cauda equina are tumors of rare incidence, with ~ 220 cases described in the world literature. They are benign lesions, grade I by the World Health Organization (WHO), whose definitive diagnosis can only be made by immunohistochemical analysis. Its neuroendocrine nature is evidenced by the presence of chromogranin. The relevance of reporting this case is because paragangliomas of the cauda equina should be included among the differential diagnoses of intradural and extramedullary tumors, and especially because they can cause perioperative and intraoperative hypertensive crises by adrenergic discharge.

The present study presents the case of a 36-year-old male patient diagnosed with a lumbar spine tumor located in the central spinal canal that presented as cauda equina syndrome involving 4 months of bilateral sciatica, paraparesis, urinary and fecal retention. The diagnosis of paraganglioma was confirmed by immunohistochemical positivity for chromogranin after microsurgical resection of the tumor.

Keywords
- paraganglioma
- cauda equina
- spinal tumors

Resumo

Paragangliomas da cauda equina são tumores de incidência rara, com ~ 220 casos descritos na literatura mundial. São lesões benignas, grau 1 pela Organização Mundial da Saúde (OMS), cujo diagnóstico definitivo apenas pode ser feito pela análise imunohistoquímica, onde se evidencia a natureza neuroendócrina dada especialmente pela presença de cromogranina. O presente relato de caso se torna importante porque este deve ser considerado entre os diagnósticos diferenciais de tumores intradurais e extramedulares, e porque há trabalhos na literatura descrevendo crises hipertensivas durante a ressecção da lesão devidas a descarga adrenérgica.

O presente estudo apresenta o caso de um paciente masculino de 36 anos diagnosticado com tumor na coluna lombar localizado no canal medular, que cursou com

Palavras-chave
- paraganglioma
- cauda equina
- tumores espinhais

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síndrome de cauda equina, com 4 meses de lombociatalgia bilateral, evoluindo à paraparesia, retenção urinária e fecal. Após microcirurgia para ressecção tumoral, o diagnóstico de paraganglioma só foi confirmado através da imunohistoquímica, com positividade para cromogranina.

Introduction

Paragangliomas of the cauda equina region are a rare incidence tumor, with ~ 220 total cases described in the world literature, and they correspond to ~ 3.5% of the tumors in this region.[1,2] The first case was described in 1970 initially as a secretory ependymoma.[3] From that date on, between 4 and 8 cases are usually described annually, with greater evidence since the eighties due to the development of more accurate immunohistochemistry techniques and the use of magnetic resonance imaging (MRI).[4]

Paragangliomas are neuroendocrine tumors classified as grade I by the World Health Organization (WHO) grading system, have a slow-growing behavior, and arise from the paraganglia cells (group of neuroepithelial cells). There are two groups of paraganglia cells: one composed by adrenal medulla cells and the other composed by the extra-adrenal paraganglia cells.[5]

The term pheochromocytoma is used for tumors that arise from the adrenal medulla, while paraganglioma is used for tumors from the extra-adrenal paraganglia. Paragangliomas may occur in any part of the body, but tumors of the carotid body and of the glomus jugulare constitute $>90\%$ of the reported paragangliomas.[2]

An accurate preoperative diagnosis of paraganglioma is very difficult to achieve. A definitive diagnosis depends basically on the pathological examination and, especially, of an immunohistochemical study in order to differentiate it from other intradural extramedullary lesions, which should always be considered for differential diagnosis, that is, ependymomas, schwannomas, meningiomas, metastatic tumors, hemangioblastomas, and lipomas.[6]

The goals of the present study are to report a case of a patient with a paraganglioma of the cauda equina region and to perform an extensive literature review on the topic.

Case Report

A 36-year-old male was admitted at the hospital with complaints of bilateral low back pain of 4 months of evolution associated with progressive paraparesis – muscle strength grade 4 on the lower limbs, proximal and distal. The patient also had urinary and fecal retention that were progressively worsening. An MRI of the lumbar spine was performed and evidenced an intradural expansive lesion at the level of the L2 vertebrae with an estimated dimension of 3.0×2.0 cm (►**Fig. 1**).

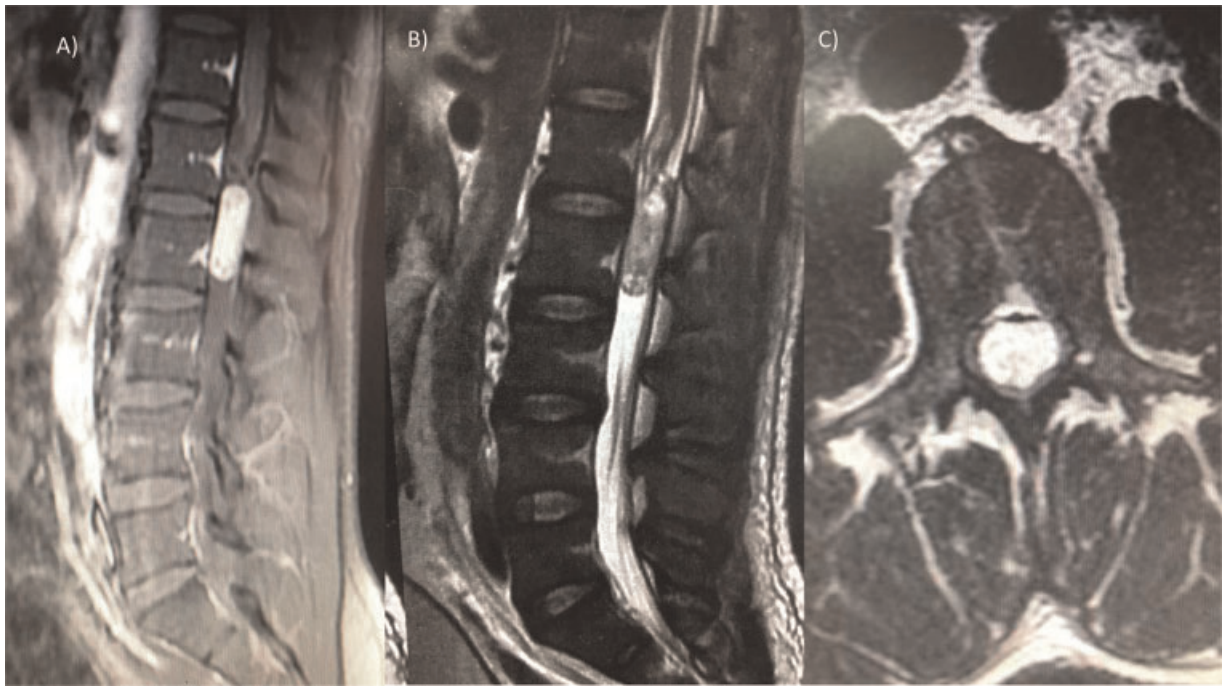

Fig. 1 Magnetic resonance imaging of the lumbar spine showing an intradural mass at L2. (**A**) T1 weighted with contrast sagittal view. (**B**) T2 weighted without contrast sagittal view. (**C**) T1 weighted with contrast axial view.

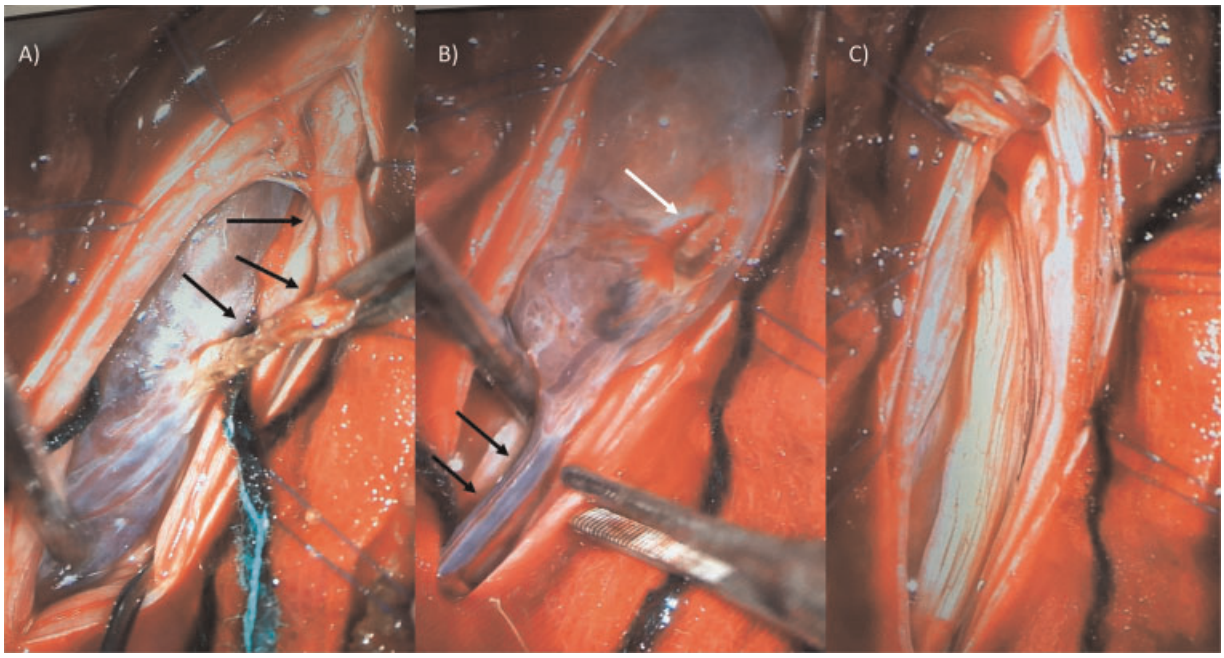

Fig. 2 Intraoperative images of the resection of the paraganglioma of the cauda equina . (**A**) Paraganglioma compressing the nerve roots of the cauda equina, black arrows evidence the proximal portion of the filum terminale after dissection prepared to be sectioned. (**B**) After sectioning the proximal portion of the filum terminale (white arrow), the distal portion is under dissection and preparation for coagulation and sectioning (black arrows). (**C**) Nerve roots of the cauda equina free from compression after tumor removal.

The patient underwent complete microsurgical resection of the tumor which arises on the filum terminale, under general anesthesia. The lumbar and sacral nerve roots were preserved. Intraoperative images are exhibited on ►**Fig. 2**. The completely excised tumor is exhibited on ►**Fig. 3**. Neuromonitoring was not available.

An anatomopathological macroscopic examination showed a well-defined encapsulated red lesion measuring $3.0 \times 1.5 \times 1.5$ cm, with a grayish smooth surface, elastic consistency, and small cystic cavities observed after slicing. The microscopic examination was suggestive of myxopapillary ependymoma under hematoxylin and eosin. However, immunohistochemistry evidenced a paraganglioma with positivity for chromogranin and negativity for glial fibrillary acidic protein (GFAP), S100, and AE1/AE3 (►**Fig. 4**).

The patient was discharged at the 4th postoperative day with complete improvement of motor function and partial improvement in sphincter disorders. There are no signs of recurrence in 2 years of follow-up (►**Fig. 5**).

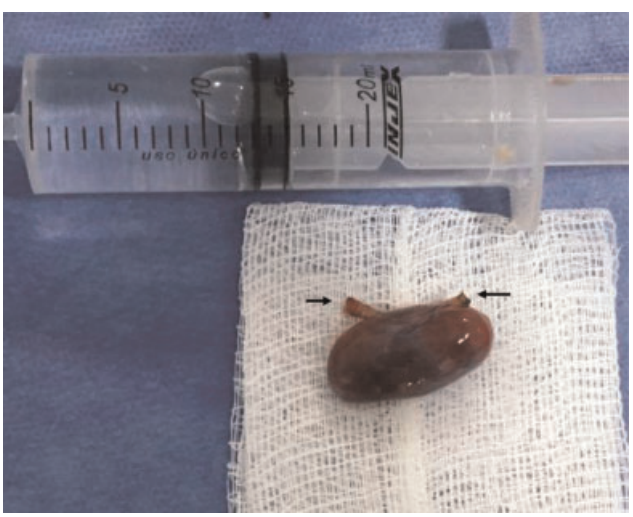

Fig. 3 Macroscopic aspect of completely excised paraganglioma. The two black arrows evidence, respectively, the proximal and distal remains of the filum terminale.

Discussion

The low incidence of this type of tumor makes this report more important in the literature. Although rare, these tumors may cause systemic manifestations because they have the biochemical feature of producing and storing biogenic amines, as well as the potential to produce peptide hormones (adrenaline, noradrenaline, and dopamine).[5]

Even though they are unusual, there are reported cases of hormonal activity with abnormal urine noradrenaline concentration and features of vasomotor amine syndrome. The limited occurrence of paroxysmal hyperadrenergic

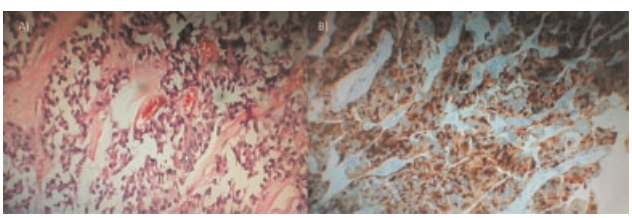

Fig. 4 Histology: (**A**) Hematoxylin and eosin, nest of tumor cell, consisting of a round small tumor cell, separated by a fine vascular network, known as a "Zellballen" pattern. (**B**) Immunohistochemical analysis positive for chromogranin.

Fig. 5 Two-year postoperative magnetic resonance imaging with no evidence of recurrence.

states in spinal paragangliomas may have two reasons: first, the incapacity of the tumor cells to secrete stored substances, or second, the incapacity of these substances to cause a clinical syndrome.[7]

The main symptoms caused by this type of tumors are low back pain, which may be present in 90% of the cases, and sciatica, described in at least 72%. Motor or sensory deficits are detected in 35% of the cases while sphincter and erectile dysfunctions were reported, respectively, in 14 and 1.2% of the patients.[8,9]

The group of patients at risk described on the literature are within the age range between 12 and 77 years old, with a peak incidence on the 4th and 5th decades of life, with a male predominance. The male to female ratio is 1.54.[8,10]

Magnetic resonance imaging is the gold standard exam, but the neuroradiological features of these lesions are not specific and demonstrate only the alternatives in the differential diagnosis.[11] There are no pathognomonic findings for cauda equina paragangliomas. The lesion is usually hypo or isointense on T1 sequences compared with the conus medullaris, whereas it is hyperintense on T2 sequences and may be heterogeneous due to subacute blood clot.[11]

Paragangliomas happen mostly sporadically, but familial forms can also occur in an autosomal dominant trait in ~ 1% of the cases. However, in the cauda equina region, inheritance in these types of tumors has never been reported.[12] The lesions are encapsulated in 80% of cases, while invasion can occur in 15%. The size of the tumor usually varies from 1.5 to 13 cm.[8,13] A complete resection is the ultimate goal of surgery. Total excision is feasible in 90% of the patients. The tumor is attached to the filum terminale in 85% of the cases, either directly or by a vascular pedicle.[8,13–15]

The step-by-step of the surgery performed on the aforementioned case is in line with the literature: prone position on surgical table, posterior lower back midline incision, laminectomy of the L2 and of the lower half of the L1, and opening of the dura mater followed by visualization of the nerve roots of the cauda equina. After careful arachnoid microdissection, the nerve roots were separated and a bright red mass was identified on the body of the filum terminale, with a large tortuous exuberant vessel coursing longitudinally on its wall. Bipolar coagulation of the referred vessel was performed, followed by coagulation of the proximal and distal portion of the filum terminale. The filum was proximally and distally sectioned and the tumor removed *en bloc* to prevent extensive bleeding and subarachnoid dissemination of the tumor.[16]

In cases in which only subtotal removal was achieved, recurrence will happen in ~ 10% in a period of 1 year. Recurrence does not necessarily mean malignancy, but a sign of suboptimal resection and regrowth. Encapsulated tumors are favorable to complete removal and have greater chance of cure. The options in cases of recurrence include reoperation and radiation therapy, and each case should be judged individually.[8,17]

Limitations

No immunohistochemical differentiation between chromogranin A or B was made in the current case. Synaptophysin was not available.

Conclusion

Paragangliomas of the cauda equina are rare tumors whose diagnosis is only confirmed by immunohistochemical analysis. They must be included among the differential diagnoses of intradural and extramedullary spinal tumors. Case reports become more important because, in addition to these tumors being in an atypical location, there are studies in the literature describing hypertensive crises during resection of the lesion due to adrenergic discharge.

Conflict of Interests

The authors have no conflict of interests to declare.

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