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Dr. Evandro de Oliveira, The Brain Whisperer

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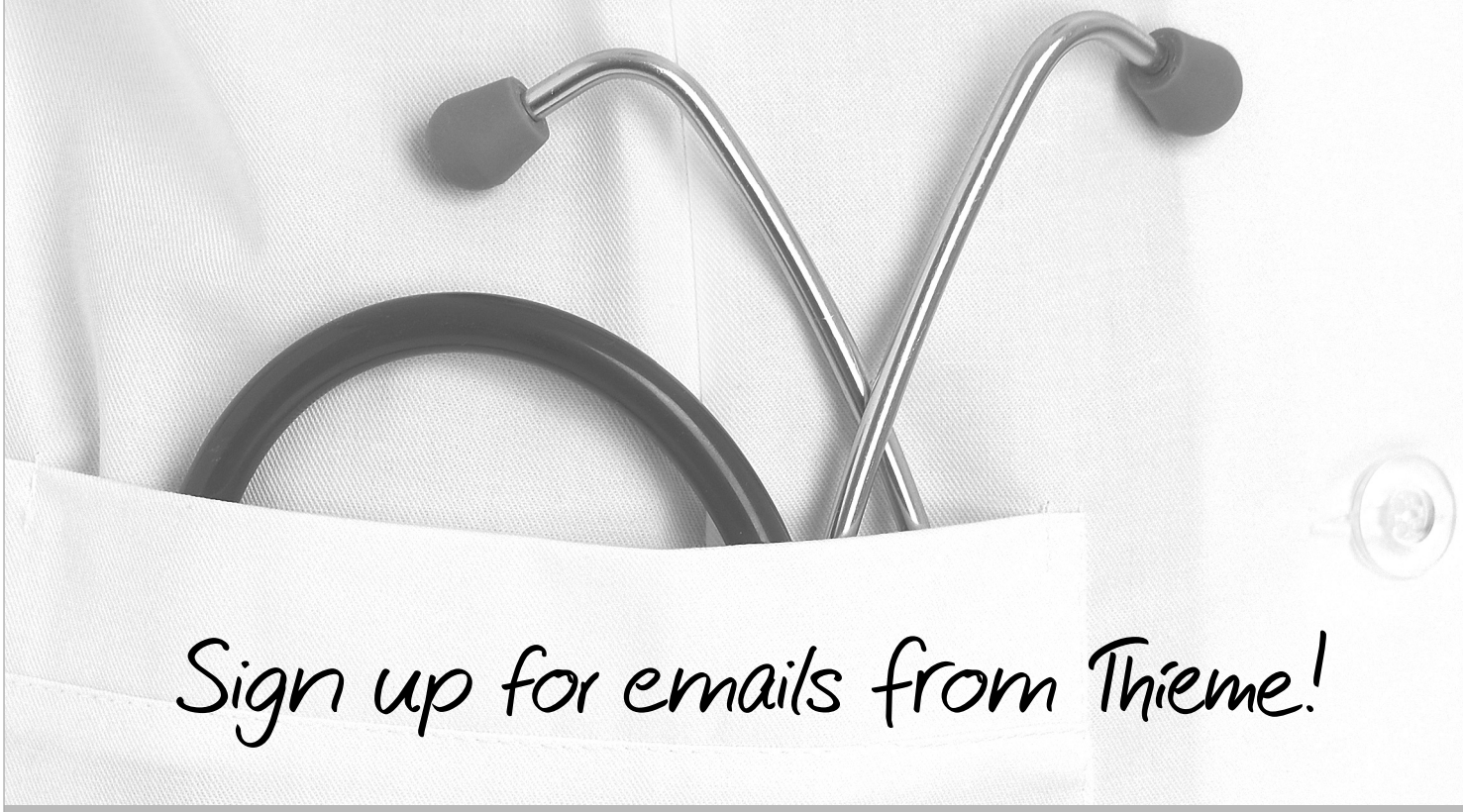

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Editorial

Evandro de Oliveira, "The Brain Whisperer"

Eberval Gadelha Figueiredo[1] Jose Marcus Rotta[2] Manoel Jacobsen Teixeira[2]

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Arq Bras Neurocir 2019;38:253.

Doctor Evandro de Oliveira

> "Be not afraid of greatness; some are born great, some achieve greatness and others have greatness thrust upon them." —William Shakespeare
>
> "We are what we repeatedly do. Excellence, then, is not an act, but a habit. " —Aristotle
>
> "No man is truly great who is great only in his lifetime. The test of greatness is the page of history." —William Hazlitt

In this edition, *Brazilian Neurosurgery*, on behalf of the entire Brazilian neurosurgical community pay its homage to one of the greatest neurosurgeon of all time, Dr. Evandro de Oliveira. Professor Sebastiao Gusmao in the next pages will present a beautiful and erudite report that traces parallels between surgical technique and art, that are amalgamated in Evandro's hands. Evandro's unique surgical technique is the perfect summary that reunites art and technique in the operative treater. However, rather than art, the Evandro's School of surgery is Philosophy, as well.

Nothing less than perfection was tolerable to him. Perfect positioning, bloodless surgical field, precise microsurgery with no parasitic movements, stepwise revelation of the beauty of the brain anatomy, these are the Evandro's commandments. These facts imposed upon his pupils a great amount of pressure, whereas solidified a powerful mindset and established his surgical school. Many neurosurgeons in the world have been educated with this kind of surgical philosophy. His work put the Brazilian neurosurgery in a new and higher standard, that might be unreachable without his contributions. Our all gratitude to him.

Professor Gusmao will say more and better, nonetheless the Evandro's surgical school will echo for years to come. As an English essayist said: the test of greatness is the page of history.

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Evandro de Oliveira: From Anatomy to Science and the Art of Microneurosurgery

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It is classic to state: medicine is science and art. Medicine and art go hand in hand. Hippocrates's medicine (460–378 BC) was born during Pericles century (495–429 BC), at the nadir of Greek art of Fidias (490–430 BC). Both submerged during the middle ages and reburned during the Italian renaissance.

Science can be defined like organized knowledge and be confirmed through observation and experimentation. However, it is difficult to define art because the term could mean multiple things in different places and time. The greek term tékhné, translated to latin as technique and also as art.The later meaning, whatever is well done by the man. For the greeks artwork was to perform a technique with excellence. Hence, in the first Hippocrates' s aphorism, "The life is short, the art last long."(ÓBios brakhys É dé tékhné makhré), the term tékné refers to art meaning technique acquisition, practical knowledge the execution of work in the medical field.

In all branches of knowledge, including medicine and surgery, there archaic civilizations referred to medicine as art, or better as technique based in mythical explanation. The "Greek miracle" exclude the mythical explanation and submitted the technical knowledge to the sieve of rationality, creating Science as we know. Therefore, medicine and surgery are old as art but new as science. In reality, way before the emergence of science in Greece at the 6th century B.C., the Neolithic man already had practiced the art of surgery as documented in several trephined skulls found in several different archeological sites.

The intimate relation between technique and science in the pre-Socratic Greece was ruptured by Plato is(428–348 B.C.) philosophy, which was disputed by the intellectual capacity of the technicians.

This fact determined the discredit of the manual labor, including plastic artists, during the medieval and classic period, being one of the main reasons for the dichotomy between theory and practice, science and technic, medicine (scientific knowledge) and surgery (technical knowledge). This dichotomy increased with the medieval scholars. Only during the Renaissance the artist and handcrafters recuperated their dignity and prestige.

The Vesalius"s (1514–1564) dissections depicted in De Humani Corpori Fabrica (1543), inaugurate the modern medicine. In his work, still considered the most outstanding in medicine, the narrow relation between science and art takes place.

The Vesalius' text is as important as the exquisite illustrations of Calcar (1499–1546), Tiziano's disciple. Therefore we can say that modern medicine was born in an anatomy laboratory and in the workshop of a renaissance painter.

The word surgery came from the Greek kheir, hand, and ergon, "work" .Until the XVI century, surgery was only manual labor, without scientific bases, and wasn't performed by doctors but by barber surgeons. Ambroise Paré (1510–1590) saw the new Vesalius's anatomy as the foundation of surgery. He transformed the barber-surgery art into the medieval art and science of surgery, giving the dignity and respect toward to the surgeon's work.

In the Seventeenth century, the knowledge acquired in the two previous renaissance centuries increased even more, leading to the birth of the modern science.

In this context neurosciences was born in 1664, with the work named **Cerebri Anatome** from Willis (1621–1675), in which medieval concepts regarding cerebral function were repealed. The pillars of modern neurosciences and neurology were established. As a matter of fact, in this work the word neurology was coined. Again, one more time we witnessed the narrow association between art and science, the outstanding text written by Willis was impeccably illustrated by Christopher Wren (1632–1723), the greatest british artist from all times. Sir Wren, himself, was responsible for the London's reconstruction after the devastating 1666 fire. The Saint Paul cathedral being his masterpiece. Wren's superb drawings revealed great elegance and precision, showing the brain in such detailed and realistic fashion never seen before in any publication.

Subsequently in the Nineteenth century, John Hunter applied experimental scientific method to surgery, creating modern surgery. At the end of the Nineteenth century, advances in general surgery and the better understanding of

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anatomy and physiology of the nervous system, made possible the creation of neurosurgery as a modern medical specialty.

The modern neurosurgery was born from the hands of an artist-scientist, Harvey

Cushing (1869–1939). The artistic talent from this neurosurgery pioneer was well portraited in his landscape drawings and pictures in his own monumental neurosurgical publications.

On the late half of the last century another scalpel genius, Yasargil, took neurosurgery to another level. Using his extensive and intensive laboratory work he created Microneurosurgery, allowing us to perform miniature art, under microscopic visualization. Indeed, that represented a true revolution in the field, debuting new surgical approaches and better treatment options. Yasargil established several steps. First, the profound and thorough knowledge in central nervous system anatomy. Second, the need of relentless laboratory training and last, but not least, to approach the pathology in the brain in as harmless way as possible through its natural pathways: the sulci and cisterns.

Another essential master to established microneurosurgery was Rhoton. He taught us, using his own exquisite anatomical preparations, to understand better tridimensional brain anatomy and microanatomy and its variations.

Rhoton created a legion of microneuroanatomists that preached their knowledge in all continents. His personal as well as his collaborators endless work constitute the unique preliminary requirement to enter into the science and art of the microneurosurgery world.

His most dear and brilliant pupil was Evandro de Oliveira (►**Fig. 1**). After training and conclusion of several projects with his mentor, Evandro returned to Brazil in the earlier eighties. Even before the adventof the internet, he disseminated mocrosurgical knowledge applied to neurosurgery among the Brazilian neurosurgeons. Actually, he initiated a new era of microneurosurgery in his country. To perform microneurosurgery is not just limited to the use of the microscope(which by the way was already present in ours operative rooms. Not too long after that he created the magnificent anatomy laboratory at Beneficência Portuguesa Hospital. For almost four consecutive decades this laboratory has been the main center for microsurgical training for residents and young neurosurgeons. It is for sure a sacred temple for science and art in microneurosurgery. The work of Evandro de Oliveira was without any doubt one of the main factors in the process to raise the Brazilian neurosurgery to the top of the latin-america neurosurgery and to be considered one of the best of the world.

Beyond this essential work in training the last generations of Brazilian neurosurgeons, Evandro de Oliveira developed and improved new microsurgical approaches, shown to our neurosurgery in all four corners of the world and abroad and subsequently opened the doors for many young Brazilian neurosurgeons.

With his skillful hands like a Chinese artist in porcelain from the Ming dynasty, he touched the brain like a priest touches a sacred icon, more so, with his restless brain that kept persuing the brain's misteries, he restored and gave life to thousands of brains. Without passion, life is meaningless. With passion, Evandro took his work to the edges of perfection, turning into pure art. His happiness is to find pleasure in this unique form of art.

It will never be redundant to state how important is the laboratory work in the learning process of microanatomy and surgical technique. Evandro had a fundamental role in improvement in the many generations from Brazil and other countries.

Actually, the modern medicine originated in a laboratory, when Vesalius in1543, performed magnificent dissections to better understand the human body and to illustrate his Fabrica. At the end of the nineteenth century the neurosurgery had its beginning with Horsley. He was summoned to

Fig. 1 Doctor Evandro de Oliveira.

initiate surgical treatment in the neurological patients of the famous Queen Square, due to his notorious skill to open monkey skulls in a laboratory installed in his own house. Yasargil also created microneurosurgery in a laboratory.

The Italian renaissance master painters were in fact the first anatomists. To place in canvas the enigmatic face of Monalisa and to carve in pure marble the harmonious lines of David, Leonardo Da Vinci e Michelangelo, they had to dissect cadavers and be aware of the representation object, the human body. In the same fashion, the similar requirements are recommended to the microneurosurgeon. Extreme dedication in studying the anatomy in the laboratory to repair the most complex organic matter ever existent in the universe, the human brain. Only by that way is possible to acquire the mastery in science and art of microneurosurgery.

Five centuries passed by and Vesalius's statement is still true: " the anatomy has to be considered the most solid pilar of the art of medicine, its preliminary essential. The central nervous system anatomy is our preliminary essential in the work field where we practice our job. The brain is the most complex and elaborated matter in our known universe. The brain named itself and creates the universe in which we realized the origin of all forms of arts. Significant art is required from someone that desires to enter in the temple of all arts.

The art has the power to emphasize and refine our senses and to stimulate our awareness in search of occult essence of life's phenomena. The antagonism between art, the daughter of inspiration, and science, originated from methodic observation of facts is only apparent. Art in the Hellenic sense of what is well done and that embroiders all mankind's achievements, including science, because the beauty is everywhere, from a mathematical equation to a Rembrandt (1606–1669) canvas.

Medicine and art complement each other. It is very superficial to imagine a conflict existent between a practical art such as surgery, that depends of judgement, intuition and skill, and the precision of science that requires elimination of all human elements. Patient care and treatment of diseases are problems to science, but the excellence in both depends on the art that the doctor applies with scientific knowledge.

In Neurosurgery, the complex central nervous system anatomy, its low threshold for manipulation and the rigidity of the cranium osseous compartment make the challenges even worse, thus requiring refined science and art.

The surgeon in action is no longer a handcrafter that cuts, ligates, detaches or sutures. However, he is not a technician either, but a physician that carries deep knowledge in the human being and his emotional problems and precise domain regarding diseases mechanisms, its diagnostics, pathological manifestations and treatment. Such knowledge, associated with the wisdom originated with experience, it is at the fundaments of abilities in surgical judgement, which is the most difficult requirement to be acquired in the art of surgery.

Our art reflects our life, because nothing can come out from the artist if it is not in the man. Be a good neurosurgeon depends on first in being a good doctor. And what defines a good doctor? Kindness, empathy, conscience, ethics, and the ability to make sensible decisions and make proper judgements, as well as the desire in doing the best for the patient. In the nervous systems there are islands of knowledge, where science can be applied, and a vast ocean where we can only offer hope and comfort. The latter is, a major part of the art of neurosurgery, where we feel and intuit, but cannot prove. Like knowledge doesn't resume life, science does not limit medicine. The art is necessary.

The accurate surgical technique, like any other ability, requires repetitive training associated with passion. We can build nothing big without passion. The passion leads to pleasure in our work and that perfects the technique until it meets the art. Therefore excellence in microneurosurgery is a matter of technique, because this originates in the brain of the technician. It is a matter of personality, attitude and character. Those qualities are present in the masters Yasargil and Rhoton. After several years of coexistence and working alongside, I could notice them well in Evandro de Oliveira. His precise microsurgical technique, reached the state of the art, and is nothing more than his character almost paranoid in chase of the truth, the essence of things, the perfect technical detail. On the foundation of all that is the respect to the brain's complexity and the love toward the human being that suffers, generating passion for his duty. According to van Gogh (1853–1890), "The essence of art is the love to the human being." The essence of medicine is the love for the human being that suffers. Only love and art can make existence tolerable, and there is the place that the art of medicine acts. A lot of dignity and humility is necessary from someone whose duty involves love, art and life.

As mentioned above, the master Yasargil, Rhoton and Evandro de Oliveira extensively contributed to the establishment of the art and science of microneurosurgery. The same way Hippocrates removed medicine from the gods temple giving to it mankind, those masters revealed upon us the safe pathways to get in all hidden compartments of the sacred temple of the human brain.

Human knowledge will continue flowing implacably, generating new technologies that probably will reinvent our specialty, that will require from us more science to dominate them and more art to apply them with wisdom in favor of our patient's life and fulfillment of our own. At last, there is only one art undebatable important: to live; everything else is secondary. To our master Evandro de Oliveira, that has helped many in the difficult and dangerous art of living, we can only to thank using the words of the genius of the Portuguese language (Camões): "E mais vos pagamos e mais vos devemos" (The more we pay you, the more we owe you).

Evaluation of Head Computed Tomography Assessment of Brain Swelling after Acute Traumatic Brain Injury: A Pilot study

Avaliação da tomografia computadorizada de crânio com edema cerebral após lesão cerebral traumática aguda: Um estudo piloto

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Abstract

Objective To evaluate the interobserver reliability of a new scale created for quantitatively assessing brain swelling in traumatic brain injury (TBI) patients using the computed tomography (CT) findings in three levels.

Methods Computed tomography scans of severe head injury patients were randomly selected from a tertiary hospital image database and evaluated by independent groups of neurosurgeons, neurosurgery residents, radiologists, and intensivists from the same hospital. Each specialist assessed the tomographic findings, applying zero to six points in a new scale. The Kappa coefficient was calculated to assess interobserver agreement.

Results The highest reliability coefficient was obtained by the neurosurgeons group (0.791; 95% confidence interval [CI]: 0.975–0.607; $p < 0.001$), followed by the neurosurgery residents group (0.402; 95%CI: 0.569–0.236; $p < 0.001$) and by the radiologists group (0.301; 95%CI: 0.488–0.113; $p < 0.002$). The lowest coefficient was found among the intensivists (0.248; 95%CI: 0.415–0.081; $p = 0.004$).

Conclusion The proposed scale showed good reliability among neurosurgeons, and moderate overall reliability. This tomographic classification might be useful to better assist severe TBI victims, allowing to identify the worsening or amelioration of brain swelling, which should be further investigated. The scale seems to be feasible, even in low income countries, where the cost of intracranial pressure (ICP) monitoring is higher than that of CTs.

Keywords
- brain injurytraumatic
- tomography
- critical care
- prognosis

Resumo

Objetivo Avaliar a confiabilidade interobservador de uma nova escala criada para avaliar quantitativamente o edema cerebral em pacientes com trauma cranioencefálico (TCE) utilizando os achados de tomografia computadorizada (TC) em três níveis.

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Métodos Tomografias computadorizadas de pacientes com TCE grave foram selecionadas aleatoriamente a partir de um banco de imagens de hospitais terciários e avaliadas por grupos independentes de neurocirurgiões, residentes de neurocirurgia, radiologistas e intensivistas do mesmo hospital. Cada especialista avaliou os achados tomográficos, aplicando zero a seis pontos em uma nova escala. O coeficiente Kappa foi calculado para avaliar a concordância interobservador.

Resultados O maior coeficiente de confiabilidade foi obtido pelo grupo de neurocirurgiões (0,791, intervalo de confiança [IC] de 95%: 0,975–0,607; $p < 0,001$), seguido pelo grupo de residentes de neurocirurgia (0,402; IC95%: 0,569–0,236; $p < 0,001$) e o grupo de radiologistas (0,301; IC 95% 0,488–0,113; $p < 0,002$). O menor coeficiente foi encontrado entre os intensivistas (0,248; IC95%: 0,415–0,081; $p = 0,004$).

Conclusão A escala proposta mostrou boa confiabilidade entre os neurocirurgiões e moderada confiabilidade geral. Essa classificação tomográfica pode ser útil para auxiliar melhor as vítimas graves de TCE, permitindo identificar o agravamento ou melhoria do inchaço cerebral, que deve ser mais investigado. A escala parece ser viável, mesmo em países de baixa renda, onde o custo da monitoração da pressão intracraniana (PIC) é maior que o dos TCs.

Palavras-chave
- lesão cerebral
- traumática
- tomografia
- tratamento crítico
- prognóstico

Introduction

Traumatic brain injury (TBI) is a major cause of death and morbidity among young adults, and many studies investigate prediction factors of mortality among these patients.[1] The severity of these lesions is increasing in developing countries.[2,3] One of the most devastating consequences of severe TBI is brain swelling, which results from either vascular engorgement or accumulation of excessive fluid in the intra- or extracellular space.[4] Brain swelling follows the increase of intracranial pressure (ICP), occurring in 16% of all TBI victims[5] and in 28% of pediatric head-injured patients.[6]

Unfortunately, even in high-income countries, ICP monitoring via a fiber optic monitor or via an adaptable external ventricular drain (EVD) system is not performed in every patient,[7] highlighting a problem on how to manage these patients. A controlled trial[8] comparing pressure monitoring with clinical evaluation and imaging by computed tomography (CT) scans has shown similar outcomes. In fact, in day-to-day practice, when the trauma team faces a patient without ICP monitoring, the use of serial CT scans (a widely available imaging tool in emergency rooms) might help the management of sedation or adjusting therapeutic intensity levels. Although CT scan findings of effacement of cortical sulci and cisterns are described as prognostic variables in some studies,[8,9] the usefulness of CT in the management of TBI patients is rarely described, probably because these variables are often assessed subjectively.

Moreover, the tomographic scales available[10,11] are assessed only to predict outcomes, and they have no role in guiding the therapy of brain swelling in the emergency room or in the intensive care units (ICUs). To our knowledge, there are no radiologic scales to assess the dynamic changes that may occur on the brain following TBI. Therefore, a tomographic classification system that allows the quantification of brain swelling and the comparison between the features of the exams is of great importance.

In the present study, the authors propose to evaluate the interobserver reliability of a new scale proposed to analyze traumatic brain swelling by using CT, which takes into consideration the status of the sylvian fissure and of the cortical sulci.

Methods

Study Design and Participants

This is a diagnostic accuracy study of interobserver reliability evaluation of CT scans of severe TBI patients showing brain swelling, in victims > 16 years old admitted in the emergency service of a public hospital for the management of closed severe TBI.

Tomographic findings of focal injuries requiring surgical intervention (hematoma volume > 25 cc) and midline shift > 5 mm were excluded from the sample. The CT scans made up to 35 minutes after the arrival at the hospital, after all life support and/or resuscitation measures had been applied, were compared with CT scans randomly selected in a tertiary hospital database for the calculation of interobserver agreement. A total of 20 brain CT scans were randomly selected (using the Web site random.org for generating sequential medical record numbers) from the image database of the hospital (Philips iSite PACS; Philips, Amsterdam, Netherlands) to be used in the present study.

Ethics

Prior approval by an ethical committee was waived in the present study (protocol number 00119/10), because it was entirely based on medical records and archival images. The participants in the present investigation were all physicians and they had no contact with the patients for the evaluations made, only with archival material. Still, confidentiality was

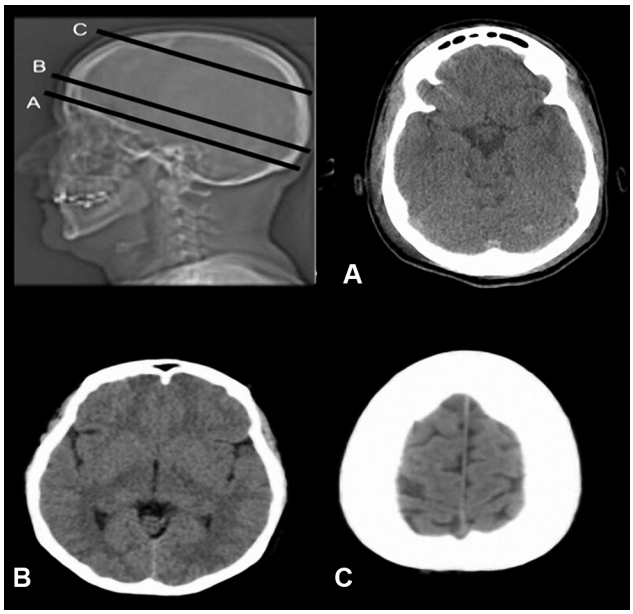

Fig. 1 Schematic evaluation of brain swelling after traumatic brain injury in computed tomography scans, assessing the anterior cisterns **(A)**, the sylvian fissure/ambiens cistern **(B)** and the cortical sulci **(C)**

assured by anonymity of all patients, as identifications were kept confidential. All of the participants in the present study (the physicians evaluating the CT scans) agreed to make the evaluations voluntarily.

Procedures

All patients had undergone a skull CT in the same service using a CT750 HD Lightspeed 64-slice CT Scanner (GE Healthcare, Chicago, IL, USA). After downloading the key images from the image database, 12 evaluators with different background and levels of experience observed the images according to the criteria described below. The criteria were explained to each professional individually and personally.

The evaluators were: three board certified neurosurgeons, three neurosurgery residents, three board certified radiologists, and three board certified intensivists. These evaluators were physicians of the hospital staff who agreed to participate in the study. Baseline data of the patients were retrospectively collected from the medical charts. The 12 evaluators were blinded for the clinical data on the medical charts and they evaluated the CT scans individually, without interference from other colleagues.

Imaging Review

The analysis should be performed based on a zero to six-point scale, created especially for the present study, which aims to quantify the degree of cerebral swelling after a severe brain injury using three tomographic slices, on three different levels: convexity cortical sulci, sylvian fissure/ambiens cistern, and anterior cisterns (►**Fig. 1**). For each level, the evaluators should assign zero points if the aspect was considered as normal, one point if the referred structure (cistern/sulci) was compressed, and two points if it was absent (►**Figs. 2** and **3**). Each participant was free to use as much time as he/she needed to evaluate the scans according to the new scales, as time was not previously set up.

Statistical Analysis

The Kappa coefficient was used to quantify the interobserver agreement between the reviewers. To verify the correlation coefficient and interpret the strength of agreement, a commonly cited scale proposed by Landis et al[12] was adopted:

(a) Almost perfect agreement: 0.81 to 0.99;
(b) Substantial agreement: 0.61 to 0.80;

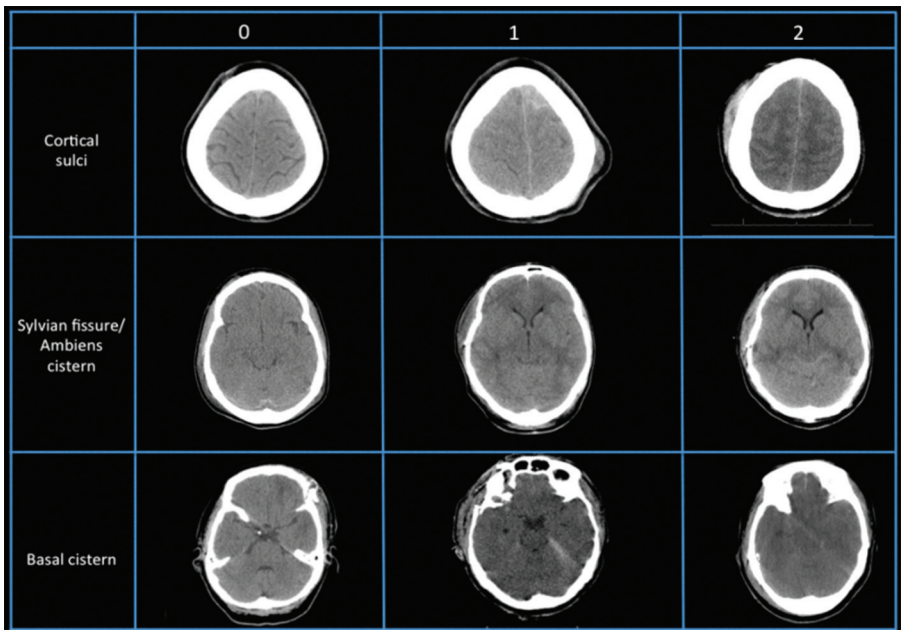

Fig. 2 Scoring system for the evaluation of brain swelling after traumatic brain injury in computed tomography scans: examples of scores 0, 1 and 2 for the cortical sulci (first row), sylvian fissure/ambient cistern (second row) and anterior cisterns (third row)

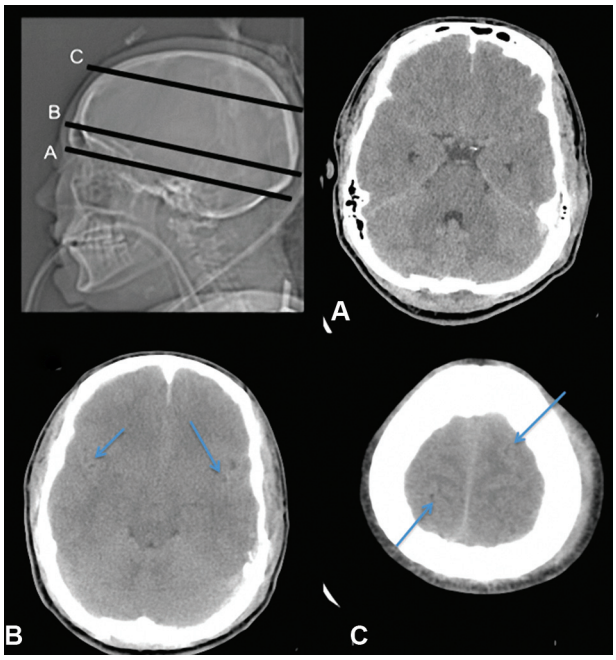

Fig. 3 Practical example of scale usefulness: computed tomography score of 2, due to compression of cortical sulci and sylvian fissure (one point each), and zero point at the lowest level (anterior cisterns), classified as normal.

(c) Moderate agreement: 0.41 to 0.60;
(d) Fair agreement: 0.21 to 0.40;
(e) Slight agreement: 0.01 to 0.20;
(f) Less than chance agreement: < 0

Results

A total of 20 nonenhanced head CT scans of 20 patients sustaining closed TBI were randomly selected for the analysis in the study period. All of these 20 CT scans were evaluated by the 12 evaluators.

A total of 16 patients were male, and the average age was 40.3 years old. A total of 13 patients sustained high impact injuries, 6 were victims of fall, and 1 had an unknown mechanism of trauma.

The reliability evaluation of the scale in the neurosurgeons group was 0.791 (95% confidence interval [CI]: 0.975–0.607; $p < 0.001$), classified as a substantial agreement according to Landis et al.[12] In the neurosurgery residents group, the coefficient was 0.402 (95%CI: 0.569–0.236; $p < 0.001$), considered as a fair agreement. The radiologists showed also a fair agreement, with a correlation coefficient of 0.301 (95%CI: 0.488–0.113; $p = 0.002$), and the lowest coefficient was found among the intensivists group (0.248; 95%CI: 0.415–0.081; $p = 0.004$), representing a slight agreement. Finally, the overall reliability showed a moderate agreement (0.503; 95%CI: 0.549–0.457; $p < 0.001$).

Discussion

The present study is, to our knowledge, the first aiming to evaluate the reliability of a classification system created to quantitatively qualify the level of brain swelling among TBI patients using CT scans and considering the convexity cortical sulci, the sylvian fissure/ambiens cistern, and the anterior cisterns. The proposed scale showed an overall moderate reliability, which makes it feasible to be used in clinical investigations.

Some studies have shown the potential role of CT in predicting outcomes (Impact, Niejemein models)[13] considering the cortical sulci and the anterior cisterns. Other CT findings known as independent predictors of prognosis, such as midline shift or subarachnoid hemorrhage, were not used, since our main aim was to evaluate the amount of brain swelling and not the prognosis of an admission scale. We believe that the radiological scales to predict outcomes based on the admission CT findings were already adequately validated in different populations. However, these scales are not used in follow-up CT scans. For instance, there is no role of these validated scales on postoperative CT scans. As we aimed to evaluate the amount of brain swelling, we have also added the evaluation of the sylvian fissure/ambiens cistern.

The best result was found among neurosurgeons. This is probably related to the high number of TBI patients evaluated by the neurosurgeons and neurosurgery residents in everyday practice, as well as the extended time in which these professionals are responsible for monitoring these patients. The level of experience may also play a role and may have differentiated the results between the neurosurgeons and residents. However, we believe that, with proper training, it will be possible to obtain better results among different specialists. Considering the overall reliability of this scale, it may be used by different specialists who take care of TBI patients. The imaging features analysis may allow early identification of deterioration or improvement of brain swelling, which may be used as another tool when it's not possible to invasively measure the intracranial pressure. The diagnostic and prognostic value of the new scale should be further tested.

In the context of traumatic brain injury, the Rotterdam scale and the Marshall scale are useful tools that enable the gradation of trauma severity using imaging features, and they are equally useful to predict death in patients with TBI.[14] The last one is the oldest and most common scale used to classify TBI. The Rotterdam CT score is a radiological scale often used to analyze the status of the basal cisterns on the initial CT scan; one or two points are added if the basal cisterns are compressed or absent, respectively. Studies have shown that effacement of the basal cisterns is a potential prognostic predictor;[15] however, no data are available regarding the possible prognostic value of the sylvian fissure and cortical sulci status — which are now included in the new scale proposed here, which takes into account the basal cistern and also these two additional regions. Although not originally developed to be a scale to assess prognosis, high scores probably lead to a worse outcome, something that needs to be tested in future studies. Additional CT findings, such as hypointensities and signs of structural damages (hematomas, for instance, were excluded), were not taken into consideration.

The implementation of standardized trauma care protocols in the initial approach of TBI patients has shown to decrease mortality.[16] The existence of a scale that allows objective and longitudinal assessment of brain swelling in everyday neurointensive care is of major importance. None of the existing scales proposes such kind of longitudinal evaluation, which would be of great importance, especially in comatose patients without ICP monitoring. Critical care physician management of sedation weaning could be optimized and become safer using this brain swelling scale, which can be used in patients classified as Marshall I to III lesions and, although not tested, may also be used on postoperative CT scans. The objective of the present study, however, was not to find correlations between the imaging findings and the clinical status (Glasgow scales, clinical outcomes, etc.); rather, the present investigation sought to verify whether the evaluation could be done by professionals of different backgrounds. The beginning of a new investigation on the clinical usefulness of the new scale should be preceded by prior evaluation of the possible lack of interobserver agreement that would arise when professionals with different backgrounds would evaluate the same images. As shown in the present study, the agreement was moderate, and can possibly improve with proper training of some of the specialists.

One may argue that the present scale does not consider some relevant predictors, such as midline shift or presence of petechial lesions. However, the main purpose of this scale is to allow the comparison of tomographic features within the same subject, mainly in patients in whom it is not clear whether the brain swelling is ameliorating or worsening. Moreover, the presence of specific hematomas or midline shift is already a clear tomographic feature that can require surgical treatment or an emergency clinical treatment. For example, considering a patient with an acute subdural hematoma with midline shift, the decision of surgical treatment can be easily defined. However, in coma patients with Marshall II lesions at admission, not monitored by ICP, the decision on whether to maintain or not the sedation is not straightforward. Therefore, the proposed scale may assist clinical decisions in these patients. Of course, the longitudinal evaluation of such a scale should be tested in properly designed studies.

There are a few limitations in our study. First of all, our sample size is small, although it has been enough to show that the scale may be feasible to assess in the clinical setting. Second, we proposed a new scale among many other radiological scales already available and well-established, which might be confusing for the professional dealing with emergencies. However, the proposed scale may be used in every CT scan, making comparison feasible between the imaging studies. Third, the groups of physicians did not receive a formal training to use the scale, only individual guiding prior to the evaluations, which was simple and not standardized. Therefore, our findings indicate that the overall agreement may possibly be increased by properly planned training, with registering of the time taken for evaluations.

Finally, a definitive outcome, such as mortality or prognosis in 6 months, was not assessed. An assessment of prognosis could definitely stratify the degree of swelling in mild, moderate or severe, for instance. However, our main objective was achieved, since the findings about the scale reliability were statistically significant and represent preliminary data of a prospective study we intend to conduct, which will address these issues.

Conclusions

The scale proposed in the present study showed moderate overall reliability and a substantial agreement in the evaluations of the neurosurgeons. The overall reliability of the scale is acceptable for the daily practice in the emergency rooms and ICUs. The highest reliability strength was found among neurosurgeons, and the lower among the intensivists. The scale seems to be feasible to be applied, especially in patients whose intracranial pressure is not monitored by an implantable catheter. The importance of this scale relies on the idea that CT scans are widely available, even in low income countries, where ICP monitoring is costly. Further studies assessing the impact of formal training of the clinicians on the overall agreement and assessing the association of the scale results with clinical outcomes and prognosis are essential.

Conflicts of Interests

The authors have no conflicts of interest to declare.

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Disorders of Consciousness: Practical Management in an Emergency Room

Distúrbios da consciência: Abordagem prática na sala de emergência

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Abstract

Lowering of the level of consciousness is a very common presentation at the emergency room, often without any history that helps finding an etiology. This emergency requires quick empirical measures to reduce neuronal mortality, with additional protection against sequelae. According to the Advanced Cardiac Life Support (ACLS) guidelines, there are current emergency neurological support protocols, such as the Emergency Neurological Life Support (ENLS) created by the Neurocritical Care Society. The present paper shows how to approach unconscious patients, highlighting possible etiologies and proposed treatments.

Keywords

- coma
- coma in emergency room
- reversible causes of coma
- ascending reticular activating system
- consciousness and coma
- brainstem

Resumo

O rebaixamento do nível de consciência é uma situação frequente na sala de emergência, muitas vezes sem qualquer história prévia que auxilie no esclarecimento etiológico. Trata-se de uma situação de emergência que exige medidas empíricas imediatas no intuito de reduzir a mortalidade neuronal com proteção adicional à zona de penumbra. A exemplo do preconizado pelo Suporte Avançado da Vida Cardiovascular (SAVC), atualmente estão disponíveis os protocolos de suporte neurológico de emergência (ENLS, na sigla em inglês) preconizados pela Neurocritical Care Society. O presente artigo apresenta os princípios gerais no manejo inicial do paciente com rebaixamento do nível de consciência, destacando as suas possíveis etiologias e seus tratamentos propostos.

Palavras-chave

- coma
- coma na sala de emergência
- causas reversíveis de coma
- sistema reticular ativador ascendente
- consciência e coma
- tronco encefálico

Introduction

Coma is an unconsciousness state defined by the inability to respond to external stimuli, in which the patient remains unaware, ignorant of the self and of other people. Didactically, consciousness has two components: the level and the content of consciousness. The level of consciousness (also referred as arousal) reflects the most primordial central nervous system (CNS) structures belonging to the reptilian brain from the MacLean model, represented by the brainstem and by the

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diencephalic structures (the thalamus and the hypothalamus), collectively referred to as the ascending reticular activating system (ARAS). The content of consciousness concerns higher cortical functions, such as gnosis, praxis, memory, learning, reasoning, and orientation in time and space, and it is represented by the neocortex. Therefore, coma represents the involvement of the brainstem and/or of any diencephalic structure, which are primordial for maintaining arousal.[1–3] Variations of the classic coma are described and collectively referred to as disorders of consciousness: minimally conscious state, vegetative state, hypersomnia, abulia, and akinetic mutism. The minimally conscious state is characterized by content impairment and unconsciousness, with some preservation of awareness of the self and of the environment. The vegetative state occurs when the comatose patient presents sleep-wake cycles, with autonomic control (including respiratory drive), and spontaneous ocular opening, but deep unconsciousness of the self and of the environment. These two situations refer to bilateral cortical lesions or to extensive lesions affecting the cortical connectivity. Hypersomnia consists in excessive sleepiness or fatigue during the day, and is primarily idiopathic or results from structural or metabolic changes. Abulia is a decrease in initiative along with apathy; it can occur after frontal lobe damage, and it may evolve with akinetic mutism.[4–8] In the clinical practice, many patients arrive at the emergency room with a lower level of consciousness: the patient may be disoriented, sleepy, obtunded (sleepy and disoriented), apathic, or already comatose. Since there are many possible causes for this clinical picture, the clinical history and a proper physical examination are fundamental to establish an etiological diagnosis. The physician should be aware of possible acute causes that require emergency procedures to reduce their morbidity and mortality.[1] Huff et al recommend an algorithm for the management of comatose patients in the emergency room based on the conventional algorithms Advanced Cardiac Life Support (ACLS) and Advanced Trauma Life Support (ATLS), called Emergency Neurological Life Support (ENLS). This algorithm, like the traditional ATLS and ACLS protocols, guides emergency professionals and intensivists on the critical measures to be adopted as priorities for the treatment of patients with acute neurological injury.[2,9]

Objectives

The author describes the current knowledge on the physiology of the level and content of consciousness, as well as the pathophysiology of unconsciousness, including coma, highlighting its major etiological factors, both acute and reversible at the first emergency room visit, following an emergency approach protocol to acute neurological injuries.

Methodology

A quantitative and descriptive research was performed per a narrative literature review in the Latin American and Caribbean Literature in Health Sciences (LILACS) and in the National Library of Medicine (PubMed) databases in May, 2016, using the following descriptors: *coma*, *emergency room*, *intensive care*, *consciousness*, *brainstem*, and *ascending reticular system*. The following combinations were used in the search: *coma in emergency room*, *reversible causes of coma*, *consciousness and coma*, and *ascending reticular system and brainstem*.

The present study asks the following question: how to correctly manage the patient in a coma at the emergency room?

The inclusion criteria for papers were updated publications from the period between 2001 and 2016, with rare exceptions, in Portuguese and English, and with online access to the full text. As exclusion criteria, in addition to papers that did not comply with the inclusion criteria, duplicate papers were eliminated.

For the analysis of the papers included in the present review, the following aspects were observed: year of publication, journal, place of study, methodology used, and main results.

Development

Pathophysiology of the lowering of the level of consciousness. Consciousness is a complex of neuronal interconnections involving cortical, subcortical, and deep nuclei areas, influenced by inhibitory and excitatory neurotransmitters. The ARAS, located in the brainstem, is responsible for the maintenance of the level of consciousness, and it consists of several nuclei in the brainstem, in the thalamus, and in the hypothalamus. The content of consciousness is represented by the cerebral cortex, as already mentioned. Moruzzi et al, in 1949, were the first to describe the ARAS, using experimental brainstem transections in cats. After midbrain lesions, the animals were unable to maintain their level of consciousness, becoming comatose (►**Fig. 1**).[10]

Brainstem. The structures related to the maintenance of the level of consciousness are the raphe nuclei, the locus coeruleus, the reticular formation, the pars compacta of the substantia nigra, the ventral tegmental area, and the mesopontine tegmentum, which includes the tegmental pedunculopontine nucleus and the laterodorsal tegmental nucleus. The dendrites of these neurons form true integrative networks between the afferent and efferent synaptic outflow. Unsynchronized discharges to the cerebral cortex, alternating low and high amplitudes, are responsible for maintaining the level of consciousness with the possible expression of its content. Physiologically, when the structures of the brainstem, of the hypothalamus, and of the thalamus synchronize their electrical discharges to the cortex, with slow waves of higher amplitude, the level of consciousness is reduced.[11,12] The cholinergic system acts at the entire cerebral cortex both during wakefulness and rapid eye movement (REM) sleep. These neurons stimulate directly the cerebral cortex and inhibit the reticular nucleus of the thalamus (responsible for slow-wave sleep induction), leading to a desynchronization of the cortical waves. Cholinergic activity, in turn, promotes cortical activation by stimulating glutamatergic, noradrenergic, serotonergic, and histaminergic neurons present in the ARAS structures. Gamma-aminobutyric acid (GABA)ergic neurons also

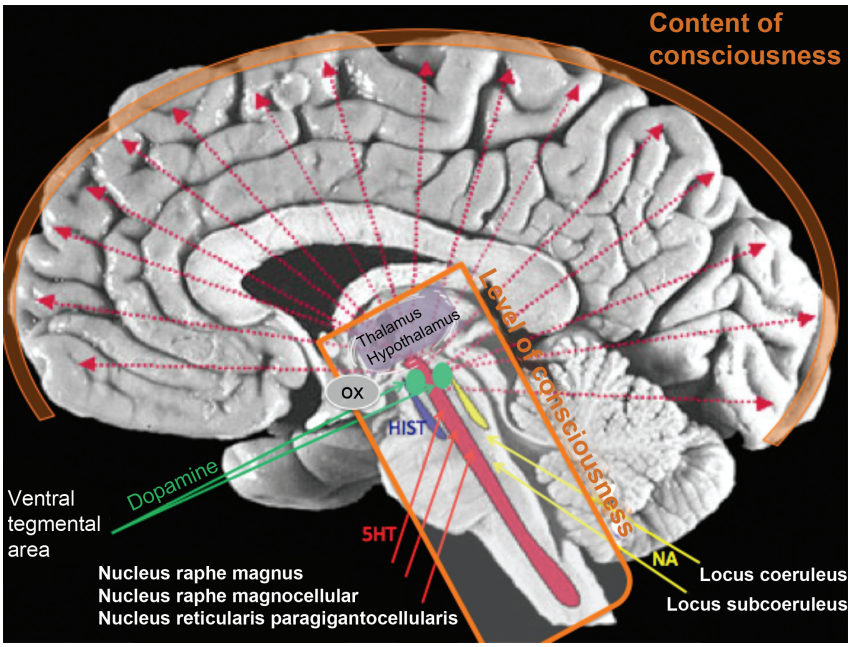

Fig. 1 Structures responsible for the content and level of consciousness. The content of consciousness requires the functioning of the cerebral cortex, which cannot generate the level of consciousness. The latter depends on subcortical structures, such as the hypothalamus and the thalamus, as well as the brainstem. Abbreviations: 5HT, 5-hydroxytryptamine (serotonin); HIST, histamine (arising from the tuberomammillary nucleus); NA, norepinephrine; OX, orexin (present in the hypothalamic periventricular nucleus).

project themselves together with cholinergic fibers through thalamic irradiation, promoting ascending disinhibition and neuronal activation. Lesions in the ventral tegmental areas and in the substantia nigra present with akinesia with no impairment of the cortical activation.[11]

Posterior Hypothalamus. This heterogeneous region, composed of histaminergic, dopaminergic, glutamatergic, and GABAergic neurons, is associated with neuropeptides such as orexin, enkephalin and substance P, and it has a great influence on the wakefulness process. During the influenza epidemic in 1918, Von Economo[11] described lesions in the posterior and in the anterior hypothalamus, respectively, associated with hypersomnia (including drowsiness and coma), and insomnia. Recently, a hypothalamic-cortical projection system, deemed responsible for maintaining the level of consciousness, has been described. Histamine and the neuropeptide orexin have great relevance in this arousal-activating mechanism. Histamine acts on its H1 receptor, activating the Gq/11 protein, causing depolarization with sodium and calcium influx; on its H2 receptor, β-adrenergic receptor and 5HT2, it activates Gs protein (adenylate cyclase-coupled), increasing the expression of the cAMP response element binding protein (CREB) transcription factor; and on its H3 receptor (a self-receptor coupled to a Gq protein and to high-voltage calcium channels), it is responsible for the negative feedback to the production and release of histamine itself (►**Fig. 1**). The excitatory neurotransmitter for orexinergic neurons is glutamate, and their inhibitory neurotransmitter is dynorphin.[11–14]

Some CNS lesions may compromise the structures responsible for the maintenance of arousal, such as traumatic brain injury (TBI), intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), ischemic stroke, and global hypoxic-ischemic brain injury. In ICH, arousal is often preserved at the beginning of the clinical picture; however, as the hematoma expands, the level of consciousness is impaired. If the origin of the ICH affects the infratentorial space, the risk of impaired consciousness is higher, due to anatomical reasons. In the supratentorial space, the bleeding affecting the medial thalamic nuclei often results in unconsciousness. Lobar lesions that deviate the midline will compromise the level of consciousness by compression of thalamic nuclei, of the brainstem, and/or of thalamic projection structures. In SAH, either traumatic or spontaneous, the intracranial pressure increases abruptly, whereas the cerebral perfusion pressure is reflexively reduced, resulting in swelling, transient ischemia, and cytotoxic edema. Subarachnoid hemorrhage can indirectly damage the hypothalamus. Indirect hypothalamic lesions (due to increased intracranial pressure and/or to vascular lesions) reduce orexin (hypocretin) levels, resulting in unconsciousness. It is not uncommon for SAH survivors to present changes in the wake-sleep cycle, including excessive daytime fatigue. In ischemic stroke, unconsciousness is not common, except in cases involving correlated structures. The decreased level of consciousness results from cerebral edema with midline deviation due to already mentioned factors. A malignant infarction of the middle cerebral artery classically presents with a major cerebral edema; decompressive craniectomy is commonly indicated, reducing its mortality by up to 50%.[1] Lastly, the global hypoxicischemic brain injury is due to brain hypoperfusion, often following prolonged cardiorespiratory arrest. Neuronal damage starts within 2 minutes of cerebral blood hypoperfusion. Some structures

are more sensitive to hypoxia: the hippocampus (CA1 and CA4 regions); pyramidal cells from layers 3, 5 and 6; the amygdaloid complex; the cerebellar worm; the caudate nucleus; and the brainstem nuclei. The reticular nucleus, the intralaminar nuclei of the thalamus, and the medial geniculate nucleus are particularly sensitive to ischemia. The return of the spontaneous circulation causes reperfusion injury. Several components of the anaerobic metabolism may damage neurons, including free radicals, extracellular glutamate causing excitotoxicity by calcium influx, changes in glial morphology, and astrocytic activation by increased levels of proinflammatory interleukins and tissue necrosis factor α.[4,15,16]

Reversible causes of lowered level of consciousness. There are innumerable possible causes of lowered level of consciousness, and some of them can be immediately reversed with emergency intervention. As already mentioned, the three major mechanisms responsible for disorders of the level of consciousness are: structural brain lesions, diffuse neuronal dysfunctions (resulting from various metabolic conditions that may compromise neuronal function), and, rarely, psychiatric causes. Except for the latter, the other mechanisms will somehow involve the ARAS and its connections, the diencephalic structures (the hypothalamus and/or the thalamus) and/or the cerebral cortex (►**Table 1**). After immediate clinical stabilization, which will be described later, the emergency physician or intensivist should consider the reversible causes of coma and actively try, even if initially empirically, to reduce the neurological damage.

Clinical management in the emergency room. The proposed creation of an algorithm for the management of the critical neurological patient in the emergency room follows the model of the traditional algorithms of the American Heart Association, namely ATLS and ACLS. It is a sequence of emergency measures for rapid diagnosis and prompt therapy, minimizing secondary neurological lesions. The 1st 60 minutes are critical for the neurological patient, and there are rare times when a neurologist and/or neurosurgeon are available in the emergency department within that time frame. In this context, the Neurocritical Care Society develops algorithms for the care of critical neurological patients.[17]

The neurological examination is the 1st step in evaluating patient with a lowered level of consciousness in the emergency room. The Glasgow coma scale was described in 1974, and it has been widely used in these situations.[18] In 2005, however, a scale called Full Outline of UnResponsiveness (FOUR) was published to better evaluate intubated patients, and it includes an evaluation of brainstem reflexes, not considered by the Glasgow scale (►**Fig. 2**). The examination of the motor and ocular functions indicates the neurological prognosis; the ocular examination seems to have a better predictive value compared with the motor examination. The absence of pupillary reflexes following cardiorespiratory arrest, for example, represents a very poor prognosis. Oculovestibular and oculocephalic reflexes also have prognostic values. The electroencephalogram (EEG) value was also studied and associated with the prognosis for neurological damage: the presence of periodic and/or generalized epileptiform discharges, generalized suppression patterns, lack of activity, or even the presence of alpha and theta waves in coma represent a worse prognosis. Somatosensory evoked potentials (SSEP) with identification of cortical N20 response after median nerve stimulation were studied: the absence of the N20 response represents a higher mortality, while a slow N20 response is associated with a persistent vegetative state and brain death. It is, therefore, a good predictor of coma prognosis; however, there are some disadvantages, including the need for specialized professionals to perform and interpret the test; electrical interference; and the required exclusion of subcortical, medullary and/or peripheral lesions that may affect cortical response. Biomarkers of neural glial lesions are now available, including a neuron-specific enolase and S100B protein. In diffuse axonal lesions, the elevated levels of these markers in 72 hours are predictors of a worse prognosis.

Proposed Algorithm for Comatose Patient Approach: Emergency Neurological Life Support

In emergency medicine, the patient is classified as comatose when he presents closed eyes, preserved reflexes, and reduced or absent response to external stimuli (►**Fig. 3**). The level of responsiveness, as well as its response pattern, is assessed by the examiner and graded by the Glasgow coma scale and by the FOUR scale.[19] Verbal and tactile-painful stimuli are performed to elicit the response of the patient. The attempt to open the eyelids of the patient is a simple and effective test; the arm drop test on the face is often used. The recommended protocol for these patients includes the initial stages of ACLS and ATLS resuscitation (cervical stability, airway viability), the assessment of respiratory rate, oxygen saturation, heart rate, and blood pressure, the establishment of one or two large-bore venous access to immediately draw blood samples for serum biochemistry analysis, blood sugar level, toxicology (including alcohol), coagulation profile, electrolytes (mainly sodium and calcium), arterial blood gases, urine and cultures.[1] If an orotracheal intubation (OT) is required, it should be performed with adequate analgesia, sedation, and neuromuscular paralysis (when indicated). There are four classic indications for OT in neurological lesions: (1) respiratory failure confirmed by oximetry (with caution regarding methodological limitations), arterial blood gas analysis and/or cyanosis; (2) inability to ensure a safe airway (absence of protective reflexes); (3) severe clinical injury with cardiopulmonary function compromise; (4) failure of noninvasive methods, such as catheters, masks, and noninvasive ventilation (NIV). Ideally, a rapid and objective neurological examination should be performed prior to the administration of sedative, hypnotic, and/or neuromuscular paralytic agents. The level and content of consciousness, the function of the cranial nerves, motor limb activity, deep osteotendinous tonus and reflexes, convulsive activity, cervical stability, and sensory level

Table 1 Some brain lesions caused by mass effect and classified as structural versus diffuse neuronal lesions

Structural brain injury	Usual treatment	Comments
Brain tumor, mass effect	Neurosurgery and corticosteroids	Intracranial pressure reduction
Status epilepticus	Anticonvulsive drugs	Sedation and induced coma may be required
Central nervous system infections, sepsis	Antibiotics, steroids and abscesses drainage	Immediate empirical treatment
Intracranial hypertension	Elevate head bed, hyperosmolar solution, hyperventilation, corticoids	Intracranial pressure monitoring should be considered
Subdural and extradural hematoma	Neurosurgical drainage	Multimodal monitoring
Intracranial hemorrhage	Neurosurgical hemostatic therapy, drainage, blood pressure control	Clinical and vascular research: angiography
Ischemic stroke	Thrombolytic therapy	Clinical and vascular research
Hydrocephalus	Ventriculostomy with drainage	Acetazolamide: inhibitor of cerebrospinal fluid production
Brain edema	Decompressive craniectomy	On a per case basis
Cerebral venous thrombosis	Anticoagulants	Etiologic search: contraceptive use, Leiden factor V mutation, prothrombin gene mutation, immune and rheumatologic markers
Diffuse neuronal lesions	Usual treatment	Comments
Hypoglycemia	Hypertonic glucose 50%, intravenously	Clinical emergency!
Hyperglycemia, DKA, HHS	Hydration and insulin therapy	Search for precipitating factor
Hyponatremia	Sodium replacement: always with 3% NaCl: 3 mEq/3 h + 9 mEq/21 h	Investigate other electrolytes
Hypercalcemia	Hydration, furosemide, intravenous bisphosphonates, calcitonin, dialysis	Investigate precipitating causes: PTH, paraneoplastic syndrome, lymphoma
Renal failure	Dialysis	Investigate cause
Hyperammonemia	According to etiology	Hepatic failure: high lactate level, hypoglycemia, coagulopathy
Hepatic failure, hepatic encephalopathy	Lactulose, mannitol, vitamin K or FFP, prophylactic antibiotic therapy, flumazenil	Head CT: cerebral edema; protein restriction: 1.0-1.5 g/kg/day via NET
Thyrotoxicosis	Beta-blockers, PTU, inorganic iodine, dexamethasone	Etiological investigation
Myxedema coma	Hormonal replacement: levothyroxine + hydrocortisone	Perform associated hydric and electrolyte corrections and correct hypothermia
Hypocortisolism (Addisonian crisis)	Hydration + steroid therapy	
Wernicke encephalopathy	Thiamin (vitamin B1)	Associated with thiamine-free glucose replacement in alcoholism
Serotoninergic syndrome	Benzodiazepines	Consider neuromuscular paralysis
Cholinergic poisoning	Atropine, pralidoxime	Poisons, organophosphates, carbamates
Opioids	Naloxone	Caused by morphine, heroin, phenylethyl, tramadol
Benzodiazepines	Flumazenil	Suicide attempts with diazepam, lorazepam, alprazolam

Abbreviations: DKA, diabetic ketoacidosis; HHS, hyperosmolar hyperglycemic state; FFC, fresh frozen plasma; PTH, parathyroid hormone; PTU, propylthiouracil; NET, nasoenteral tube.

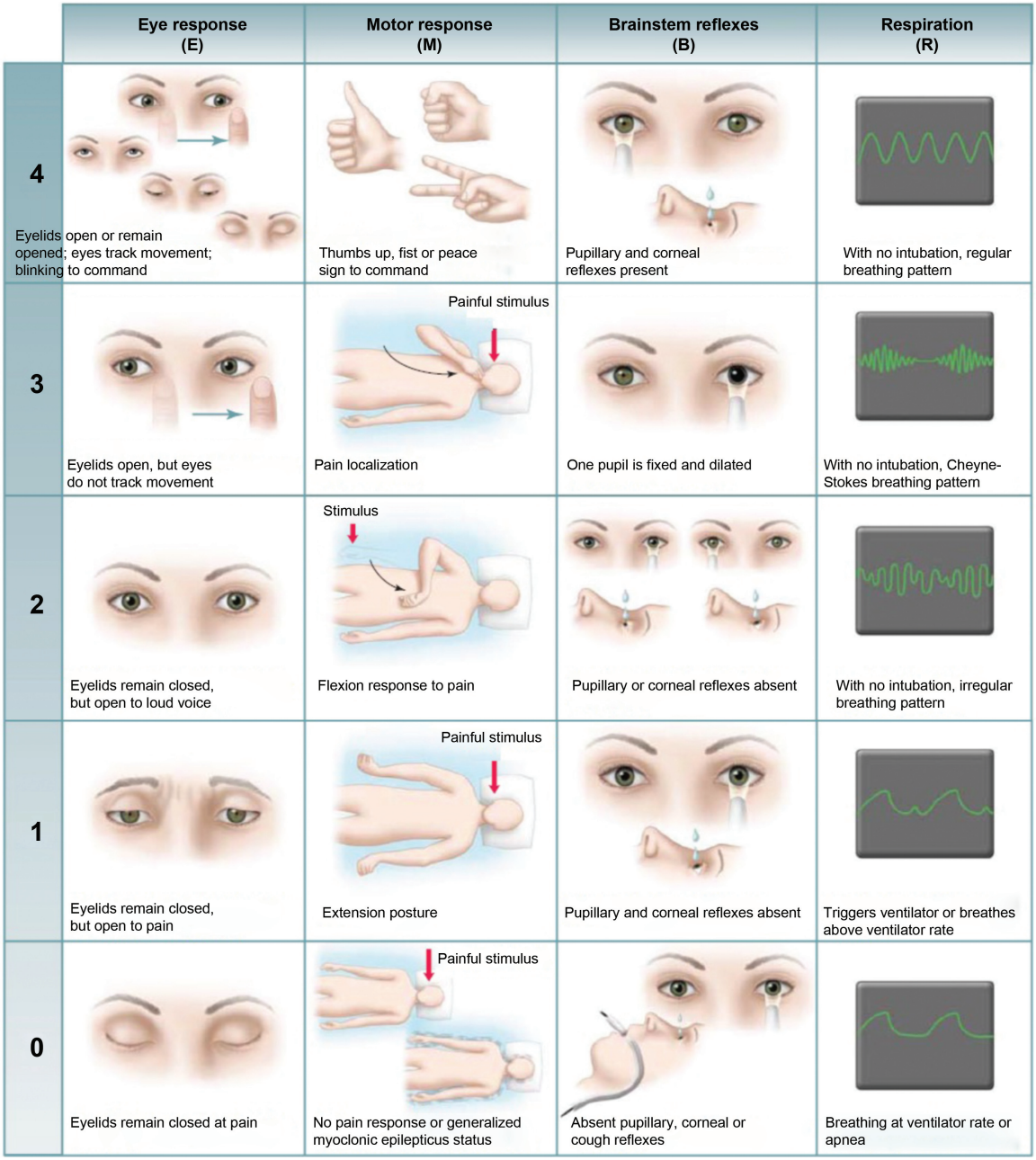

Fig. 2 FOUR (Full Outline of UnResponsiveness) coma scale.

should be evaluated in cases with suspicion of spinal cord injury. The rapid intubation sequence is the method of choice for cases with suspicion of intracranial hypertension, reducing the risk of its reflexive increase (mediated by the autonomic sympathetic nervous system) during laryngoscopy. The presence of coma is not an indication for the nonuse of hypnotic and analgesic agents. Even a comatose patient may present laryngoscopy reflexes that increase the intracranial pressure due to a higher neuroendocrine and immunological response. The mean arterial blood pressure (MAP) and the intracranial pressure (ICP) should be carefully controlled to maintain the cerebral perfusion pressure (CPP) ~ between 60 and 70 mm Hg.[20,21]

Three preintubation medications can prevent the increase of the ICP: lidocaine (1.5 mg/kg intravenously [IV], administered 1 minute before OT); fentanyl (2-3 µg/kg IV, administered 30 seconds to 1 minute prior to OT), but it must be avoided in hypotensive patients; and esmolol (1-2 mg/kg IV, 3 minutes before OT), which acts as a short-term β-blocker for heart rate and blood pressure control during OT, but which it is rarely used due to coexistent hypotension. The hypnotic agents recommended due to their little interference with ICP are etomidate (0.2-0.4 mg/kg IV), which promotes sedation and neuromuscular relaxation without hemodynamic damage (this is the hypnotic of choice in cases with increased ICP); propofol (0.5-3.0 mg/kg IV), despite its potent vasodilator effect; and thiopental (3 mg/kg IV), which is considered a brain protective agent for reducing the basal cerebral metabolic rate and the fraction of oxygen extraction by brain tissue, diminishing the ICP (however, it has a

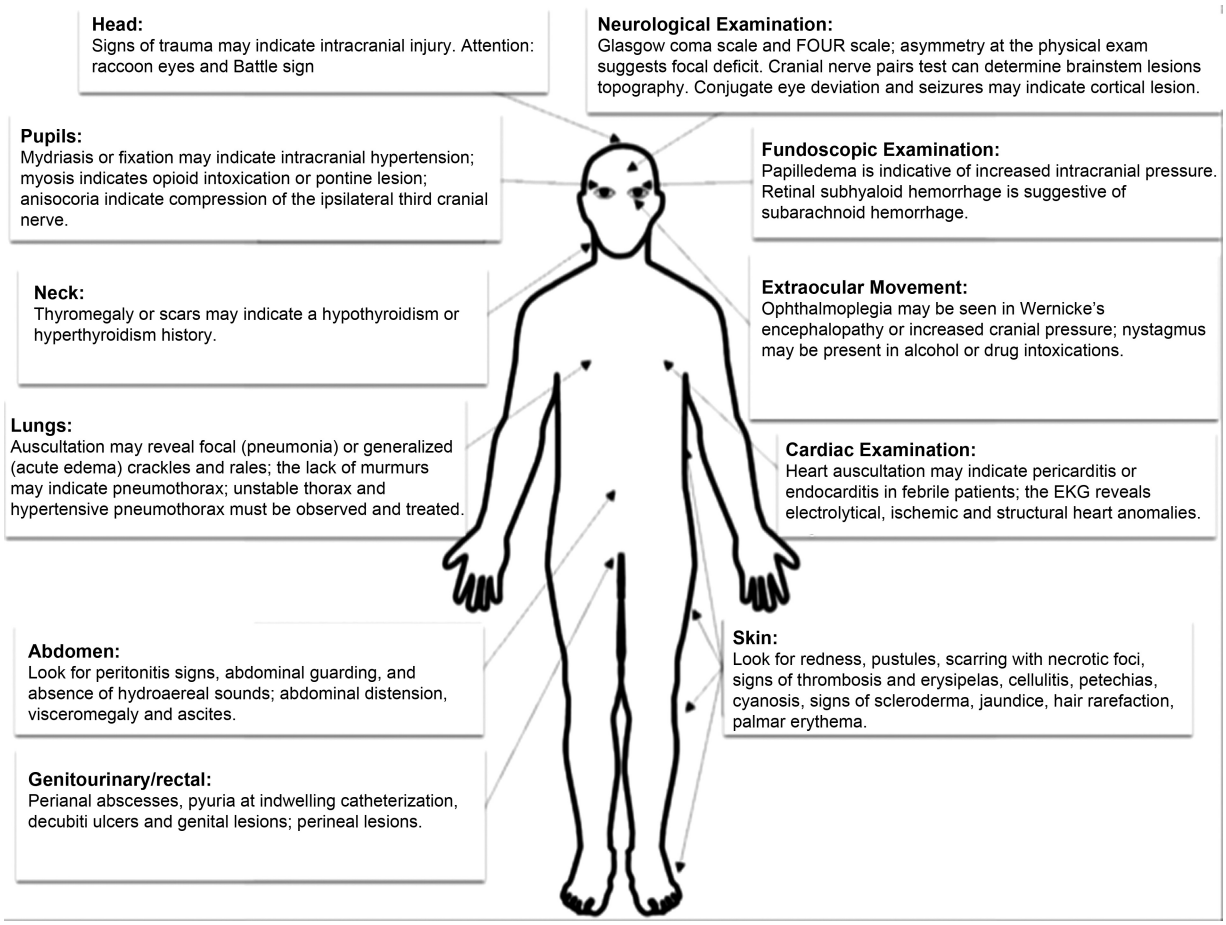

Fig. 3 Physical examination of the comatose patient in the emergency room. Modified from Han et al.[27]

negative inotropic effect and is a venous dilator with major hypotensive potential). Ketamine (0.5-2.0 mg/kg IV) is also a good option in cases with increased ICP with little influence over the hemodynamic pattern. Succinylcholine (1.0-1.5 mg/kg IV) is the depolarizing neuromuscular blocking agent of choice in patients with elevated ICP. Even though there are reports of slight ICP increases, the very short half-life of succinylcholine does not appear to impair nerve cells. However, studies have shown that patients with brain injuries, spinal cord injuries, major atrophies, and prolonged immobility are more susceptible to succinylcholine-induced hyperkalemia. In such high-risk patients, the use of non-depolarizing neuromuscular blockers, such as rocuronium (0.5-0.6 mg/kg IV), and vecuronium (0.2 mg/kg IV), seems to be a good alternative.[22–26]

Immediately after the bedside determination of the capillary blood sugar level, if it is < 70 mg/dL, 40 mL of hypertonic glucose at 50% should be infused intravenously. If there is suspicion of alcohol intoxication or a history of use, malnutrition or a history of bariatric surgery, the emergency physician should administer 100 mg of thiamine IV. The suspicion of opioid intoxication should be based on unconsciousness with bilateral miotic pupils, and the empirical IV administration of 0.4-2.0 mg naloxone (with a maximum dose of 4 mg) is indicated. The "coma kit", including naloxone, atropine, flumazenil and thiamine, is not indicated without the proper assessment of the patient for clinical signs warranting its use. The electrocardiogram (EKG), performed on arrival, can provide indications about the cause of unconsciousness: electrolytic changes, ischemia, arrhythmias, and structural heart diseases can be diagnosed at this first ECG. At the neurological examination, asymmetry findings strongly suggest focal lesions, while symmetry suggests lesions due to metabolic causes. The neurological evaluation of the patient in coma should follow four steps: (1) level of consciousness (Glasgow coma scale and FOUR scale); (2) brainstem reflexes (oculocephalic and oculovestibular maneuvers, cranial pairs test with pupil evaluation); (3) motor assessment (spontaneous, reflexive, or induced by painful stimuli); (4) evaluation of the respiratory pattern, which is important to determine the topography of the lesion (a Cheyne-Stokes pattern suggests supratentorial lesions; neurogenic hyperventilation suggests mesencephalic lesions; apneustic pattern suggests pons lesions; ataxic breathing suggests medulla oblongata lesions).[27]

A brief clinical history may be obtained from family members, from bystanders, or from the prehospital care team. Some history features are strongly suggestive of the coma etiology: sudden onset (suggesting a vascular etiology, seizure, or drug overdose); tumor history (suggesting metastasis); hemorrhagic disorders (suggesting ICH, subdural hematoma, SAH); hypercoagulability states (suggesting dural sinus thrombosis);

assisted seizures and gradual worsening to coma (suggesting tumoral or inflammatory diseases).[27]

At that time, neuroimaging is a fundamental part of the assessment: structural lesions are potentially treated with an early neurosurgical approach and should be diagnosed as soon as possible. A computed tomography (CT) scan of the skull without contrast medium is the test of choice due to of its great availability, low cost, and fast execution; however, it requires hemodynamic stability. Focal hypodensities suggestive of stroke, ICH, SAH, brain edemas, herniations, and acute hydrocephalus are readily diagnosed. In the infectious hypotheses, CT scans with and without contrast medium can be useful in the exclusion of cerebral abscess, of extra-axial collections, of hemorrhagic transformations, and of hydrocephalus, even before lumbar puncture. Comas due to non-structural lesions include hypoxicischemic encephalopathy, sepsis, epilepsies, metabolic alterations, endocrinopathies, toxins, and drugs. More specific lesions – including white matter involvement, neoplasms, posterior fossa and brainstem lesions – are better investigated by more accurate methods, such as magnetic resonance imaging (MRI) of the brain, magnetic resonance angiography, and digital angiography. In the hyperacute phases of the ischemic stroke, a brain MRI with diffusion will be diagnostic, since the skull CT will not show lesions.[1,2]

In undetermined cases, a lumbar puncture may aid the diagnosis. Infections, inflammation, neoplasms, demyelinations, and autoimmune diseases can be diagnosed by a cerebrospinal fluid (CSF) analysis. If a status epilepticus is suspected, an EEG should be requested[2] (►**Fig. 4**).

Some neuroprotective therapies are advocated in cases of lowered level of consciousness. With the current knowledge about neuroanatomic structures corresponding to the level and content of consciousness, the patient in coma, in vegetative state, and in minimally conscious state may benefit from some clinical measures. Therapeutic hypothermia has been used in the last 10 years in patients who have undergone cardiopulmonary arrest and, to date, is the only truly effective neuroprotective measure. Hypothermia is known to reduce the inflammatory process, decreasing the production of reactive oxygen species, excitotoxicity, apoptosis, and neuronal death. Amantadine inhibits N-methyl-D-aspartate (NMDA) channels, preventing calcium influx. In addition, amantadine is a dopaminergic agonist in the cortical regions related to attention and arousal, showing benefits in the recovery of patients who evolved to a permanent vegetative or minimally

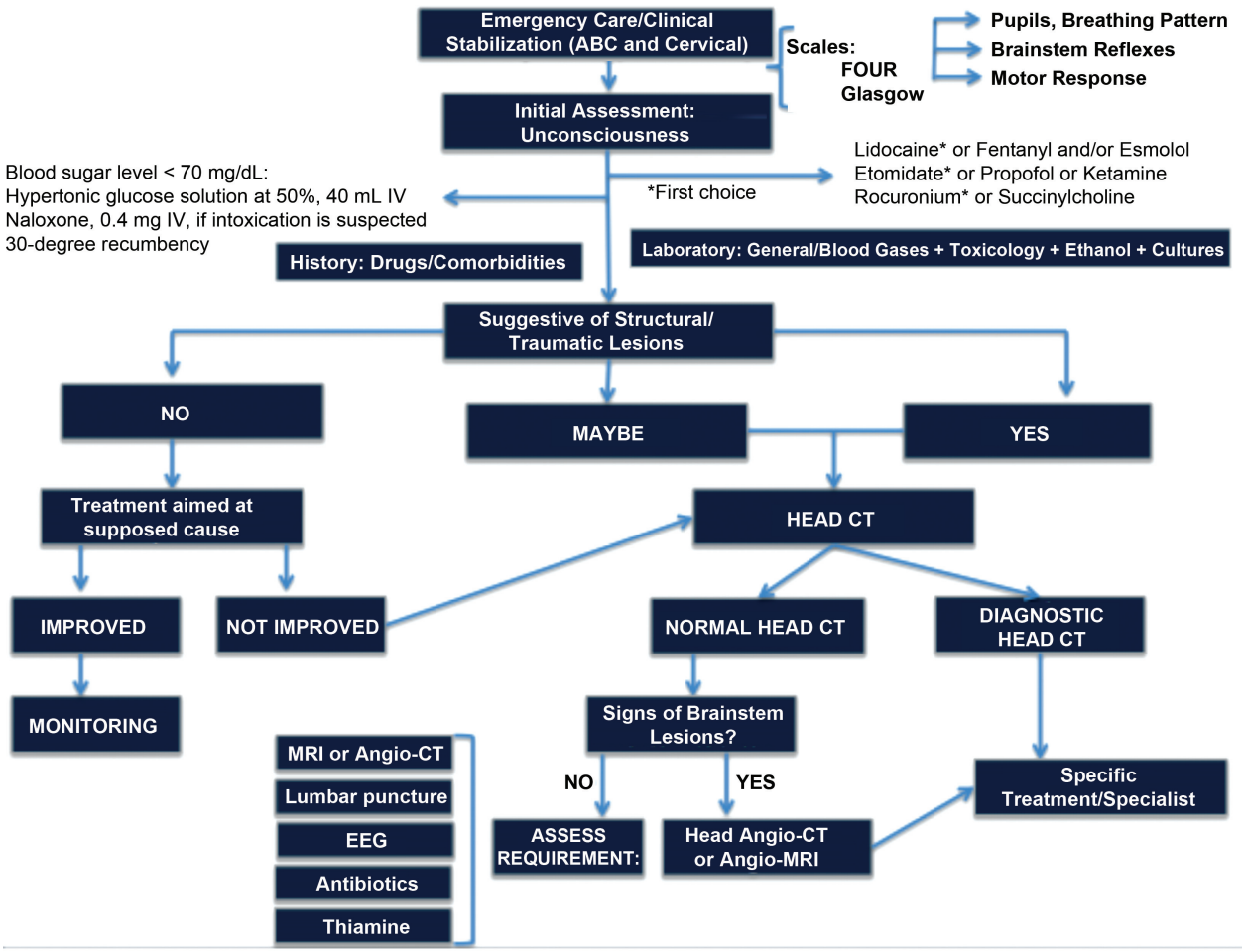

Fig. 4 Algorithm recommended for the initial care of the unconscious patient. Abbreviations: Angio-CT, angiography by computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging. Source: adapted from Edlow et al and from Huff et al.[1,2] Source: Adapted from Han et al.[27]

conscious state. Methylphenidate, an amphetamine, is a noradrenergic and dopaminergic stimulant, acting on the prefrontal cortex. Some studies show that the administration of methylphenidate to patients with severe TBI reduces the length of stay in the intensive care unit (ICU) and the hospitalization period. Modafinil (an orexin agonist), zolpidem (a GABAergic agonist) and baclofen (a GABAergic agonist) resulted in improvement of some persistent vegetative states; however, no randomized, multicenter, prospective, double-blind study has been conducted to date, and only empirical measurements based on the individual observation of some centers are available.[4,28]

Conclusions

Lowering of the level of consciousness (coma status and its variants) is one of the main causes of emergency room admission. Its diverse etiological possibilities associated to the absence of clinical history, very common in this scenario, are a challenge to the emergency physician. However, initial measures should be promptly instituted according to an established protocol, based on ATLS and ACLS. Some steps recommended by the ENLS, in order to not aggravate a potentially reversible lesion, may increase the time for an investigative work on a clearer etiological definition.

Conflicts of Interests

The author has no conflicts of interests to declare.

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Spinal Cord Electrical Stimulation for Refractory Angina Treatment

Estimulação elétrica da medula espinal no tratamento da angina refratária

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Abstract

Cardiovascular disease (CVD) is the main cause of death worldwide, including in Brazil. Angina pectoris is a challenging disease because its clinical manifestation is not always related to the degree of obstruction. Visceral pain from any source can be totally disabling. It influences all aspects of the life of a patient and it can be one of the main causes of absence from work and of family disruption. Spinal cord electrical stimulation (SCES) has been traditionally applied for the treatment of neuropathic pain, with good to excellent results. Visceral pain syndrome can be as debilitating and disabling as somatic or neuropathic pain; however, there seems to be a lack of consensus on the appropriate treatment and strategies for these disorders. The major difference of SCES for visceral pain, compared to postlaminectomy syndrome or to regional complex syndrome, is the number of stimulated dermatomes. In most viscera, the somatotopic arrangement has two to four medullar levels, sometimes requiring laterality. After reviewing the literature, we have concluded that SCES is now a viable, low-risk option with satisfactory results for the treatment of neuropathic and visceral pain; therefore, it can be used in refractory angina after the failure of standard therapy. However, further studies are required to increase the application and efficacy of this procedure in the clinical practice.

Keywords
- functional neurosurgery
- visceral pain
- chest angina
- angina pectoris
- unstable angina
- spinal cord electrical stimulation

Resumo

A doença cardiovascular (DCV) é a principal causa de morte em todo o mundo, inclusive no Brasil. A angina do peito permanece como entidade clínica desafiadora devido ao fato de sua manifestação clínica nem sempre estar relacionada com o grau de obstrução. A dor visceral de qualquer origem pode ser totalmente incapacitante. Ela influencia todos os aspectos da vida de um paciente, podendo ser uma das principais causas de interrupção das

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atividades laborais e da estrutura familiar. A estimulação elétrica da medula espinal (EEME) tem sido tradicionalmente aplicada para o tratamento de dor neuropática apresentando de bons a excelentes resultados. A síndrome de dor visceral pode ser tão debilitante e incapacitante quanto as dores somáticas ou neuropáticas; no entanto, parece haver uma falta de consenso sobre o tratamento adequado e as estratégias para estes transtornos. A grande diferença na estimulação medular para a dor visceral, em comparação com a síndrome pós-laminectomia ou com a síndrome complexa regional, é o número de dermátomos a serem estimulados. A grande maioria das vísceras tem somatotopia de dois a quatro níveis medulares, algumas das vezes necessitando de lateralidade. Após uma revisão da literatura, conclui-se que a EEME é hoje uma opção viável, de baixo risco e com resultados satisfatórios para o tratamento de dores de origem neuropática e visceral, portanto, passível de utilização na angina refratária, sendo indicada após a falha da terapia padrão. Porém, ainda há necessidade de mais estudos para maior empregabilidade e eficácia do procedimento na prática clínica.

Palavras-chave
- neurocirurgia funcional
- dor visceral
- angina de peito
- angina pectoris
- angina instável
- estimulação elétrica da medula espinhal

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, including in Brazil.[1] Data provided by the World Health Organization (WHO) show that CVD accounted for $\sim$ 17 million deaths in 2011 (or 30.4% of all deaths in that year).[2] In Brazil, according to data from the Department of Health, CVD accounted for 28.6% of all deaths in the country in 2011, and data from 2008 reported that circulatory system disorders were responsible for 80.2% of the hospitalizations of people $>$ 50 years old and for 10% of hospitalizations for all causes.[3] Most deaths due to CVD are related to coronary artery disease (CAD) or to ischemic heart disease.

The most important heart diseases presenting with chest pain are ischemic heart diseases (stable angina, unstable angina, acute myocardial infarction) and noncardiac diseases (pericarditis, acute aortic and valvular dissection).[4] It is estimated that between 5 to 8 million individuals with chest pain or with other symptoms suggestive of acute myocardial ischemia are seen in emergency rooms in the United States every year.[5]

Stable coronary artery disease, whose main clinical manifestation is angina pectoris, is characterized by reversible episodes of imbalance between blood supply and myocardial metabolic demand, usually inducible by physical exercise, emotion, or other types of stress; eventually, these episodes may be spontaneous.[6]

The various stable angina clinical presentations are related to several pathophysiological mechanisms, including: (1) epicardial coronary arteries obstruction by atherosclerotic plaques; (2) focal or diffuse vasospasm of coronary arteries; (3) microvascular disease; and (4) left ventricular dysfunction secondary to a previous myocardial infarction and/or to hibernating myocardium (chronic ischemia). Several of these processes can coexist in the same patient, contributing to the diversity of clinical manifestations associated with CAD.[6]

Angina pectoris remains a challenging clinical entity because its clinical manifestation is not always related to the degree of obstruction, being different in each patient, which results in a variety of clinical presentations: from completely asymptomatic to classical angina exertion-associated symptoms, refractory angina pain, and even sudden death.[4]

Visceral pain from any source can be totally disabling. It influences all aspects of the life of a patient and it can be one of the main causes of absence from work and of family disruption.[7]

The goal of chronic pain treatment is to improve quality of life; considering all of the aspects involved, this is a complex, arduous, and stressful task. When the goal is to improve viscerovascular pain, in addition to all of these adjectives, we can add challenging and laborious, since the pathophysiology is not fully understood yet.[8]

Treatment is always individualized, since its goal in an active and healthy patient is usually the complete elimination of pain and the return to vigorous physical activity. On the other hand, in an elderly patient with more severe angina and numerous associated comorbidities, a satisfactory result would be a reduction in symptoms, which would allow limited daily activities.[8]

The present paper searches for new techniques for pain control, reduction of suffering, and improvement of the quality of life for those with refractory angina.

Refractory Angina and Spinal Cord Electrical Stimulation

The classical chest pain in acute coronary syndrome is a painful, uncomfortable, burning or oppressive sensation located in the precordial or retrosternal region, which may irradiate to the shoulder and/or to the left arm, to the right arm, to the neck, or to the jaw, and it is often accompanied by diaphoresis, nausea, vomiting, or dyspnea. The pain may last for a few minutes (usually between 10 and 20 minutes) and relapse, as in cases of unstable angina, or about 30 minutes, as in cases of acute myocardial infarction.[5]

Chronic post-thoracotomy pain is a common condition, observed in 67% of the patients who underwent this procedure; according to Fabregat,[34] 38% of these individuals still

report pain > 3 years later. Most patients complain of mild to moderate pain, but > 5% describe it as severe and/or incapacitating. Several clinical studies report positive long-term results with neuromodulation to control this type of pain.

The etiology of post-thoracotomy pain, although not fully understood, is related to the mechanical trauma of chest opening, which directly damages nerve bundles. Moreover, there is a secondary injury to the thoracic vascular network. In addition, the existence of a visceral component in pain formation is confirmed in more than half of the cases.

Until recently, chronic visceral pain was characterized as somatic and nociceptive pain, and therefore, not amenable to treatment by spinal cord electrical stimulation (SCES). However, recent evidence indicates that chronic visceral pain may not be nociceptive, but rather neuropathic in nature.[9,10] The viscera have fewer nerve endings compared with the skin, and involvement is usually multisegmental. Refractory angina, which affects more than 6 million Americans, is an example of visceral pain.[11]

Traditionally, nociception passes through peripheral or first-order neurons (such as the celiac plexus) – which synapses with the second-order neurons from the dorsal horn of the spinal cord – and ascends through the lateral spinoreticular and/or the spinothalamic tract.[12]

In recent years, there have been important advances in angina treatment, both in pharmacological and reperfusion techniques (angioplasty or surgery). In 1999, the American Heart Association defined angina pectoris as a clinical syndrome characterized by discomfort in the chest, in the chin, in the shoulder, in the back, or in the arm, usually intensified by exertion or by emotional stress,[13] whereas refractory angina was defined according to the lack of control of painful symptoms even when the therapies previously described are associated.[14]

Spinal cord electrical stimulation has been traditionally applied for the treatment of neuropathic pain, with good to excellent results. Visceral pain syndrome can be as debilitating and disabling as somatic or neuropathic pain; however, there seems to be a lack of consensus on the appropriate treatment and strategies for these disorders.[10,15,16]

Neurostimulation is a revolutionizing functional surgery because it has modulatory purposes and low risk. Thus, it has been used to treat a variety of conditions, including regional complex syndrome, postlaminectomy syndrome, peripheral vascular disease, neuropathic pain, refractory angina and, more recently, visceral pain and chronic pelvic pain.[11] Moreover, several clinical studies report its effectiveness.

Although analgesic SCES was proposed by Shealy et al in 1967,[17] it was only in 1987 that Murphy et al[35] described the first case of refractory angina.[14,18] Several controlled studies have confirmed the efficacy of SCES in the control of ischemic pain, mainly in limbs, but they have also demonstrated the lack of statistical difference compared with amputation. Spinal cord electrical stimulation, however, provided pain relief, increased locomotion capacity, and improved overall limb function and quality of life.[19] Jivegard et al[36] demonstrated the benefit to 51 patients with severe inoperable limb ischemia, followed-up for 18 months, and found out that their amputation-free survival (62%) was higher compared with that of the control group (45%), with a statistically significant difference ($p > 0.05$).[19]

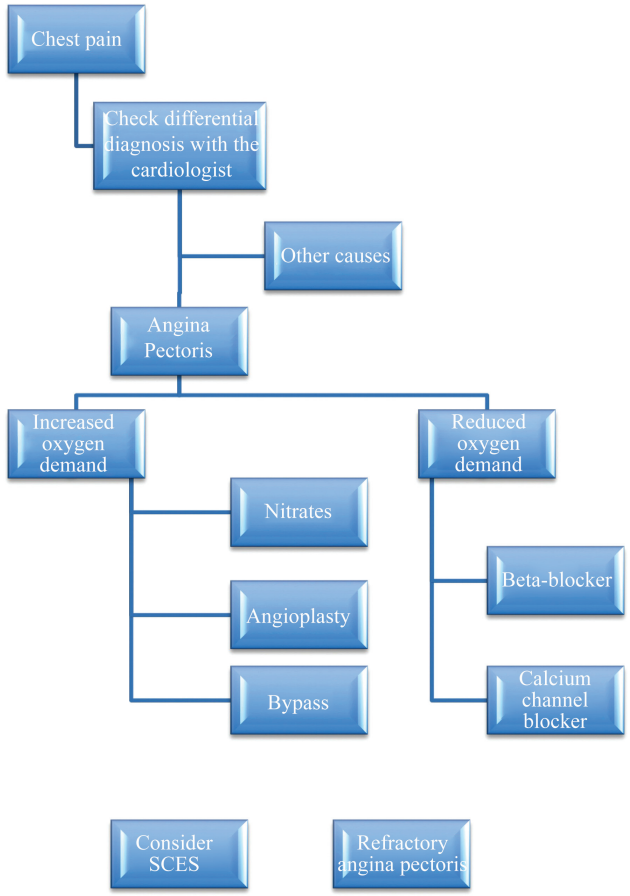

Fig. 1 Flowchart for the indication of spinal cord electrical stimulation (SCES) in patients with refractory angina.

In 2000, Ceballos et al were the first to use analgesic neurostimulation for visceral pain in a patient with chronic mesenteric ischemia-induced pain.[13] In 2004, Krames et al[20] reported a case of stimulation for irritable bowel syndrome.

Pain management in refractory angina was investigated by two prospective randomized studies about SCES.[9,14] The results demonstrated a better ability and quality of exercise in the group submitted to SCES compared with the control group.[21,22]

A prospective, randomized, comparative study between SCES and myocardial revascularization with 104 patients and a 5-year follow-up period performed by Mannheimer et al[37] demonstrated that angina symptoms and quality of life improved in both groups; however, mortality was higher in the revascularization group.[23,24] Today, its effectiveness is considered under category 2B + .[24]

The flowchart below may help in cases of refractory angina and the best indication for SCES in these patients[24] (►**Fig. 1**).

In Brazil, SCES is indicated mainly for complex regional syndrome and postlaminectomy syndrome cases. Mekhail et al[11] demonstrated the incidence of SCES in 707 patients, as shown in the graph below (►**Fig. 2**).

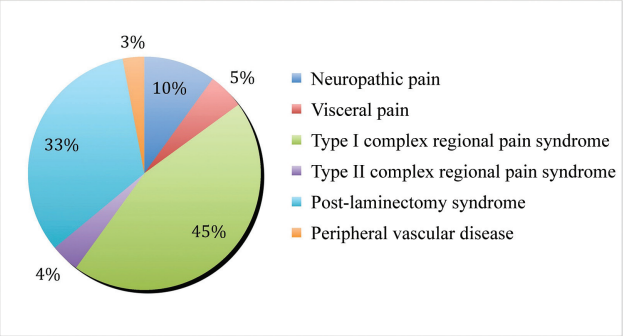

Fig. 2 Incidence of indication of spinal cord electrical stimulation (SCES). Source: Mekhail et al., 2011.[11]

Clinical Example

W. M., 61 years old, male, with a history of ischemic heart disease since 2011 and 2 acute myocardial infarctions (AMIs). After the ischemic events, he presented with angina and, despite extensive therapy, pain control was unsuccessful. The patient underwent two angioplasty procedures and a coronary artery bypass grafting with three saphenous conduits, resulting in the same outcome.

In order to reduce pain, a new angioplasty was performed, this time with a drug-coated stent; however, the pain persisted.

The three catheterizations reports are the following:

June 27, 2012:

1. Right coronary artery with a severe, 80% lesion in its medial third (intrastent restenosis).
2. Right coronary artery posterior descending branch with a moderate, 50% ostial lesion.
3. Anterior descending artery with a severe, 90 to 95% ostial lesion.
4. First diagonal branch (moderate significance) with a subocclusive, 95% ostial lesion.
5. Second diagonal branch (significant) with a moderate, 50% lesion at its proximal third (intrastent restenosis).
6. Circumflex artery with a subocclusive (98%) ostial lesion (intrastent restenosis).

October 4, 2012:

1. Right coronary artery with a severe, 80% lesion in its medial third (intrastent restenosis).
2. Anterior descending artery with a severe, 90 to 95% ostial lesion.
3. First diagonal branch (moderate significance) with a severe, 90% ostial lesion.
4. Second diagonal branch (significant) with a moderate, 50% lesion at its proximal third (intrastent restenosis).
5. Circumflex artery with a subocclusive (98%) ostial lesion (intrastent restenosis)
6. Saphenous graft between the aorta and the marginal branches with no significant lesions.
7. Saphenous graft between the aorta and the posterior descending artery with no significant lesions.
8. Severe, 80% lesion at the anastomosis between the left mammary artery and the anterior descending artery.

January 5, 2013:

1. Right coronary artery with a severe, 80% lesion in its medial third (intrastent restenosis).
2. Anterior descending artery with a severe, 90 to 95% ostial lesion.
3. First diagonal branch (moderate significance) with a severe, 90% ostial lesion.
4. Second diagonal branch (significant) with a moderate, 50% lesion at its proximal third (intrastent restenosis).
5. Circumflex artery with a subocclusive (98%) ostial lesion (intrastent restenosis)
6. Saphenous graft between the aorta and the marginal branches with no significant lesions.
7. Saphenous graft between the aorta and the posterior descending artery with no significant lesions.
8. Patent left mammary artery anterior descending artery and stent with a good angiographical aspect.

After a new catheterization, no vascular lesion warranted the condition, and a functional analysis was initiated for pain control.

Thus, the patient was referred to the functional neurosurgery department of the Hospital Dilson Godinho, in Montes Claros, state of Minas Gerais, Brazil. The patient complained of a continuous, burning pain in a neuropathic pattern, worsening with physical exertion, in the anterior region of the left hemithorax; pain intensity, determined by the verbal numerical scale (VNS), ranging from 0 (absence of pain) to 10 (the most intense pain imagined by the patient), was rated as 5. The patient was being treated with atenolol, 50 mg, every 12 hours; Sustrate (propatylnitrate), 10 mg, every 12 hours; hydrochlorothiazide, 25 mg, once a day; Adalat oros (nifedipine), 30 mg, once a day; gabapentin, 600 mg, every 8 hours; nortriptyline, 25 mg, at night; and tramadol, 100 mg, when in severe pain.

The patient also reported that walking small distances, of < 100 m, caused his pain to change pattern, characterizing it as a sting with VNS $= 8$, and requiring frequent pauses.

After the psychological evaluation, which did not identify any psychical contraindication for the surgical procedure, it was decided to implant a medullary neurostimulator with a $5 \times 6 \times 5$ electrode (Medtronic, Minneapolis, MN, USA) at the T2 spinous process level.

The procedure was performed in August 2014. The electrode was placed in contact with the posterior aspect of the spine through a microlaminectomy, with a $\sim$ 6-cm skin access, 1 to 2 levels below the desired level.

After 2 months, the programming (35 Hz, 2.4 V, 60 milliseconds) had been reached and is sustained until now. A myocardial scintigraphy performed on February 02, 2015 showed normal conditions, with no ischemic and/or cicatricial lesions in the left ventricular myocardium.

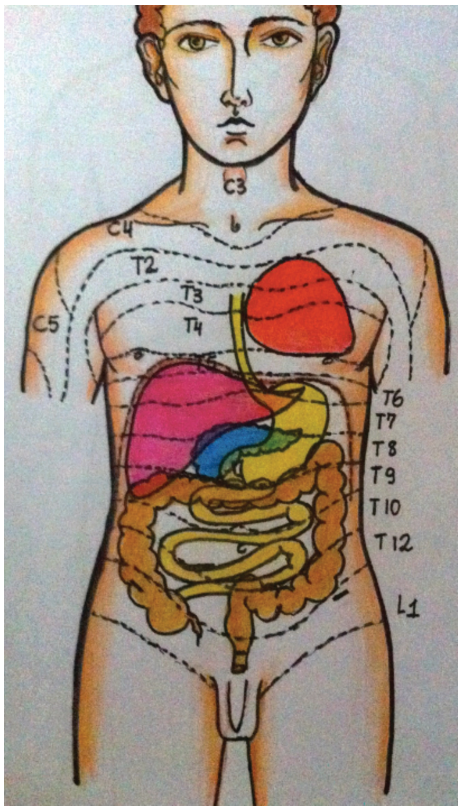

Fig. 3 This adapted figure[33] schematically represents the table above.

Table 1 Summary of organs and respective spine levels for spinal cord electrical stimulation

Target organ	Level	Note
Pancreas	T7/T8	Midline
Liver	T6 to T9	Midline or lateralized (right)
Stomach	T6 to T9	Midline or lateralized (left)
Ascending colon	T9 to L1	Midline or lateralized (right)
Transverse colon	T9/T10	Midline
Descending colon	T9 to L1	Midline or lateralized (left)
Heart	T2 to T4 (*C7 to T1)	Midline or lateralized (left)

*Some reports indicate that this level would be more efficient.[13]

Discussion

The major difference in spinal stimulation for visceral pain compared with postlaminectomy syndrome or with regional complex syndrome is the number of stimulated dermatomes. In most viscera, the somatotopic arrangement has two to four medullar levels, sometimes requiring laterality.

Since some electrodes have a size limiter, the positioning, the choice of material, and the correct case selection are critical to positive outcomes and patient satisfaction.

Visceral diseases are often manifested by secondary hyperalgesia in the dermatomes provided by the same spinal segments supplying the viscera. This hyperalgesia may involve all dermatomes or only a specific part.[25]

Latif[24] states that, pathologically, unstable angina does not correlate with the extent of previous coronary stenosis. The lesion results from the temporary formation of thrombus, which is mediated by a complex cascade of cellular interactions between the vascular endothelium and platelets in the atherosclerotic coronary artery,[26] leading to an imbalance between myocardial oxygen supply and demand that causes ischemia, injury, and, consequently, pain.[27]

Physiologically, SCES provides analgesia through its action on the segmental neuronal units of the spinal cord, leading to the antidromic excitation of the posterior funiculus fibers or nonspecific sensory conduction pathways of the spinal cord. Its activation causes a perception of paresthesia that is associated with the obtained analgesia.[8,28]

The beneficial effect of SCES on vascular pain and on peripheral ischemic pain is to promote the rebalancing of oxygen supply and demand, repairing and attenuating additional ischemic effects.[9,12] Increased stimulation levels, resulting from antidromic activation, activate the afferent fibers from the dorsal roots, leading to the peripheral release of nitric oxide and calcitonin gene-related polypeptide (PRGC), which produces cutaneous vasodilation.[21,29]

There is also an inhibition of wide-dynamic-range (WID) neurons, previously activated by the lesion, thus reducing their algiogenic action.[22] Some studies have shown that neuronal hyperexcitability is related to low GABA levels and that, after SCES, this neurotransmitter is normalized and the level of its excitatory analogue, glutamate, is reduced.[22]

Stimuli that do not generate a paresthetic effect may have a beneficial sympatholytic effect, better demonstrated in studies on refractory angina.[30]

Visceral pain treatment depends on a combination of pharmacological therapy with cognitive and behavioral therapies, as well as lifestyle changes. In addition, the pain secondary to low blood flow requires its restoration or improvement of oxygenation, which is not always possible with conventional surgeries.[9]

The use of transcutaneous electrical nerve stimulation (TENS) and of SCES for the treatment of type I complex regional pain syndrome (reflex sympathetic dystrophy) has been extensively documented. Because of this association between SCES and a sympathetically-mediated pain syndrome, SCES can be theoretically applied to the treatment of visceral pain, which is probably similarly mediated[7,16,25] (►**Fig. 3**).

►**Table 1** summarizes the target organs and the medullary level to be stimulated.

The rate of SCES complications ranges from 30 to 40%. Electrode migration is one of the most common complications, with an incidence of 13.2 to 22.6%.[7,31]

Electrode migration is defined as the displacement of its desired original location, and it is caused by mechanical stress, increased mobility (cervical region), inadequate surgical fixation technique, trauma, infection, and muscle spasm, and it results in the loss of effective stimulation. This complication increases the risk of infection at review surgeries, and it also increases costs.[7]

Dural fistula, headache, neurological deficit, medullary compression, hemorrhage, epidural fibrosis, system malfunction (considered by many the most frequent complication, with an incidence ranging from 20 to 25%), electrode or connection fractures are other examples of complications.[31–33]

Conclusion

Spinal cord electrical stimulation is now a viable, low-risk option with satisfactory results for the treatment of neuropathic and visceral pain and, therefore, it can be used in refractory angina. With this purpose, today SCES is indicated after the failure of standard therapy, resulting in significant pain control and in improvement of the quality of life. However, further studies are required to increase the application and efficacy of this procedure in the clinical practice.

Conflicts of Interests

The authors have no conflicts of interests to declare.

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Non-Invasive Intracranial Pressure Evaluation in an Emergency Room – Point-of-Care Ultrasonography

Avaliação não invasiva da pressão intracraniana em uma sala de emergência – ultrassonografia point-of-care

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Abstract

Point-of-care ultrasound is modifying conducts in emergency care. The various medical specialties, in addition to traditional indications in cases of multiple trauma, are using this technique for rapid diagnosis at the bedside without patient mobilization and without radiation. Point-of-care ultrasound in neurocritical patients, through its transorbital window, can estimate the intracranial pressure by a non-invasive method. Through the measurement of the diameter of the optic nerve sheath 3 mm posterior to the retina, the intracranial pressure is estimated if the value of the diameter is $>$ 5 mm, as it has been verified in other studies. The present article describes the most current data on this topic, and it also highlights the need for more multicentric and randomized trials to determine the correct cut-off points that represent the high sensibility and specificity of the method.

Keywords

- point-of-care ultrasound
- ultrasound in emergency room
- ultrasound in neurocritical patients
- optic nerve sheath ultrasound
- intracranial hypertension
- bedside point-of-care ultrasound

Resumo

A ultrassonografia *point-of-care* está modificando as condutas na sala de emergência. As diversas especialidades, além das indicações tradicionais ao politraumatizado, estão utilizando esta técnica para um rápido diagnóstico à beira do leito, sem a necessidade de mobilização do paciente e sem irradiação. Nos pacientes neurocríticos, a ultrassonografia *point-of-care*, através de sua janela transorbital, oferece uma técnica não invasiva para avaliação da pressão intracraniana. Por meio da medida do diâmetro da bainha do nervo óptico 3 mm posterior à retina, estima-se a pressão intracraniana se o valor desse diâmetro for superior a 5 mm, conforme verificado em alguns estudos. Este artigo apresenta os dados mais atuais sobre o tema, destacando, ainda, a necessidade de mais estudos multicêntricos, randomizados, para a correta determinação dos valores de corte que representem a alta sensibilidade e especificidade do método.

Palavras-chave

- ultrassom point-of-care
- ultrassom na sala de emergência
- ultrassom em pacientes neurocríticos
- ultrassom do diâmetro da bainha do nervo óptico
- hipertensão intracraniana
- ultrassonografia point of-care à beira do leito

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Introduction

For more than 50 years, ultrasound has been a safe and efficient method to make clinical diagnoses. Currently, the equipment has become smaller, more precise, cheaper, with immediate results, and without causing any trauma to the patient. Its use has spread to practically every great reference center. It has been included in the syllabus of medicine schools, and it has been considered "the stethoscope of the future." Point-of-care ultrasound is currently being used in emergency rooms in almost every medical specialty. Images are obtained ate the bedside instantly, and can be reproduced as many times as necessary, in real time, and recorded for posterior assessment, if needed.[1]

The concept for point-of-care ultrasound has been developed for non-radiology physicians who wish to use another diagnostic tool at the bedside, in a non-invasive, safe, and fast way. Up to date, the most prominent uses of this tool included: guided vascular access in emergency rooms and intensive care, thoracenteses, paracenteses, as well as for the assessment of the free liquid in cases of polytrauma, with the focused abdominal sonography for trauma (FAST), having been replaced for the extended focused assessment sonography for trauma (E-FAST), which includes a broader view, considering pulmonary and cardiac assessments, apart from the windows already adjusted on the FAST. In this new concept, lesions of the lungs, including hemothorax and pneumothorax, as well as aortic and cardiac lesions, can also be diagnosed. More recently, however, some questions that are common in emergency settings can be answered with point-of-care ultrasound, such as: what is the patient's volemic state? Should we use inotropic or vasoactive drugs? Does the respiratory insufficiency have pulmonary or cardiac origins? Is there indication for decompressive craniectomy? Is there any midline shift?[2–4]

Objectives

The goal of the present article is to describe the current knowledge on the use of point-of-care ultrasound to assess intracranial pressure measuring the diameter of optic nerve sheath through the transorbital window in critical patients.

Materials and Methods

The present is a descriptive and quantitative research that was performed through a literature narrative review on the Latin American and Caribbean Literature in Health Sciences (LILACS, in Portuguese) and the National Library of Medicine (PubMed) databases in July 2016, using the following descriptors: *point-of-care ultrasound*; *ultrasound in emergency room*; *ultrasound in neurocritical care*; *intracranial hypertension*; *optic nerve sheath*; and *optic nerve ultrasound*. The descriptors were combined for the search as follows: *point-of-care ultrasound* and *optic nerve sheath*; *point-of-care ultrasound* and *neurocritical care*; *point-of-care ultrasound* and *emergency room*; and *point-of-care ultrasound* and *intracranial hypertension*.

The study has as a guide the following question: can point-of-care ultrasound be used to assess intracranial pressure in a neurocritical patient?

The inclusion criteria were: updated publications mostly from 2001 to 2016, with rare exceptions, written in Portuguese, Spanish and English, with online access to the full text. Duplicate articles were excluded.

For the analysis of the articles included in this review, the following aspects were observed: the year of publication; the type of periodical; the place where the study was conducted; the methodology used; and the main results.

Development

Intracranial hypertension (IH) in the emergency setting. Intracranial hypertension (IH) is a frequent problem in emergency rooms and intensive care facilities, and in the case of an intracranial lesion, the recommendation is to maintain the pressure below 20–25 mmHg. The techniques currently available for this monitoring are invasive, with the introduction of an intraparenchymal and/or intraventricular catheter, with risk of hemorrhage and/or associated infections. Aa alternatives to the gold standard measurement, the invasive technique, there are options such as computed tomography (CT) of the brain or magnetic resonance imaging (MRI) of the encephalon, which will reveal indirect signs of IH with deletion of the cisterns of the base, deletion of the cortical grooves, loss of the interface between the white and gray matters, and midline deviation, but the accuracy of these imaging techniques is still uncertain. In this context, point-of-care ultrasound is shown to be a fast, reliable, safe and inexpensive method, which can be performed at the bedside. The sheath around the optic nerve is a continuation of the dura mater, reflecting the subarachnoid environment. The increase in intracranial pressure is immediately transmitted to the interior of the sheath that covers the optic nerve, promoting its distension, and, subsequently, papilledema. However, papilledema is a late event, which can take from hours to days to manifest, unlike its acute character, which can take seconds until the thickening of the optic nerve sheath. Point-of-care ultrasound can identify this distension in the optic nerve sheath starting from a prefixed distance from the retina, and it is an extremely useful tool in cases of cranioencephalic trauma, intracranial hemorrhages, and other brain lesions.[5]

Optical nerve anatomy. The optic canal, which is located on the lower wing of the sphenoid bone, receives the optic nerve (pair II of the cranial nerve) from the intraorbital region, bringing retinal afferences. This nerve is wrapped by a meningeal sheath consisting of the dura mater (pachymeninges), the arachnoid and the pia mater (both leptomeninges). Thus, the liquor content is also present in the subarachnoid space, reflecting its intracerebral pressure. The thickness of the optic nerve sheath directly translates the pressure of this liquor into the subarachnoid space, correlating directly to the measurement of the intracranial pressure.[4] The closer to the eyeball, the greater the meningeal distensibility found, and this establishes a dilation visualized through the ultrasound as having a bulbous aspect. While papilledema may take a period ranging

from days to weeks to appear, the distension of this bulbar region of the optic nerve sheath can be visualized almost instantaneously, in seconds, after the elevation of the intracranial pressure.[6,7] The first ultrasonographic description of the eyeball was performed in 1956 to estimate intracranial pressure in cadavers. However, the low quality of the equipment and the lack of methodology made its interpretation quite difficult. Only in 1996, with more sensitive equipment, it was possible to identify the dilation of the optic nerve sheath and its appropriate point of observation, at 3 mm posterior to the retina: this is the point most sensitive to ultrasound with the use of linear transducers.[4,7]

Ultrasonographic appearance of the optic nerve. At the transorbital ultrasound, the eyeball is visualized as round, darken (black) and full of fluid. The anterior chamber is anechoic and corresponds to the lens, while the iris is observed as bright or echogenic. The choroid and the retina are visualized as a thin greyish layer on the posterior face of the eyeball. The optic nerve reveals itself as a black band running out of the eyeball, in the posterior direction, and it is necessary to position it in the center of the ultrasound screen. The optic nerve sheath is visualized through the ultrasound with higher reflectivity, that is, it will be clearer compared with the nerve itself. Some authors describe the signs of dilation of the optic nerve bulb, 3 mm from the retina, as a sign of the crescent, indicating the presence of IH.[8,9]

Technique recommended to estimate intracranial pressure. Although there still is no universal consensus, some general principles should be observed for optimization and to be able to draw comparisons between professionals. The transducer used should be of linear high frequency (7–10 MHz), preferably with a good quality resolution equipment and viewing capacity of structures at depths of 5–6 cm. The examiner should apply gel on the closed eyelids, supporting his hand with the transducer on a rigid bone structure, to avoid pressure on the eyeball. Initially, the transducer will be placed in the transverse position, and will be slowly shifted to the parasagittal position; the optic nerve should be centered on the ultrasound screen, with concomitant visualization of the lens and iris; Both eyes should be evaluated in this exam. Once properly positioned, the image is frozen, and the transducer is removed from the eyelid; the examiner locates the spot 3 mm from the retina and assesses the diameter of the sheath of the optic nerve (►**Fig. 1**). The authors usually recommend that this measurement be made at least 2 or 3 times for greater reliability of the results. It is also important to emphasize that there is no greater precision in measurement made with the transducer positioned parasagittally (longitudinally) or transversally. The patient's head can be in horizontal ventral decubitus, or even in decubitus elevated at 20–30°.[2,5,7,10]

Reference values of the optic nerve sheath diameter and its correlation with intracranial pressure. The value of the diameter of the sheath of the optic nerve that can reflect intracranial hypertension is subject to debate, and has not yet been clearly defined in the literature. Based on the maximum normal value for intracranial pressure of 15 mmHg, with IH defined when this value is $\geq$ 20 mmHg, several authors believe that 5 mm of thickness for the sheath is a reasonable limit. However, many studies (with small samples) don't agree with this value: Rajajee et al[5] use

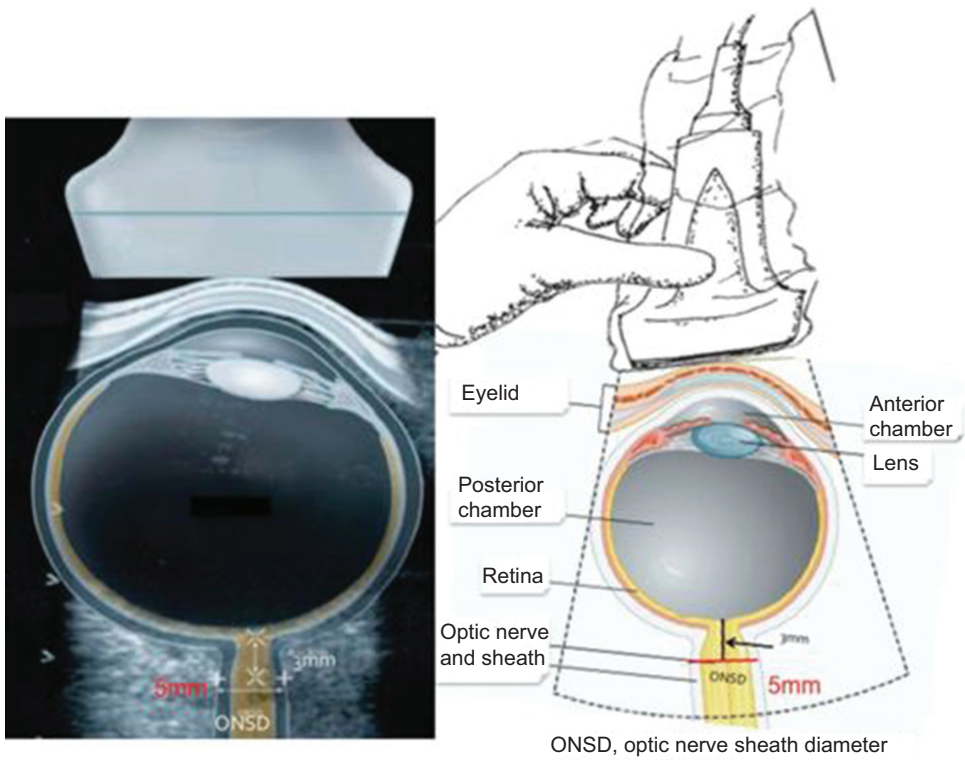

Fig. 1 Recommended technique to measure the diameter of the optic nerve sheath and anatomical structures of the eye and the nerve correlated with the ultrasound image.

Table 1 Studies that propose a cut-off point for the optic nerve sheath diameter that would best correspond to intracranial pressure > 20 mmHg, with their respective sensitivity and specificity

Study	Optic nerve sheath diameter	Patients (n)	Sensitivity	Specificity
Blaivas et al[10]	5.0 mm	35	100%	95%
Goel et al[17]	5.0 mm	100	98.6%	92.8%
Tayal et al[18]	5.0 mm	59	100%	63%
Kimberly et al[19]	5.0 mm	15	88%	93%
Moretti et al[20]	5.2 mm	63	94%	76%
Geeraerts et al[14]	5.9 mm	37	90%	84%
Soldatos et al[12]	5.9 mm	76	74.1%	100%
Shirodkar et al[21*]	4.8 mm	101	75%	100%
Wang et al[22**]	4.1 mm	279	95%	92%

Notes: Source: Adapted from Shevlin[7] and Ochoa-Pérez and Cardozo-Ocampo.[2] *Indian population. **Chinese population.

5.2 mm; Soldatos et al,[4] 5.7 mm; and Bäuerle and Nedelmann,[11] 5.8 mm. Shevlin[7] observed that the variation in the limit in the several studies to this moment is between 4.8 mm and 6.0 mm, which is a complicating factor to define IH. Several studies that proposed these different reference values cannot be compared, since they use different methodologies and were performed on different populations, making new prospective and multicentric studies directed to this end necessary. (►**Table 1**).[5,11–16]

Confirmation of IH through different ultrasound methods. The measurement of intracranial pressure by intraventricular catheterization is considered the gold standard method in the evaluation of IH. However, the risk of infection and hemorrhage is inherent to the procedure, as well as to the clinical status of the patient. The correlation between the increase in the diameter of the optic nerve sheath and the intracranial pressure measured by intraventricular catheter has not been well established, due to the aggressiveness of the procedure and the clinical condition of the patients. Rajajee et al[5] assessed 536 patients with intraventricular catheter and correlated the data with the diameter of the sheath of the optic nerve, finding a strong correlation between IH > 20 mmHg and a mean sheath diameter of 5.3 mm (5.1–5.7 mm), while intracranial pressure < 20 mmHg correlated to the mean of 4 mm in diameter of the optic nerve sheath ($p < 0.0001$). It is important to highlight that the authors did not find a statistically significant difference between patients submitted to mechanical pulmonary ventilation and those who did not intubate.[5] Neuroimaging criteria to confirm increased optic nerve sheath thickness (> 5 mm) findings were used and correlated with midline shifts (> 3 mm), ventricle III deletion, mass effect, hydrocephaly, and signs of early or late cerebral edema, and significant results, with 100% of sensitivity and 95% of specificity, were found when the cranial CT was used.[5,10] Ochoa-Pérez and Cardozo-Ocampo[2] emphasize that, in addition to the measurement of the optic nerve sheath diameter to estimate IH, a bone window performed through the temporal bone scale with a low frequency transducer (1–5 MHz) is able to detect the midline shift. The technique is essentially the same used in transcranial color Doppler, except for the fact that the structures are visualized in ultrasound B (brightness) mode. The compressions of the lateral ventricles and midline shifts resulting from ischemic vascular accidents, sub- and extradural hematomas, as well as hemorrhages from the basal nuclei, may be visualized. Shunts can be placed with the help of this technique. However, due to the interference of the bone, the authors report that, in ~ 15% of the cases, the images of the cerebral parenchyma are not satisfactory. In those undergoing decompressive craniectomies, the use of point-of-care ultrasound becomes an even more useful tool, with the area of absence of bone as the most appropriate window.[2,9]

Arguments in favor of and contrary to the use of the optic nerve sheath diameter for the evaluation of intracranial pressure. The advantages of using ultrasound at the bedside are: reproducibility, non-invasiveness, low cost, portability, rapid execution, absence of ionizing radiation, and possibility of performance without transfer of the patient out of the emergency room or intensive care unit. Among the factors considered to be disadvantageous, one can mention: lack of preparation of intensivist and emergency physicians in the use of point-of-care ultrasound at the bedside, which is a new technique; the need for a learning curve, since ultrasound is a technique dependent on the operator's ability; lack of reference values based on large prospective and multicenter population studies; relative risk of ocular globe injury due to excess pressure of the transducer on the patient's eyelid; risk of thermal injury by the absorption of the apparatus energy and heat transformation; and inability to use it in cases of suspicion of lesions of the eyeball.[4,7]

Conclusion

Point-of-care ultrasound is a reality in large, high complexity centers around the world. Its characteristics contribute to its dissemination: it is a low-cost exam, with good accuracy, fast, non-invasive, recommended for the non-specialist physician, with no ionizing radiation, and it can be performed at the bedside. Several medical specialties have been using point-of-care ultrasound, and neurology and neurosurgery

are no exception. The idea of estimating intracranial pressure using at the bedside a tool that is non-invasive and fast has been gaining space in emergency medicine. The transorbital window enables the visualization of the optic nerve sheath bilaterally, enabling the estimation of the intracranial pressure transmitted by the liquor to this structure. Its diameter measured 3 mm posterior to the retina seems to represent an intracranial pressure within the limits of normality when lower than 5 mm. However, there are still no large prospective and multicenter studies that validate these values. It is also not known for certain whether all intracranial injuries, in victims of polytrauma, may have the same reference value. Another possibility is through the transtemporal window, in which midline shifts, the size of the lateral ventricles, and the presence of hematomas can be observed. Despite the need for further studies to validate the reference values, point-of-care ultrasound in neurology is an extremely promising tool for neurocritical patients.

Conflicts of Interest
The authors have none to declare.

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Brain Concussion: New Classifications and Current Physiopathological Knowledge of the Disease

Concussão cerebral: Novas classificações e conhecimento fisiopatológico atual da doença

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Abstract

The present review paper aims to update the definition and classification of cerebral concussion, highlighting its pathophysiological mechanisms. The high prevalence of cerebral concussion in emergency rooms around the world makes it necessary to know its proper management to avoid its late sequelae, which traditionally compromise cognitive aspects of behavior. New evidence on potential neuroprotective treatments is being investigated.

Keywords
- concussion
- brain trauma
- concussion management
- axonal injury

Resumo

O presente artigo aborda, por meio de revisão bibliográfica, uma atualização acerca das novas definições e classificações da concussão cerebral, destacando seus mecanismos fisiopatológicos. A elevada prevalência da concussão cerebral nas salas de emergências de todo o mundo torna necessário o conhecimento do seu adequado manejo, a fim de se evitarem suas sequelas tardias, que tradicionalmente comprometem aspectos cognitivos do comportamento. Novas evidências sobre potenciais tratamentos neuroprotetores estão sendo investigadas.

Palavras-chave
- concussão
- traumatismo cranioencefálico
- manejo da concussão
- lesão axonal

Introduction

At the beginning of the 20th century, Joseph Babinski had already shown interest in understanding the injury mechanism of cerebral concussions in World War I soldiers. Later, Derek Denny-Brown tried to describe the physiopathology of concussion.[1] The clinical scenario was uncertain, often coursing with transient symptoms, not attributed to cerebral lesions. Currently, cerebral concussion is defined as a complex physiopathological cerebral process induced by external biomechanical forces that cause injuries. Originated by forces directed against the skull, face and/or neck, concussion typically results in rapid and transient neurological dysfunction, which resolves spontaneously and does not necessarily compromise the level of consciousness, as believed in the past. The symptoms of cerebral concussion are directly related to the intensity of the impact, reflecting functional and structural alterations. Until recently, no neuroimaging modality could "see" the brain

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injury caused by concussion. With the advent of tractography by magnetic resonance imaging, it was concluded that cerebral concussion compromises the integrity of the white matter.[2,3] There are many symptoms of cerebral concussion, and they may compromise the level of consciousness, motricity, somatic sensitivity, the vestibular system, the psychic apparatus, oculomotricity and vegetative functions. The symptoms may present hours or even weeks after the traumatic injury, which hinders the emergency room professionals from defining its severity at the time the patients arrive at the hospital.[2,4]

Currently, cerebral concussion is classified as possible, probable and defined. The lesion considered possible occurs when the patient has another clinical cause that better explains the symptoms and cannot be attributed to concussion as it was classically described. In this case, the injury mechanism cannot be clearly established. The symptoms include headache and fatigue during physical activities, which can be attributed to dehydration, migraine, hyperthermia or viral infections. In the lesions considered probable, the symptoms are no longer well explained by other causes than cerebral concussion, but there is presence of comorbidities, such as migraines, sleep disorders, anxiety, mood disorders and attention deficit hyperactivity disorder (ADHD). Finally, in the defined form, the symptoms can only be explained by cerebral concussion.[5]

Epidemiologically, over the last decades, there has been an increase in the prevalence of concussions in emergency rooms. In the United States, the prevalence is around 128/100,000 people.[6] In the pediatric age group, the estimated incidence is around 304 cases for every 100,000 children, being higher in children between the ages of 5 and 9 years and in males.[7] In the past 10 years, the incidence has increased by 200%, and this is largely attributed to the concussions resulting from playing sports, including football, soccer, hockey, martial-arts and general contact sports.[8,9]

Objective

The present article describes the clinical management of cerebral concussion in the emergency room, taking into account the current concepts regarding its definition and classification, including the physiopathology of the injury.

Materials and Methods

A quantitative and descriptive research through a systematic review of the literature was conducted in the following databases: the Latin American and Caribbean Literature on Health Sciences (LILACS, in Portuguese), the National Library of Medicine (PubMed), the Scientific Electronic Library Online (SciELO), the Cochrane Library and the Excerpta Medica Database (EMBASE) in the month of July 2016. The following descriptors obtained from the medical subject headings (MeSH) were used: *concussion*; *brain concussion*; *concussion management*; *concussion and brain trauma*; *traumatic brain injury*; *axonal injury*; and *concussion in an emergency room*.

The following question guided the study: considering the new definitions and classifications for cerebral concussion, how should it be managed in the emergency room to avoid its chronic consequences?

The inclusion criteria for the research were: updated publications from 2000 to 2016, written in Portuguese, Spanish and English, with access to the full text online. Duplicate articles were eliminated.

For the analysis of the articles included in the present review, the following aspects were observed: year of publication, type of periodical, place where the study was performed, methodology used, and main results.

Development

Injury Mechanism

Concussion is a brain injury triggered by a biomechanical mechanism described in the 20th century. The brain suffers a process of abrupt acceleration and deceleration, in the anteroposterior plane, often associated with rotational movements, colliding against the internal board of the skull, maintaining a relatively fixed point, the brainstem. The most recent studies have observed that in this closed traumatic mechanism there are electrophysiological alterations (compromising neuronal activity) in the ascending reticular activating system (ARAS) and in the diencephalon (►**Fig. 1**).[10]

Physiopathology: Neurometabolic Cascade

The animal models of moderate cranioencephalic trauma (CET) have revealed biochemical alterations compatible with cerebral concussion. The elucidation of the neurometabolic cascade involves cellular bioenergetic, cytoskeletal, and axonal alterations, neurotransmission impairment, delayed cell death, and chronic functional impairment.

Physiopathology of Cerebral Concussion: Acute Stage

Ionic influx and excitotoxicity. In the acute stage of the lesion, there are neuronal influxes of glutamate, calcium and sodium with potassium efflux, observed after the traumatic injury of the plasma membrane. Postconcussion syndrome is marked by a wave of cellular depolarization followed by a phenomenon similar to cortical spreading depression.

Alteration in cerebral blood flow self-regulation. Immediately after the concussion, there will be a reduction in cerebral blood flow, which may take days to normalize. The relative hypoxia occasioned will initiate the process of neuronal excitotoxic damage. The mechanism of reduction of blood flow comprises the loss of brain self-regulation sensitive to trauma, compromising the hypothalamic functions, leading to cellular energetic imbalance associated with sympathetic dysautonomia.

Energy crisis. In an extremely early postconcussion stage, there is an increase in energy consumption by ionic pumps, with relative reduction in the cerebral blood flow, resulting in an uncoupling of energy, that is, an imbalance between supply and cellular energy demand. Calcium influx is the most common and lasting ionic disorder, and is attenuated by mitochondrial calcium sequestration. However, this "blockade" will result in mitochondrial impairment regarding its oxidative metabolism. After this stage of initial hyperglycolysis with energy decoupling, the glycolytic metabolism will be

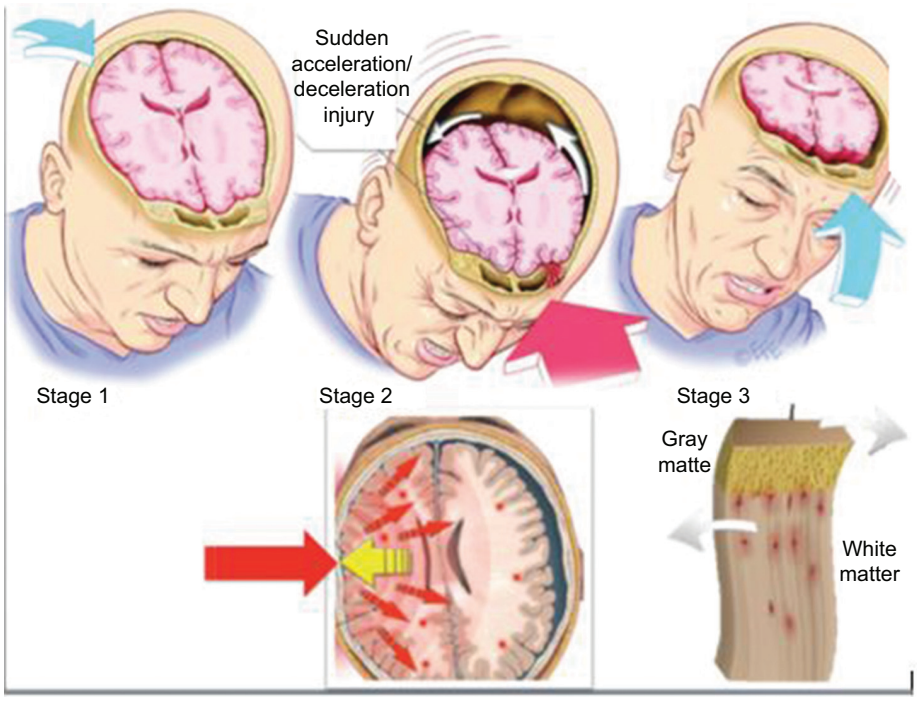

Fig. 1 Injury mechanism attributed to cerebral concussion. Note that there is an acceleration provided by an external force that closes instantaneously before a bulkhead (collision); however, the nervous tissue remains accelerated, colliding against the inner board of the skull, slowing abruptly, and performing a movement contrary to the initial one. At this moment, the heavier gray matter performs its movement slower compared with the white matter, promoting shearing, that is, the stretching of the nerve fibers.

compromised (hypometabolism) for ~ 7 to 10 days after the trauma.

Cytoskeletal injury. Biomechanical forces directed against neuronal and glial structures course with intra-axonal calcium inflow, neurofilament collapse and axonal integrity loss, compromising the anterograde and retrograde molecular flow.

Axonal dysfunction. The lesions to the microtubules and axonal neurofilaments can disrupt the cellular connections, evolving with complete functional loss. Recent studies have shown that non-myelinated axons are more susceptible to traumatic injuries, especially in the corpus callosum region. In the brain still under development, repeated traumatic lesions to the white matter often result in cognitive impairment.[11]

Neurotransmission impairment. After traumatic injuries, alterations are observed in the subunits of the N-methyl-D-aspartate (NMDA) receptors, resulting in reduction in their electrophysiological, cognitive, and memory consolidation capacity. In animal models, several patterns of calcium inflow are observed, resulting in the activation of genes and phosphorylation that will modify the calcium/calmodulin-dependent signal transductions of protein kinase II (CaMKII), the extracellular signal-regulated kinase- (ERK), the cyclic adenosine monophosphate response element binding (CREB) protein, and the brain-derived neurotrophic factor (BDNF). The imbalance in the binomial excitation-inhibition is also associated with the loss of gamma-aminobutyric acid (GABAergic) interneurons, reflected by the drop in the glutamic acid decarboxylase (GAD67) marker (precursor of GABA synthesis) in the region of the amygdaloidal complex. The postconcussion clinical manifestations associated with anxiety and posttraumatic stress disorder seem to be able to reduce this inhibition promoted by GABA.

Cerebral inflammation. After a moderate traumatic injury, there is activation of proinflammatory genes with microglia infiltration. When analyzed microscopically, the black substance of the mesencephalon has intense inflammatory activity, with excitotoxicity mediated by glutamate, corroborating with the physiopathological mechanism of posttraumatic Parkinson disease. The attenuation of the neuroinflammatory mechanism has been the target of several therapeutic proposals, since there is an increase in proinflammatory interleukin (IL), such as IL-6, tumor necrosis factor α (TNFα) and IL-1β, and several substances are being tested, such as: lithium, N-acetylcysteine and minocycline, all with promising results.[12–14]

Cell death. Cell death is a final phenomenon in the process of traumatic brain injury observed in cerebral concussions, especially in recurrent lesions. It is not yet clear the exact moment when acute concussion injuries become chronic: hippocampal atrophies and loss of dopaminergic neurons, clinically manifested in the form of cognitive deficit, persistent headache, sleep disorders and reduction in concentration are observed (►**Fig. 2**).[15,16]

Physiopathology of Cerebral Concussion: Chronic Stage

The aspects regarding the chronification of the lesions associated with cerebral concussion are related to recurrent traumas. Studies with professionals who play contact sports reveal that successive, recurrent traumas are responsible for neuronal degenerative lesions, including the accumulation of

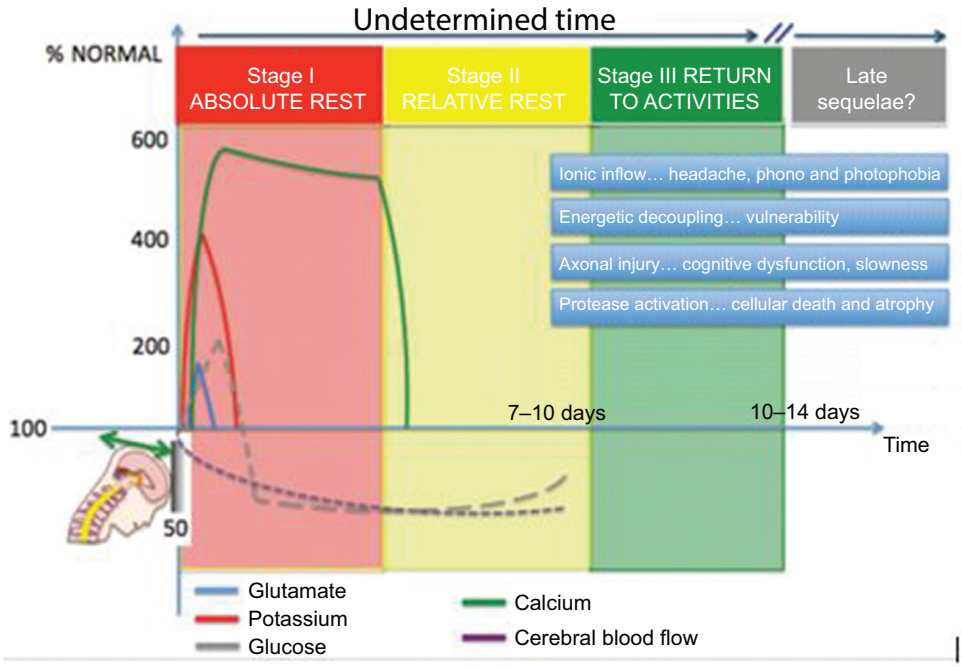

Fig. 2 Neurometabolic cascade associated with cerebral concussion. Note the temporal evolution of ionic disarrangements compromising neuron neurophysiology, which is related to the postconcussion clinical symptoms. Giza and Hovda[17] describe three stages of cerebral concussion, and in the first two, the patient should stay at rest (absolute and relative respectively). However, the duration of the clinical stages of cerebral concussion is individualized. The figure only provides an approximate temporal mean for each of these phases, and clinical revaluation is recommended. Chronically, cerebral concussions may lead to functional impairment, including ADHD, depression, psychoses, chronic headache, and even suicide. Modified from Giza and Hovda, 2014.[17]

tau protein. The early return to sports activities after a cerebral concussion aggravates the aforementioned metabolic damage (acute stage), inducing neuronal apoptosis. Studies with professional fighters demonstrated that the repetition of trauma, with strokes directed to the skull, evolve with cortical and hippocampal atrophy associated with ventriculomegaly. Animal studies reveal that a single severe cerebral concussion can result in chronic evolution of brain damage, with cell death and atrophy in one year.[17,18]

The physiological protein degradation depends on the ubiquitin-proteasome system for its proper functioning, requiring energy in the form of adenosine triphosphate (ATP). Since there is energy decoupling due to a cerebral concussion, there will be failure of the ubiquitin-proteasome system, resulting in the accumulation of non-degradable toxic material, which is currently considered the precursor mechanism of posttraumatic neurodegeneration.[19,20] There are several reports of cerebrospinal fluid (CSF) and tissue deposition of phosphorylated tau protein, in addition to extracellular amyloid and CSF deposits after cerebral concussion.[21]

As described, the chronic mechanisms triggered by cerebral concussion will manifest clinically in the form of a slowness in reasoning, loss of concentration, aggressiveness, impulsiveness, cognitive dysfunction, sleep alteration and emotional lability, including depression, which is a direct reflex of neurotransmission impairment. Tractography neuroimages can detect, already in early stages, the white-fiber compromise resulting from the concussion. It is not yet known to what extent an axonal injury can be repaired. Myelinization seems to protect the axon against trauma; however, in repeated concussions, with no time for axonal recovery, immature or even incomplete myelinization, it is not possible to avoid the sequelae of the initial trauma.[22–25]

Symptomatology. Respecting the topography of the lesion. Any portion of the nervous system may be affected by cerebral concussion, leading to its characteristic clinical presentation. Several regions are commonly affected concomitantly, resulting in a wide variety of symptoms.

Cortical structures. Due to its anatomical location, the frontal lobe is frequently affected by concussion, presenting cognitive dysfunction. The diagnosis is made through neurocognitive and neuropsychological tests. The affected temporal lobe may present memory deficits with anterograde amnesia and impairment of the consolidation of long-term memory. During the verbal and visual memory tests, in more than 75% of the cases, positron emission tomography (PET) and single-photon emission tomography (SPET) present alterations. The lesions to the parietal lobe traditionally result in complex impairments, such as: aphasia, apraxia, alexia, agraphia, dyscalculia and dysesthesia.[2,26]

Subcortical structures. The concussive lesions that affect the hypothalamus may be characterized by autonomic, endocrine, sexual (erectile) dysfunctions, as well as analgesic and circadian rhythm dysfunctions. Hypopituitarism is described as a lesion to the hypophysial stem, with consequent hormonal deficit, involving the adenohypophysis and the neurohypophysis. Damiani et al[27] describe that hypocortisolism may mimic postconcussion syndrome, and it should be considered in the clinical investigation.[27] Milroy et al[28] describe changes in the sleep-wake cycle, often manifested in the form of dyssomnias

and/or parasomnias resulting from cerebral concussion.[28] After trauma, appetite alterations can also be observed, often leading to central obesity due to hyperphagia and gastroparesis. Mortality increases significantly if there is central diabetes insipidus, compromising electrolyte balance, which must be controlled with desmopressin acetate (DDAVP, Ferring GmbH, Kiel, Germany).[2,27] Lesions to the base cores may course with choreoathetosis, dystonia, chorea, hypertonic-hypokinetic movements, aphasia, hemiparesis and emotional lability.[29,30]

Trigeminal-facial structure. One of the main symptoms associated with cerebral concussion is the presence of recurrent and persistent headache. The lesion often involves the trigeminal-vascular system, with subcortical cellular alteration. Headache has several characteristics, and may present in a migraine, tensional, cluster, occipital or supraorbital form. Commonly, headache is accompanied by nausea and vomiting, malaise and abdominal pain. The physiopathology of this type of headache involves injury to the trigeminal-vascular system associated with the distension of the dural vessels, with the presence of spreading depression. The treatment for postconcussion headache includes: biofeedback, psychotherapy, non-steroidal anti-inflammatory drugs, triptans, ergotamine, opioids, muscle relaxants and selective serotonin reuptake inhibitors.[31,32]

Cerebellar structure. Purkinje cells are especially susceptible to blow-counterblow lesions, with neuronal loss in the first 24 hours after the trauma. The symptoms attributed to cerebellar lesions include: dysdiadokokinesia, positive Romberg test, dysmetria, intention tremor, dysphemia, motor incoordination and cognitive-affective dysfunction.[33]

Table 1 New Orleans and Canadian CT Head Rule criteria used as warning signs for indication of cranial computed tomography in cases of cerebral concussion

NEW ORLEANS CRITERIA — GLASGOW COMA SCALE 15
Headache
Vomit
Age $>$ 60 years
Alcohol or drug intoxication
Persistent anterograde amnesia
Convulsion
Traumatic lesion to the soft tissues or bone lesion above the clavicle
CANADIAN CT HEAD RULE CRITERIA — GLASGOW COMA SCALE 13–15 FOR PATIENTS AGED $\geq$ 16 YEARS
↙HIGH risk of neurosurgical intervention:
Glasgow coma scale $<$ 15 2 h after the trauma
Open or sinking cranial fracture
Cranial base fracture: rhino/otorrhea; raccoon eye; Battle
Two or more vomit episodes
Age $>$ 65 years old
↙MODERATE risk of neurosurgical intervention
Retrograde amnesia $\geq$ 30 minutes
Injury mechanism: collision; vehicle ejection; fall $>$ 1 m high; fall $>$ 5 steps

Clinical Management in the Emergency Room

The diagnosis of cerebral concussion is clinical. It is a lesion of diffuse nature, without focal manifestations upon clinical examination.[34] Loss of consciousness only occurs in $\sim$ 10% of the cases, while anterograde and/or retrograde amnesia occurs in 30 to 50% of the cases. Headache occurs in most cases ($\sim$ 85%). It is noteworthy that the symptoms may not be present at the time of patient admission; they may appear hours after the trauma, or only be diagnosed after neurocognitive or neuropsychological tests.

In the emergency room, clinical measures should be established as a priority, according to the treatment protocols recommended by Advanced Trauma Life Support (ATLS), following this sequence: Ac (airway/cervical stabilization); B (respiration); C (circulation); D (neurological status); E (exposure). Once diagnosed or suspected, concussion should be handled with frequent clinical reassessments. Special attention should be given to those patients with lowering levels of consciousness (or prolonged periods of unconsciousness after head trauma), seizures, focal neurological signs and/or suspicion of cervical injury.

Due to the impact, there is a risk of subdural and extradural hematomas, bone fractures and/or cerebral contusion, with the need for neuroimaging exams, usually computed tomography (CT) of the skull without contrast. Less than 10% of the patients present bleeding in the neuroimaging exam, and less than 2% of them require neurosurgical intervention.[5]

In the clinical practice, two scales are recommended to evaluate these patients in the emergency room regarding the need for cranial CT: the New Orleans criteria and the Canadian CT Head Rule, both validated in prospective studies. The presence of at least one criterion in any of the scales is indicative of the need for a neuroimaging exam (►**Table 1**).[10,35–37]

A useful tool developed for the diagnosis of cerebral concussion in sports is called Sport Concussion Assessment Tool, Third edition (SCAT3). It is a list of 22 relevant symptoms. In cases of suspicion of cerebral concussion, the presence of only one symptom concludes the diagnosis. A new scale called childSCAT3 was developed for children aged between 5 12 years with suspicion of cerebral concussion.[38]

Patients with cerebral concussion diagnosis should remain at rest to reduce the cerebral metabolic demand, which could otherwise exacerbate cellular lesions.[39] The observation period will depend on the severity of the trauma, represented by the symptomatology presented. Patients with a normal neurological examination should be observed for $\sim$ 2 hours.[40] It is always useful to leave written guidance on warning signs for the presence of intracranial lesions with later manifestations: intense headache, vomiting, dizziness, postural instability, or loss of fluid through the nose or ear. It should also be clear to the patient and caregivers that headache and irritability are absolutely frequent for a few days after cerebral concussion, and may manifest over the subsequent days, not being a cause for concern. Regarding the drowsiness that the patient may

present in the days after the trauma, it is also a common postconcussion sign, but it is still unclear whether waking the patient overnight has any benefits. It is recommended that patients do not return to their daily activities until the headache and malaise have improved.[10]

In the presence of new symptoms, such as hemiplegia, dizziness and drowsiness, after cerebral concussion, a clinical reassessment with neuroimaging is mandatory, to discard subdural and/or extradural hematomas. With the hypothesis of axial collections discarded, posttraumatic ischemic strokes should be considered, commonly due to traumatic injuries of the carotid and/or vertebral arteries. Once the aforementioned lesions have been discarded, the migraine-like phenomenon may be considered as an etiology for the new signs and symptoms.[10,41,42]

Some neuroimaging findings may prolong the observation time, requiring the hospitalization of the patient. The presence of a small cerebral contusion or even discrete subarachnoid hemorrhage is observed in $\sim$ 5% of the cases. Generally, these lesions do not result in functional impairment, only persistent headache, requiring that the patient be observed for a longer period ($\sim$ 12 hours on average). In the presence of intracranial lesions such as those mentioned, a neuroimaging evaluation is indicated for the comparison with the initial image.[10]

Management of postconcussion syndrome. This syndrome is characterized by a constellation of symptoms observed in victims of cerebral concussions in the days following trauma. Headache and irritability occur frequently, followed by dizziness, anterograde/retrograde amnesia and somnolence. About 25% of these patients still present symptoms 1 year after the concussion.

Anxiety and depression are described by more than one third of the victims, and are more intense in hypochondriac patients. Imbalance and dizziness reflect vestibular concussion, which can be evidenced in the vestibulo-ocular reflex (VOR) test.

The pharmacotherapy indicated for the victims of cerebral concussion is poorly studied. The use of medications that interfere little with the level of consciousness is recommended. Common analgesics are used for headache, and non-hormonal anti-inflammatory drugs should be avoided in the initial stage of the trauma, due to the potential risk of hemorrhage. Opioids should not be used, since they impair neuronal regeneration and are associated with chronic pain in patients. Labyrinth system depressants are used (preferably those with an associated antiemetic effect): promethazine, betahistine dihydrochloride, meclizine, diphenhydramine and flunarizine. Serotonin reuptake inhibitors are also widely used, however, with poorly-studied results. For individuals who already suffer from migraine and who develop chronic postconcussion headache, several drugs are used: triptans, anticonvulsants, β-adrenergic blockers, steroids and calcium channel blockers.[5,10,43] Neuropsychological and neurocognitive approaches should be performed after the first week of trauma. Complaints of lack of attention, impulsiveness and hyperactivity are often already observed in this stage. Suicidal ideation is a possible consequence of cranial trauma, reinforcing the need for psychiatric follow-up.[44] Neuropsychological follow-up can be useful, as well as the prescription of psychostimulants.[5]

Temporal Classification of Concussions

Current studies classify cerebral concussions in stages (periods of time) of recovery based on the physiopathological knowledge and the neurometabolic cascade described before. However, the same authors consider that each individual has his/her own particularities, and this subdivision is only a generalization. In this context, stage I comprises a temporal variation of zero to 5 days, constituting a period in which the individual is unfit to return to his/her daily activities, and is usually very symptomatic, requiring analgesic medications. Stage II varies from 2 to 10 days, and the patient remains symptomatic, limiting his/her daily activities, restricting the workload, but already participating again in his/her routine. The return to studies should also be gradual, and the resting time is considered relative. Medications should be removed gradually. Ultimately, in stage III, which consists of a period ranging between 7 and 14 days, the patient no longer has symptoms related to cerebral concussion, and should no longer take medications. In those athletes who are victims of trauma, this is the ideal time to return to sports. Special attention should be given to those athletes who experience the symptoms of the concussion again when they return to their routines, and they should be instructed to do so more gradually. It is recommended that these athletes should initially be subjected to mild aerobic exercises, evolving to sport-specific exercises that require balance and movement control, and training in the field of play and without contact with opponents (minimizing possible new traumas), but, at the same time, improving their agility and cognition. Finally, after this evolution, and being asymptomatic, the athlete will be able to return to normal training and competition (►**Fig. 2**).[45–47]

Drugs with Neuroprotective Potential

Once the physiopathological mechanisms involved in cerebral concussion have been recognized, several drugs become promising to interrupt the harmful neurometabolic cascade. The therapeutic targets include: reduction of glutamatergic excitotoxicity, limitation of the damage caused by the production of free radicals and lipid peroxidation, and, finally, reduction of the permeability caused by the breakdown of the blood-brain barrier. Since the 1980s, several studies have tested magnesium sulfate, calcium channel blockers, bradykinin inhibitors, immunoreceptor blockers, vitamins, anti-inflammatories and minerals, with frustrating results in humans.[48,49] Despite previous results, some pharmacoprotective possibilities continue to be investigated:

1. Magnesium sulfate. Its action mechanisms include the blockage of N-methyl-D-aspartate (NMDA) glutamate receptors and calcium-dependent receptors, and reduction of the neuroinflammatory cascade associated with cranioencephalic trauma. However, in human studies, there was an increase in mortality.
2. Progesterone. This drug can reduce the oxidative stress to the cell membranes, with decreased lipid peroxidation and blood-brain barrier breakage. Recent studies,

however, have shown no benefit of their administration in humans.

3. Erythropoietin. This hormone has potential neuroprotective activity by several mechanisms, and continues to be investigated for its best form of administration in cases of CET.
4. Ziconotide (SNX-111; Prialt) is an atypical analgesic agent for the amelioration of severe and chronic pain. These are drugs that act in the reduction of calcium accumulation in the cerebral cortex and in the white matter, including the restoration of mitochondrial function. However, clinical studies have been interrupted due to the increased mortality in humans. Calcium antagonists with greater selectivity, such as SNX-185, continue to be investigated.
5. Substance P and neurokinin A receptor antagonists. They are drugs with neuroprotective potential, because they reduce cellular edema, as well as capillary permeability, with improved motor and cognitive functions after CET. Clinical studies are still underway.
6. Minocycline. An antibiotic with a post-CET immunomodulator effect, as well as antioxidant and anti-inflammatory effects. Studies are underway to prove its efficacy in humans.
7. Ciclosporine. It is an immunosuppressant with neuroprotective effects, because it stabilizes the mitochondrial function, reducing the production of free radicals and preventing the cellular calcium inflow. In animal models, there are proven benefits of ciclosporine in cases of CET; however, in humans, its benefits are still being investigated.[48,50]
8. Toll-like receptors. They are receptors of the immunologic innate response that activate the intracellular inflammatory cascade. The blockade of these receptors is being investigated with potential benefits in cases of CET.[48,51]
9. Vitamins, minerals and antioxidant agents (omega-3). These drugs, including B-complex vitamins and nicotinamide, showed benefits in animal models, reducing cortical lesion and inflammation. They still need studies that prove their efficacy in humans.
10. Micronutrients (zinc and magnesium). Both zinc and magnesium are necessary for proper cell functioning, and their neuroprotective effect after CET is still being investigated.[48]

Conclusion

The clinical diagnosis of cerebral concussion is often difficult. The symptoms are extremely varied, and go beyond the classic compromise of the level of consciousness. The injury mechanism involves the sudden acceleration and deceleration with axonal shearing, which can irreversibly compromise the cortical functioning. In the present work, the authors present the cellular alterations resulting from cerebral concussion and its potential treatment in the emergency room. To date, the physiopathological correlated mechanism did not have a recommended therapeutic algorithm. The relative or absolute physical and cognitive rest in the first days protects the nervous system from the phenomenon of the "second lesion." Anti-inflammatories should be avoided due to the risk of bleeding, and analgesia should be recommended for symptomatic relief. The patient should maintain the rest at the discretion of the clinician, and should be alerted to the fact that the symptoms may arise in the first hours after the trauma. New pharmacological possibilities are being studied for early intervention to minimize the possible cognitive sequelae.

Conflicts of Interest
The authors have none to declare.

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The Influence of the Type of Surgical Thread and Suture in the Open Carpal Tunnel Syndrome Surgery

A influência do tipo de fio cirúrgico e sutura nos resultados da cirurgia aberta da síndrome do túnel do carpo

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Abstract

Carpal tunnel syndrome (CTS) is the result of compression and/or traction of the median nerve in the carpal tunnel. It is the most frequent compressive neuropathy of the upper limbs and it is usually idiopathic. Diagnosis is essentially clinical, defined by symptoms and provocative tests. Decompression of the median nerve by section of the transverse carpus ligament is the treatment of choice, but the lack of consensus on the type of suture and surgical thread to be used in the open carpal tunnel decompression surgery justifies the importance of evaluating the comparative results of existing studies, aiming to describe the influence of different types of sutures and surgical threads to guide the professionals about the most appropriate conduct. This is a systematic review of the international and national literature. Four studies comparing the influence of surgical threads and one study evaluating the influence of the type of suture were found. From the comparative studies, it was observed that there is advantage in the use of nonabsorbable suture due to the lower occurrence of inflammation and postoperative wound complications. When using Donatti sutures, wound edge inversion is less likely to occur compared with single individual sutures, but they are also related to longer postoperative pain.

Keywords
- carpal tunnel syndrome
- sutures
- suture techniques

Resumo

A síndrome do túnel do carpo (STC) é resultante da compressão e/ou tração do nervo mediano no túnel do carpo. É a mais frequente neuropatia compressiva dos membros superiores e, geralmente, tem causa idiopática. O diagnóstico é essencialmente clínico através dos sintomas e testes provocativos. A descompressão do nervo mediano por secção do ligamento transverso do carpo é o tratamento de escolha, mas a ausência de consenso sobre o tipo de sutura e fio cirúrgico a serem utilizados na cirurgia aberta de

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descompressão do túnel do carpo justifica a importância de se avaliar os resultados comparativos dos estudos existentes, tendo como objetivo descrever a influência dos diferentes tipos de suturas e fios cirúrgicos e, assim, orientar os profissionais quanto à conduta mais adequada. Trata-se de um estudo de revisão sistemática da literatura internacional e nacional. Foram encontrados quatro estudos comparando a influência dos tipos de fios cirúrgicos e um estudo avaliando a influência do tipo de sutura. A partir dos estudos comparativos, observou-se que a utilização de sutura não absorvível se mostra vantajosa pela menor ocorrência de inflamação e complicações de ferida pós-operatória. Ao utilizar suturas Donatti, a inversão de bordas da ferida é menos provável de ocorrer em comparação com suturas individuais simples, porém estas estão relacionadas com dor pós-operatória mais prolongada.

Palavras-chave
- síndrome do túnel do carpo
- suturas
- técnicas de sutura

Introduction

Carpal tunnel syndrome (CTS) is characterized by compression and/or traction of the median nerve at the level of the carpal tunnel, located in the fist. It is the most frequent compressive neuropathy of the upper limbs, with prevalence ranging from between 0.125 1% to between 5 and 16%, depending on the population group studied.[1–3] Recent transversal studies evidenced a CTS prevalence of 9.2% in women and of 0.6% in men, with a peak incidence in the 6th decade of life.[1]

The first description of CTS is attributed to Paget, in which a case of compression of the median nerve was described from a distal radius fracture.[4] In 1913, the first anatomical and histopathological description of an hourglass lesion and median nerve neuroma was published, made by Marie et al.[5] But it was only in 1950, in works conducted by Phalen, that the CTS principles were stablished.[6]

There is controversy among surgeons about the type of suture and surgical thread to be used in the closure of the skin in carpal tunnel decompression (CTD), considering the postoperative results. A consensus regarding the theme justifies the importance of evaluating study results that investigated the influence of suture and surgical thread types in postoperative evolution after CTD.

Several authors have compared the use of absorbable and nonabsorbable suture threads in carpal tunnel surgery, evaluating pain in the immediate and late postoperative period, patient satisfaction, as well as the incidence of complications, mainly infection and formation of granuloma. We have evaluated the results of these studies aiming to describe the influence of the different types of surgical sutures and thread on the evolution of the open surgery of carpal tunnel syndrome and, thus, guide professionals to the most appropriate approach.

Methodology

This is a systematic review of the international and national literature, in which systematic reviews and basic research studies were evaluated in an attempt to identify prognostic differences in the evolution of carpal tunnel syndrome surgery as to the type of surgical thread and suture used.

The search for data occurred between the months of October and November of 2016, through the public domain PubMed (National Library of Medicine [NLM]), Scientific Electronic Library Online (SciELO), Latin-American and Caribbean Literature in Health Sciences (LILACS), MEDLINE (NLM) and Virtual Health Library (BVSMS). The following health descriptors were used for the research: *carpal tunnel syndrome*, *suture* and *suture techniques*.

The inclusion criteria were: primary and flooded studies that addressed the influence of the different types of sutures and threads in the result of carpal tunnel syndrome open surgery, in the English and Portuguese languages. The exclusion criteria were: articles that did not refer to the influence of suture threads and suture type on the open surgical procedure of CTS.

The studies were analyzed and selected in two distinct phases: the first was based on searches guided by the inclusion and exclusion criteria, and the studies were selected or discarded based on their respective titles and abstracts. In the second phase, there was a complete trial of the studies, in which the type of research, the methods used, and the results were carefully analyzed to subsidize the development of the present systematic review.

All of the selected studies were distributed into five levels of evidence, according to the model proposed by the U.S. Preventive Services Task Force (USPSTF): (1) well-conducted randomized controlled clinical study; (2a) controlled clinical study without well-conducted randomization; (2b) a well-conducted cohort or case-control study; (2c) multiple longitudinal studies with or without intervention; and (3) opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports from expert committees.

Results

Regarding the type of surgical thread, six comparative studies were found that met the inclusion criteria, being: (1) a prospective randomized study that used to Liou 64 patients comparing the use of an absorbable thread (polyglactin 910–Vicryl [Ethicon Inc., Sommerville, NJ, USA) in suture, and a nonabsorbable thread (polypropylene monofilament – Prolene [Ethicon Inc., Sommerville, NJ, USA]); (2) a prospective and randomized

study that observed 47 patients undergoing suture closure with Vicryl Rapide (Ethicon Inc., Sommerville, NJ, USA) (absorbable) or Novafil (Medtronic, Dublin, Ireland) (nonabsorbable); (3) a randomized clinical trial comparing nylon, polyglactin 910 (Vicryl) or stainless steel in the closure of the skin in 61 patients; (4) A study evaluating 53 patients undergoing surgery for CTS with polypropylene (Prolene) or polyglactin (Vicryl Rapide) for skin closure; this study was also aimed at comparing the results of simple suture and subcutaneous suture; (5) a prospective randomized study that was performed to compare the influence of absorbable and nonabsorbable sutures on pillar pain, on scar sensitivity, on the extent of the wound inflammation, and on the overall result of open surgery of CTS in 33 patients; (6) the type of suture used was also evaluated in a prospective randomized controlled study with 89 patients, in which the results obtained between simple single suture and Donatti sutures were compared (►**Table 1**).

Discussion

The carpal tunnel is an inextensible and osteofibrous-aspect structure, delimited by the carpal bones and the flexor retinulus (FR), in which the nerve is present.[7] Typically, the carpal tunnel also houses nine tendons of flexor muscles: the tendon of the flexor muscle along the thumb, four tendons of the superficial flexor muscles of the fingers, and four tendons of the deep flexor muscles of the fingers.[5] The median nerve has motor and sensory branches. In the distal region of the carpal tunnel, the median nerve is divided into its terminal branches: (1) recurrent motor branch, which directs the thenar eminence, by the short abductor muscles of the thumb, opponent of the thumb and the superficial portion of the short flexor of the thumb; (2) branches for lumbrical muscles I and II; (3) sensory branches for the digital palmar nerves that, on the palmar surface, will innervate the skin of the thumb, the 2nd and 3rd fingers, besides the lateral half of the 4th finger and, on the dorsal surface, the middle and distal phalanx of the 2nd, 3rd and half of the 4th finger.[7,8]

Under the physiopathological aspect, CTS shares the same mechanism of other neuropathic syndromes that combine compression and tension phenomenon to provoke sensitive and or motor functional alterations. Such functional changes are, sequentially, due to intraneural blood microcirculation disturbances injuries in the myelin and axon sheath and, lastly, alterations in the supportive connective tissue. The compression of the median nerve can occur in two anatomically distinct sites, the first being at the proximal limit of the carpal tunnel, and the second at the level of the narrower portion of the tunnel, near the hamulus of the hamate bone.[7,9]

In the vast majority of cases, CTS is said to be idiopathic, since the actual cause of the condition cannot be identified. Secondary frames may be related to anomalies of the carpal tunnel walls (anomalies of the continent), or abnormalities that modify structures passing through the carpal tunnel (anomalies of the content). Authors also describe that occupational association pathologies are frequent in dynamic CTS.[7]

Carpal tunnel syndrome is evidenced by a clinical picture of pain, burning, tingling and numbness in the territory innervated by the median nerve, of insidious evolution and progressive character. Characteristically, the symptoms accentuate in the night period, even awakening the patient, and they tend to improve with hand movement. In more than half of the cases, the involvement is bilateral. With the progression of the disease, it can be associated with the reduction of sensitivity in the distribution of the median nerve and with a decrease in strength, and, when there is severe compression of the nerve, atrophy of the thenar eminence, usually related to short abductor thumb muscle atrophy.[7,10] In the physical examination, hypoesthesia is observed in the median nerve territory, as well as thenar muscles paresis, positive Tinel, Phalen and Paley and McMurphy signals.[7] The Paley and McMurphy signal and the Phalen signal show greater specificity, and the Tinel signal is the most sensitive.[7,11]

Table 1 General characteristics of the main studies evaluating the outcomes of carpal tunnel surgery according to the type of surgical wire and type of suture used

Authors	Number of patients	Study type	Study objective
Erel et al[20]	64	Randomized prospective	Evaluated the use or absorbable thread (polyglactin 910–Vicryl) and nonabsorbable thread (polypropylene monofilament – Prolene) in subcutaneous suture.
Kharwadkar et al[21]	33	Randomized prospective	Compared the influence of absorbable and nonabsorbable thread on pillar pain, scar sensibility, wound inflammation extension.
Theopold et al[22]	47	Randomized prospective	Compared the use of suture com Vicryl Rapide (absorbable) or Novafil (nonabsorbable).
Menovsky et al[23]	61	Randomized clinical trial	Compared the use *nylon* thread, polyglactin 910 (Vicryl) or stainless steel in skin suture.
Macfarlane et al[24]	53	Randomized clinical trial	Compared the use of polypropylene (Prolene) and polyglactin (Vicryl Rapide) threads for skin suture.
Bolster et al[25]	89	Randomized prospective	Compared the results between simple individual sutures and Donatti sutures.

The diagnosis of CTS is primarily clinical and can be firmed based on patient history and clinical examination. The use of complementary exams, such as electroneuromyography (ENMG) and imaging exams (ultrasonography and magnetic resonance imaging [MRI]), assists mainly in the differential and etiological diagnosis.[7]

Carpal tunnel syndrome treatment can be accomplished through two distinct approaches: conservative treatment and surgical treatment.[12]

Evidence suggests that conservative treatment may assist in the recovery of CTS patients with intra-articular injection of corticosteroids associated with lidocaine, as well as oral corticosteroid therapy and nocturnal immobilization, as effective therapies. Other therapeutical means, such as weight loss, ultrasound, laser, diuretics and vitaminotherapy B6, still remain controversial, not being recommended.[12–14]

In surgical treatment, the retinaculum section of the flexor muscles is done to increase the volume of the carpal tunnel and, consequently, reduce the intratunnel pressure.[12] The decompression of the median nerve by section of the transverse ligament of the carpus is the treatment of choice, providing excellent results in 75% of the patients.[15,16]

Currently, three techniques are used to perform decompression of the carpal tunnel, which are: the open technique; the techniques known as mini-open; and endoscopic techniques.[12]

The endoscopic technique of CTD has become popular in recent years, allowing an early functional recovery of the hand, with low morbidity and faster return to habitual activities.[14] The open surgery is characterized by a small incision of between 3 and 4 cm, made between the flexion fold of the wrist, in the prolongation of the radial edge of the fourth finger, to the Kaplan Cardinal line.[12] The FR is then incised in its middle part on the ulnar side of the shaft on the 4th finger, leaving an ulnar margin to limit the subluxation of the flexor. The FR section remains cautiously distal to the superficial palmar arch and the median-ulnar anastomosis. Proximally, the FR is deeply separated from the synovia of the flexors with dissection shears. The closure of the skin is then done.[12]

The use of absorbable sutures is more and more frequent in hand surgery, since they do not require removal. Absorbable sutures have been associated with immunogenic response during the postoperative period, which can lead to complications such as residual inflammation of the wound, suture abscesses, and formation of sterile granuloma. This inflammatory response is a local reaction to the foreign body, with infiltration of macrophages that respond to proinflammatory cytokines, and the subsequent formation of Gigan cells.[17] However, nonabsorbable sutures require postoperative removal, and some cases may also leave marks on the skin.[18,19]

Erel et al evaluated 64 patients in a prospective randomized clinical trial comparing the use of an absorbable thread (polyglactin 910–Vicryl) in subcutaneous suture with that of a nonabsorbable thread (polypropylene monofilament – Prolene) in simple suture for surgical wound closure. An increase in pain perception in 10 days postoperatively was reported by patients in the group in which nonabsorbable polypropylene (Prolene) thread was used. In the evaluation after 6 weeks, there were differences in terms of cure, complications and pain score, with a higher level of residual inflammation in the group in which absorbable polyglactin 910 (Vicryl) thread was used.[20]

A prospective randomized study was performed to compare the influence of absorbable and nonabsorbable sutures on pillar pain, on scar sensitivity, on the extension of the wound inflammation and on the overall result of CTS open surgery in 33 patients. There was no significant difference between the two groups for any of the measures resulting from the final follow-up.[21]

In a prospective randomized study, Theopold et al[22] observed 47 patients undergoing suture closure with Vicryl Rapide (absorbable) or Novafil (nonabsorbable). There were no differences in the appearance of the wound, pain or satisfaction at 2 or 6 weeks postoperatively. This study recommends using Vicryl Rapide to close the palmar incisions, in view of the convenience and cost savings associated with absorbable sutures.[20]

In a larger study, Menovsky et al performed a randomized clinical trial comparing nylon, polyglactin 910 or stainless steel in the closure of the skin in 61 patients undergoing open surgery for the treatment of CTS. Based on this study, absorbable sutures using polyglactin 910 should not be performed, since the incidence of complications, including infections and presence of suture granulomas, was much higher than in the nylon and steel suture groups.[23]

Macfarlane et al analyzed 53 patients who underwent surgery for CTS with polypropylene (Prolene) or polyglactin (Vicryl Rapide) for skin closure. They did not observe any difference in the complications using the two types of suture, which can reflect the use of Vicryl Rapide, faster dissolution with a lower incidence of suture granulomas. It is important to note that this study analyzed the use of Prolene and Vicryl Rapide, which had not yet been directly compared by other authors when used in carpal tunnel surgery, finding little difference between the two products, with positive results, similar in both groups, regarding functionality, wound healing, and aesthetics.[24]

As for the type of suture, the use of simple sutures allows the nodes to be placed on the surface of the skin, far from the section point of the flexor rectangle, without the risk of delayed absorption under the skin, which is sometimes seen with the placement of a subcutaneous node in a continuous suture technique.[24]

Inversion of wound edges is one of the potential causes of fragility in the postoperative scar after CTS open surgery. When using Donatti sutures, the inversion of wound edges is less likely to occur in comparison with simple individual sutures. A prospective randomized side study was performed comparing simple single suture and Donatti sutures with 89 patients. After 8 weeks postoperatively, scar formation was good/very good in 94% (individual points) and 97% (Donatti) of the patients. Pain and disability scores in both groups improved after 8 weeks postoperatively, although patients who received Donatti sutures had a twofold higher score in pain scales.[25]

Conclusion

From the comparative studies, it was observed that the use of absorbable sutures is associated with an immunogenic response during the postoperative period, which can lead to complications such as residual inflammation of the wound, abscesses and formation of granulomas, justifying the use of nonabsorbable sutures. Thus, the studies infer that the use of absorbable thread presents results inferior to those observed when using nonabsorbable thread.

According to the data obtained, the use of nonabsorbable suture with polypropylene monofilament (Prolene) proved to be advantageous due to the lower occurrence of inflammation and postoperative wound complications.

If an absorbable suture thread is chosen, it is preferable to use Vicryl Rapide, since it has faster dissolution, decreasing the occurrence of inflammatory processes, with results similar to nonabsorbable threads.

As for the type of suture, both the Donatti suture and simple sutures presented excellent scar formation, but Donatti sutures are related to more prolonged postoperative pain. The simple suture obtained better results due to its more superficial location, with lower risk of delayed absorption under the skin, often observed in subcutaneous continuous suture.

Conflicts of Interests
The have no conflicts of interests to declare.

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Neurosurgery Simulators Developed for Neurosurgical Training in Brazil: A Systematic Review

Simuladores de neurocirurgia desenvolvidos para o treinamento neurocirúrgico no Brasil: Revisão sistemática da literatura

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Abstract

Introduction Simulation in neurosurgery is a growing trend in medical residency programs around the world due to the concerns there are about patient safety and the advancement of surgical technology. Simulation training can improve motor skills in a safe environment before the actual setting is initiated in the operating room. The aim of this review is to identify articles that describe Brazilian simulators, their validation status and the level of evidence (LoE).

Methodology This study was conducted using the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A search was performed in the Medline, Scielo, and Cochrane Library databases. The studies were evaluated according to the Medical Education Research Quality Instrument (MERSQI), and the LoE of the study was established according to the classification system of the Oxford Centre for Evidence-Based Medicine (OCEBM), which has been adapted by the European Association of Endoscopic Surgery.

Results Of all the studies included in this review, seven referred to validated simulators. These 7 studies were assigned an average MERSQI score of 8.57 from 18 possible points. None of the studies was randomized or conducted in a high-fidelity environment. The best evidence was provided by the studies with the human placenta model, which received a score of 2b and a degree of recommendation of 3.

Keywords
- simulation training
- neurosurgery
- spine
- education
- Brazil

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Conclusion Brazilian simulators can be reproduced in the different laboratories that are available in the country. The average MERSQI score of Brazilian studies is similar to the international average score. New studies should be undertaken to seek greater validation of the simulators and carry out randomized controlled trials.

Resumo

Introdução A simulação em neurocirurgia é uma tendência crescente em programas de residência médica em todo o mundo devido às preocupações que existem sobre a segurança do paciente e o avanço da tecnologia cirúrgica. O treinamento com simulação permite aprimorar as habilidades motoras em um ambiente seguro antes de partir para o cenário real na sala de cirurgia. O objetivo desta revisão é identificar artigos que descrevam simuladores brasileiros, determinar o status de validação e nível de evidência (LoE).

Metodologia Esse estudo foi realizado utilizando o *Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines*. Foi realizado uma busca nas bases de dados Medline, Scielo e Cochrane. Os estudos foram avaliados de acordo com o *Medical Education Research Quality Instrument (MERSQI)* e o LoE foi estabelecido de acordo com o *Oxford Centre for Evidence-Based Medicine (OCEBM)* adaptado pela Associação Européia de Cirurgia Endoscópica.

Resultados De todos os estudos incluídos nessa revisão, sete se referiam a simuladores validados. Estes receberam uma pontuação MERSQI média de 8,57 de 18 pontos possíveis. Nenhum dos estudos foi randomizado ou conduzido em ambiente de alta fidelidade. A melhor evidência foi fornecida pelos estudos com a placenta humana que recebeu uma pontuação 2b e um grau de recomendação de 3.

Conclusão Os simuladores brasileiros podem ser reproduzidos nos diferentes laboratórios disponíveis no país. O escore médio do MERSQI de estudos brasileiros é semelhante a pontuação média de estudos internacionais. Novos estudos devem buscar maior validação dos simuladores e maior nível de evidência com ensaios clínicos randomizados.

Palavras-chave
- treinamento de simulação
- neurocirurgia
- espinha
- educação
- Brasil

Introduction

The reduction of the working hours of residents in the United States and Europe has made simulation training a reality in all surgical specialties.[1] Simulation allows residents to acquire a skill quicker and more safely before they go into the real scenario of the operating room.[2] A recent meta-analysis has shown the benefits of simulation for motivated individuals who receive feedback for their performance.[3]

While simulation training has just started in Brazil and is taking its first steps, simulators in other countries are developing as new technologies are now emerging. Simulations are being done on synthetic models, using virtual reality and 3D printing,[4–6] rather than human cadavers and live animals. There is now the possibility of pathology-specific training with an educational purpose and preoperative planning.[7,8]

Simulation training in neurosurgery has become even more important because one error can lead to devastating consequences for the patient. Kirkman et al demonstrated the benefits of simulation in the first systematic review of simulation in neurosurgery.[9] However, most of the simulators demonstrated were expensive and so would be costly if they were used in Brazilian neurosurgery simulation laboratories.

The objectives of this systematic review are: 1. To identify studies that describe simulation methods developed by Brazilian neurosurgeons. 2. To determine the quality of the study, the validation status, the level of evidence (LoE) and the degree of recommendation.

Material and Methods

This study was conducted by using the approved guidelines of the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA).[10]

Inclusion and Exclusion Criteria

Articles describing validated and non-validated simulators for neurosurgical training were included in this review, while studies describing simulators for lumbar puncture, central venous access and rhizotomy procedures were excluded. Articles that were not written in either English or Portuguese were also excluded.

Information Sources and Search

A search in the databases at Medline, Scielo and Cochrane Library was performed and the studies took place between January 1, 1998, and September 29, 2018. The search terms

used were "*neurosurgery*," "*spine surgery*" and "*simulation training*" as these were found to provide the largest number of articles. A more specific search was then performed afterwards using the terms "*skill transfer*," "*skill retention*," "*motor performance*" and "*haptics*." This allowed the researcher to find other supplementary studies.

Studies Selection and Data Collection

Articles approved in the inclusion criteria were submitted to evaluation of their abstracts, according to the PRISMA protocol. Duplicate papers, conference publications and articles that were not related to neurosurgery or surgery simulation were all excluded. The selected studies were submitted to a full-text evaluation. Articles that did not describe or validate simulators were also excluded. Studies with patient-specific planning simulators were considered simulators. Only studies by the main Brazilian authors were selected. The relevance tests were performed by two authors, and the study inclusion was done when consent had been obtained from both of them. When there was any disagreement, a third author defined the selection.

Collected Data

The data extracted from each study was categorized according to the type of simulator, the neurosurgical subspecialty addressed, the type of procedure, the validation of the simulator, the Medical Education Research Study Quality Instrument (MERSQI)[11,12] **(►Table 1),** and the (LoE of the study , according to the classification system of the Oxford Centre for Evidence-Based Medicine (OCEBM), adapted by the European Association of Endoscopic Surgery[13,14] **(►Table 2** and **3**).

The simulators were categorized according to their neurosurgical subspecialty: vascular, functional, pediatric, spine, skull base, oncology, trauma, and basic neurosurgery. The results were then tabulated, and the simulators from each neurosurgical field grouped. The type of validation of the simulator was classified, according to the definitions of McDougall and Van Nortwick et al[1] (►**Fig. 1**). All the studies were evaluated for the LoE, and the studies' quantitative analysis also received a MERSQI score.

Results

Selected Articles

Our search strategy found 512 articles. After the duplicates and articles that were not published in either English or Portuguese had been excluded, 494 remained for the screening of the title. After this stage, 191 articles were submitted to the abstract evaluation. Two authors agreed on the selection of 19 papers for a review of the full text version, out of which 15 were selected for inclusion in this systematic review (►**Fig. 2**).

Characteristics of the Selected Studies

The neurosurgery fields that had the largest number of simulation studies were the vascular and pediatric, with 4 (26.66%) studies each. The most described simulator type was the human placenta (33.33%), followed by 3D printed simulators (26.66%), and the synthetic simulators (20%). Only one study (6.66%) reported the use of virtual or mixed reality. Eleven studies (73.33%) had the resident's skill training as their main purpose and 4 (26.66%) had patient-specific simulation. The most simulated neurosurgical procedure was ventricular neuroendoscopy (20%). ►**Table 4** shows the relationship between the type of simulator that was used for each simulated procedure.

Study Quality and Level of Evidence

Of all the studies included in this review, 7 (46.66%) referred to simulators that were validated. These studies were evaluated according to the MERSQI score and they presented an average score of 8.57 from 18 possible points (►**Table 1**). The studies with the highest scores were the models in the human placenta (MERSQI 12 to 8.5). No study was randomized to the control group. No studies were conducted in a high-fidelity environment. Only one study demonstrated the skill transfer from the simulator to the surgical center.[15] The studies with the best evidence were the models in the human placenta, which received a score of 2b and a degree of recommendation of 3 (►**Table 5**).

Data Synthesis

Validated Simulation Models

Of the 15 studies included in this systematic review, 7 (46.66%) had at least 1 type of validation. The most used of these were construct and face validity, which occurred in 4 studies (57.14%). Three studies (42.85%) showed content validity, 2 (28.57%) concurrent validity, and 1 (14.28%) presented predictive validity. Vascular neurosurgery was the area that had the highest number of validated studies.

Non-Validated Simulation Models

Eight studies (53.33%) were not validated. Four of them (50%) were related to patient-specific simulation. A descriptive study using the placenta was subsequently validated in further studies. The area of pediatric neurosurgery was the one that presented the most non-validated studies (►**Table 6**).

Vascular Neurosurgery

Four studies were presented, with three of them being validated and one descriptive. The human placenta was the only type of simulator that was described for vascular neurosurgery simulation. It was used in the four mentioned studies. These studies received the highest scientific evidence and the highest MERSQI score. The descriptive study demonstrated the potential of the placenta for simulation in vascular neurosurgery[16] (LoE—3, level of recommendation [LoR]—4). The study with the highest MERSQI score (12) used the placenta to demonstrate the transfer of skills that are acquired in the simulator to help with the neurosurgical procedure[15] (LoE 2b, LoR 3). The validated intracranial-intracranial (IC-IC) bypass model presented the possibility

Table 1 Medical Education Research Quality Instrument score for validated simulators

Items of the scale (possible points)	Sub items of the scale (points if present)	Number of studies (%)	Mean
Study design (3)	Single group cross-sectional or single group posttest only (1)	4 (57)	1.28
	Single group pretest and posttest (1.5)	2 (28)	
	Nonrandomized, 2 groups (2)	1 (14)	
	Randomized controlled trial (3)	0.00	
Sampling (3)	*Number of institutions studied:*		
	1 (0.5)	4 (57)	0.5
	2 (1)	2 (28)	
	3 (1.5)	1 (14)	
	Response rate, %:		
	Not applicable		
	< 50 or not reported (0.5)	7 (100)	
	50–74 (1)	0.00	
	> 75 (1.5)	0.00	
Type of data (3)	Assessment by study participant (1)	4 (57)	1.85
	Objective measurement (3)	3 (42)	
Validity of evaluation instrument (3)	*Internal structure:*		
	Not applicable		
	Not reported (0)	3 (42)	1.14
	Reported (1)	4 (57)	
	Content:		
	Not applicable		
	Not reported (0)	3 (42)	
	Reported (1)	4 (57)	
	Relationships to other variables:		
	Not applicable		
	Not reported (0)	3 (42)	
	Reported (1)	0.00	
Data analysis (3)	*Appropriateness of analysis:*		
	Data analysis inappropriate for study design or type of data (0)	3 (42)	2.57
	Data analysis appropriate for study design or type of data (1)	4 (57)	
	Complexity of analysis:		
	Descriptive analysis only (1)	3 (42)	
	Beyond descriptive analysis (2)	4 (57)	
Outcomes (3)	Satisfaction, attitudes, perceptions, opinions, general facts (1)	4 (57)	1.21
	Knowledge, skills (1,5)	3 (42)	
	Behaviors (2)	0.00	
	Patient/health care outcome (3)	0.00	
Total score			8.57

of performing several different bypass techniques[17] (MERSQI 8.5, LoE 2b, LoR 3). The placenta was also used to demonstrate how useful it is in simulating endovascular procedures[18] (MERSQI 9.5, LoE 3, LoR 4).

Pediatric Neurosurgery

Four studies were presented for simulation in pediatric neurosurgery, but none of them were validated. Two studies were used for patient-specific simulation. Ghizoni et al

Table 2 Modified levels of evidence classification for validation studies, adapted from the Oxford Centre for Evidence-Based Medicine classification by the European Association of Endoscopic Surgeons (Carter et al, 2005)

Level of evidence	Criteria
1a	Systematic reviews (meta-analysis) containing at least some trial of level 1b evidence, in which results of separate, independently controlled trials are consistent
1b	Randomized controlled trial of good quality and of adequate sample size (power calculations)
2a	Randomized trials of reasonable quality and/or of inadequate sample size
2b	Nonrandomized trials, comparative research (parallel cohort)
2c	Nonrandomized trials, comparative research (historical cohort, literature controls)
3	Nonrandomized, non-comparative trials, descriptive research
4	Expert opinions, including the opinion of Work Group members

Table 3 Levels of recommendation for training models, adapted from the Oxford Centre for Evidence-Based Medicine Classification by the European Association of Endoscopic Surgeons (Carter et al, 2005)

Level of evidence	Criteria
1	Based on one systematic review (1a) or at least two independently conducted research projects classified as 1b
2	Based on at least two independently conducted research projects classified as level 2a or 2b, within concordance
3	Based on one independently conducted research project level 2b, or at least two trials of level 3, within concordance
4	Based on one trial at level 3 or multiple expert opinions, including the opinions of Work Group members (e.g., level 4)

demonstrated the use of 3D printing in both planning and preoperative simulation in three cases of craniosynostosis.[19] Coelho et al performed the patient-specific simulation for an encephalocele on the face using a multimaterial 3D print. This was later replicated in surgery.[20]

Coelho et al presented two studies with the same simulator (ASPEN) that was developed for the simulation of craniosynostosis and ventricular neuroendoscopy.[21,22] The studies of pediatric neurosurgery were evaluated with a LoE of 3 e a LoR of 4.

Neurosurgical Oncology

Two studies were included with simulators to remove brain tumors. Both of these simulators were validated. Oliveira et al described the use of the human placenta to simulate microsurgery for an intracranial tumor.[23] (MERSQI 9.5, LoE 2b, LoR 3). Filho et al described and validated a synthetic simulator called Sinus Model Oto-Rhino Neuro Trainer (S.I.M.O.N.T.)[24] for the simulation of neuroendoscopy for the resection of a ventricular tumor (MERSQI 9.5, LoE 2b, LoR 3) and access to the base of the skull.

Spine

Two simulators were described for the spine. One simulator underwent validation and the other was a patient-specific simulation description. Coelho et al described and validated a simulator to perform lumbar spine procedures, such as arthrodesis and laminectomy.[25] They used the mixed reality that combines virtual reality with the synthetic model (MERSQI 5.5, LoE 3, LoR 4). Paiva et al described the patient-specific simulation with a 3D printed model for surgical planning of a corpectomy and removal of a complex tumor in the cervical spine[26] (LoE 3, LoR 4).

Basic Neurosurgery

There was no validation for any of the three studies that were related to the basic procedures of neurosurgery. Drummond-Braga et al described the use of a coconut fruit as a simulator for cerebrospinal fluid leak avoidance during craniotomy for residents of the first year.[27] Ferreira et al described a method that is used for dilation of the ventricular system in cadavers to simulate ventricular endoscopy.[28] Grillo et al presented the creation of a phantom used

Face validity – Opinions, including those of non-experts, regarding the realism of the simulator

Content validity – Opinions of experts about the simulator ant its appropriateness for training

Construct validity

A – one group – Ability of the simulator to assess and differentiate between the level of experience of an individual of the group measured over time

B – between groups – Ability of the simulator to distinguish between different levels of experience

Concurrent validity – Comparison of the new model against the older and gold standard, usually by Objective Structured Assessment of Technical Skills

Predictive validity - Correlation of performance with operating room performance, usually measured by Objective Structured Assessment of Technical Skills

Fig. 1 Types of validity. Definitions from McDougall et al; van Nortwick et al.[30,31] Translated by Aydin et al.[1] Current Status of Simulation and Training Models in Urological Surgery: A Systematic Review. DOI: 10.1016/j.juro.2016.01.131.

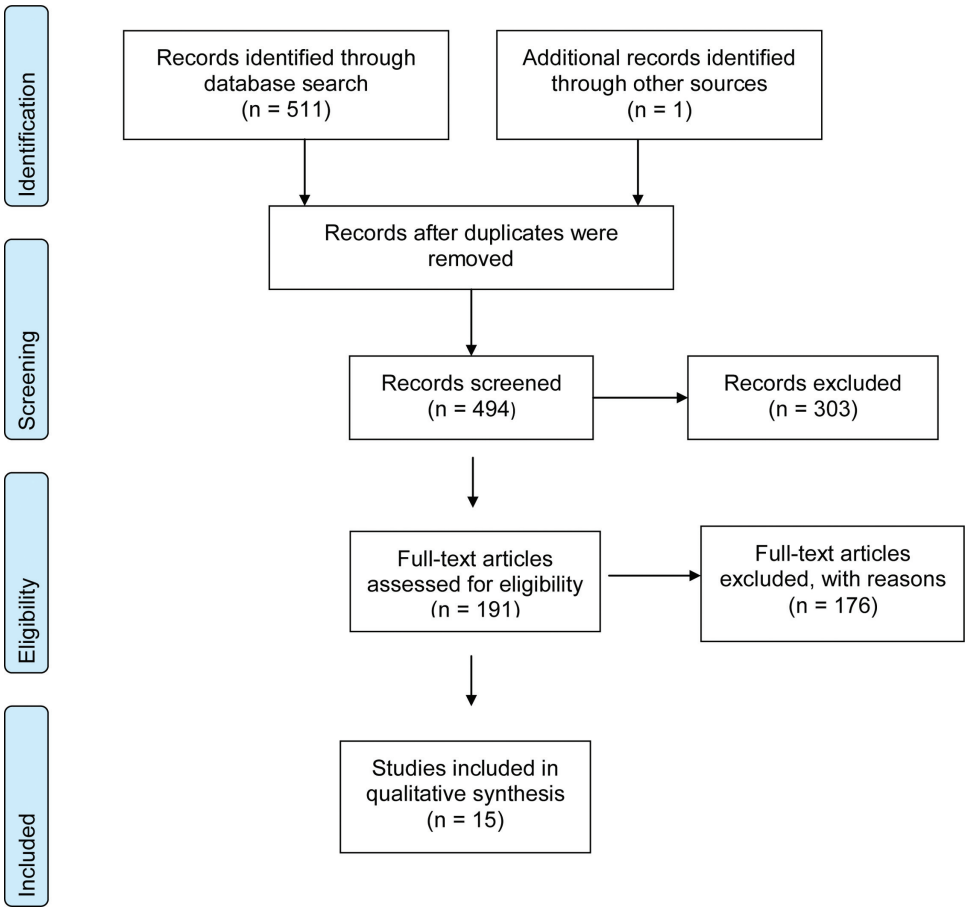

Fig. 2 Preferred Reported Items for Systematic Reviews and Meta-Analysis flow diagram.

Table 4 Type of simulator used for training in each neurosurgical procedure

Subspeciality	Procedure	Human Placenta	Synthetic Model	3D Printing	Mixed Reality	Corpse	Fruit
Neurovascular	Vascular microsurgery	x					
	Intracranial bypass	x					
	Angiography/ Endovascular	x					
	Microsurgery aneurysm	x					
Neuropediatric	Neuroendoscopy		x				
	Craniosynostosis		x	x			
	Meningocele			x			
Neuroncology	Microsurgery for tumor	x					
	Neuroendoscopy		x				
Spine	Arthrodesis				x		
	Corpectomy			x			
Basic Neurosurgery	Craniotomy						x
	Anatomy			x			
	External ventricular drain/neuroendoscopy					x	

Table 5 Level of evidence of validated studies

Author	MERSQI	LoE	LoR	Simulated Procedure	Type of Validation
Oliveira M. M. R. 2018	12	2b	3	Aneurysm clipping	Predictive and competition
Oliveira M. M. R. 2018	8.5	2b	3	Bypass	Competition and construct
Oliveira M. M. R. 2015	9.5	3	4	Endovascular	Construct, content and face
Oliveira M. M. R. 2014	9.5	2b	3	Microsurgery tumor	Construct, content and face
Grillo F. W., 2018	5.5	4	4	Craniotomy	Content
Filho F. V. 2011	9.5	2b	3	Neuroendoscopy	Construct and face
Coelho, G. 2018	5.5	3	4	Arthrodesis	Construct and face

Abbreviations: LoE, level of evidence; LoR, level of recommendation; MERSQI, Medical Education Research Study Quality Instrument.

Table 6 Level of evidence of non-validated studies

Author	LoE	LoR	Simulated procedure
Coelho, G. 2014	3	4	Neuroendoscopy
Ghizoni E. 2017	3	4	Craniosynostosis
Oliveira M. M. R. 2014	2b	3	Vascular microsurgery
Paiva W. S. 2007	3	4	Spine tumor
Coelho G., 2014	3	4	Craniosynostosis
Ferreira C. D., 2014	3	4	Neuroendoscopic
Coelho, G. 2017	3	4	Meningocele
Drummond-Braga B. 2016	3	4	Craniotomy

Abbreviations: LoE, level of evidence; LoR, level of recommendation.

for neurosurgical training and preoperative planning.[29] All the studies in this area were classified according to their LoE, which was 3, and the LoR, which was 4. ►**Table 7** shows a summary of each study's main characteristics.

Discussion

The Brazilian studies that underwent validation presented an average score of 8.56 points in the MERSQI. This value approximates the score described in the systematic review by Kirkman et al in 2014 (9.21 points).[8] The worst scores were received by validation topics that related to study designs and the number of institutions involved.

Few of the studies on simulation were able to demonstrate the transfer of skills from the simulator to the surgical room.[2] However, in 2018, Oliveira et al were able to demonstrate the transfer of an acquired ability in simulations of vascular microsurgery in the placenta to the real scenario in aneurysm surgeries. It was the only Brazilian study that described predictive validity.[15]

The highest LoE found was 2b and the best grade of recommendation was 3. This demonstrates the lack of a randomized blind study in Brazilian simulators. When analyzed in conjunction with the MERSQI score, the indication is that further Brazilian studies in simulation should be performed that search for randomization with control groups and multicentric studies.

The majority of the studies were of vascular and pediatric subspecialties. The most simulated procedures had the greatest demand for manual skills, such as vascular microsurgery and recent technological evolution, such as ventricular endoscopy. The least frequently simulated were functional neurosurgery and neurotrauma.

Among the non-validated simulators, the use of patient-specific or pathology-specific simulators is noteworthy. These simulators were used to provide education about specific conditions found in neurosurgery, as well as preoperative planning and rehearsal in complex cases. Three-dimensional printing was the most described type of simulation used for this purpose. Craniosynostosis surgery was the most simulated patient-specific procedure described.

This systematic review had its limitations. The main ones being the different forms of methodology of each study, and the different groups of evaluated participants and heterogeneous simulators. Perhaps the greatest limitation was the difference in the quality of the studies and the fact that most simulators lack a validation instrument.

Future research should focus on the creation of high-fidelity simulators that are accessible to the resident physician and could be introduced to neurosurgical training

Table 7 Summary of the main characteristics of each study

Author	Validity	Type of validation	Neurosurgery field	Procedure	Simulator type	Function	Participants	Objective	Main results	Limitations
Grillo F. W., 2018	Yes	Contend	Basics	Craniotomy	3D print	Patient-specific simulator	($n=17$) Neurosurgeons	Creation of a realistic phantom for reproduction of the cerebral cortical morphology, cerebrospinal fluid, meninges and scalp.	Most neurosurgeons rated the model as very good for realism and educational purpose.	It is not a simulator created for a specific neurosurgical technique.
Oliveira M. M. R., 2018	Yes	Predictive and concurrent	Vascular	Aneurysm microsurgery	Human placenta	Skill training	($n=12$) Residents and neurosurgeons	This study assessed concurrent and predictive validity of brain aneurysm surgery simulation in a human placenta model compared with a "live" human brain cadaveric model.	Residents trained in the human placenta simulator consistently had the highest overall performance scores when compared with those who had trained in the cadaver model and those who had simply watched operative videos ($p<0.001$).	The fresh human placenta can be used for only 1 to 2 weeks. After this time, the vessel walls become weaker, more difficult to dissect and suture.
Filho F. V., 2011	Yes	Construct and face	Oncology	Neuroendoscopy	Synthetic	Skill training	($n=22$) Residents and neurosurgeons	Assess both the quality of the model and the development of surgical skills by trainees.	The experts considered the simulator capable of reproducing surgical situations as if they were real and presenting great similarity with the human brain.	Expensive, not largely available, poor haptic feedback.
Oliveira M. M. R., 2016	Yes	Construct, Contend and face	Oncology	Tumor microsurgery	Human placenta	Skill training	($n=16$) Residents and neurosurgeons	To describe and asses face, contend and construct validity of the model	The human placental brain tumor microsurgical resection model is a high-fidelity training model that may have significant potential in the evaluation and training of neurosurgical residents.	The model does not replicate all aspects of tumor resection.
Oliveira M. M. R., 2018	Yes	Concurrent and construct	Vascular	Intracranial-intracranial bypass	Human placenta	Skill training	($n=9$) Residents	To describe the human placenta vascular anatomy to guide IC-IC bypasses apprenticeship.	An ex vivo bypass model offers great similarity to main brain vessels with the possibility to practice a variety of IC-IC bypass techniques in a single simulator. Placenta vascular anatomy knowledge can improve laboratory microsurgical training.	Biological risks, patient consent issues, placenta need to be fresh.

Table 7 (*Continued*)

Author	Validity	Type of validation	Neurosurgery field	Procedure	Simulator type	Function	Participants	Objective	Main results	Limitations
Coelho, G., 2018	Yes	Contend and face	Spine	Arthrodesis	Mixed reality	Skill training	($n=16$) Spinal surgeons	To propose and validate a new tool for neurosurgical education, associating virtual and realistic simulation (mixed reality), for spine surgery	The surgery team considered that this virtual simulation provides a highly effective training environment, and it significantly enhances teaching of surgical anatomy and operative strategies.	Expensive, not largely available.
Oliveira M. M. R., 2015	Yes	Construct, contend and face	Vascular	Neurointer-ventional	Human placenta	Skill training	($n=12$) Residents and neurosurgeons	To describe and asses face, contend and construct validity of the model	Excellent haptics, low startup costs, and ready availability for any institution with interventional capabilities.	Biological risks, patient consent issues.
Ghizoni E., 2018	No	N/A	Pediatrics	Craniosynostosis	3D print	Patient- specific simulator	($n=2$) Residents and neurosurgeons	Describe the use of three models for craniosynostosis practice made with a 3D printer	Single sagittal stenosis, bilateral coronal stenosis and complex stenosis of multiple sutures were simulated prior to the surgical procedure and anatomical variations were observed by surgeons	Descriptive only, with two participants.
Drummond-Braga B., 2016	No	N/A	Basics	Craniotomy	Fruit-Coconut	Skill training	N/A	To describe an original model for learning craniotomy first steps with CSF leak avoidance using a coconut.	Its main advantages are that coconuts are affordable and widely available and simulate CSF leaks. It has a potential pedagogic neurosurgical application for freshman residents, and further validity is necessary to confirm this hypothesis.	Complete absence of anatomic landmarks and the consistency of the coconut layers.
Paiva W. S., 2007	No	N/A	Spine	Corpectomy	3d print	Patient- specific simulator	N/A	The purpose of this work is to demonstrate the practical use of the stereolithography an auxiliary method for training and surgical simulation	It is easier for the surgeon to understand the complexity of the case and plan the approach before any surgical procedure. Careful planning and previous rehearsal reduce the risk of surprises during an operation.	High cost involved in prototyping process.

(*Continued*)

Table 7 (*Continued*)

Author	Validity	Type of validation	Neurosurgery field	Procedure	Simulator type	Function	Participants	Objective	Main results	Limitations
Coelho G., 2014	No	N/A	Pediatrics	Craniosynostosis	Synthetic	Skill training	N/A	To describe a synthetic simulator for the practice of craniosynostosis	This training model may represent a very useful method to simulate the steps of surgery for scaphocephaly. This training provides an alternative to the use of human cadavers and animal models.	High cost for maintenance.
Ferreira C. D., 2014	No	N/A	Basics	Neuroendoscopy	Cadaver	Patient- specific simulator	N/A	Create an anatomical model that simulates hydrocephalus and can be used in training in neuroendoscopy techniques.	The adequate use of the anomalous chemical–physical characteristics of the water molecule may provide a good mechanism to expand the ventricular cavity, to create an experimental model of hydrocephalus.	Biological risk. Difficulty of availability of cadavers.
Coelho, G. 2014	No	N/A	Pediatrics	Neuroendoscopy	Synthetic	Skill training	N/A	In this study, we present a new pediatric neuroendoscopic simulator that facilitates training. Description	Description of the simulator This realistic simulator was built with a synthetic thermo-retractile and thermosensible rubber called Neoderma®	High cost for maintenance.
Coelho, G. 2017	No	N/A	Pediatrics	Encephalocele	3d print	Patient- specific simulator	N/A	To describe a case of frontoethmoidal encephalocele, (nasofrontal subtype) of a 19-month-old girl, whose surgical correction was planned using 3D printing modeling.	The 3D model allowed predicting with millimetric precision the bilateral orbitotomy measurements, reducing the time of surgery, and precontouring the osteosynthesis material.	Demand computer design expert, high cost.
Oliveira, M. M. R. 2014	No	N/A	Vascular	Vascular microsurgery	Human placenta	Skill training	N/A	To describe an aneurysm surgical model that recreates the acquisition and maintenance of the specific microneurosurgical skills used in clipping cerebral aneurysms	The human placenta provides an inexpensive, convenient biological model for modeling cerebral aneurysms with high fidelity to neural tissue. In addition, it can be used to create aneurysms of various morphologies.	The fresh human placenta can be used for only 1 to 2 weeks. After this time, the vessel walls become weaker, more difficult to dissect and suture.

Abbreviations: CSF, cerebrospinal fluid; IC, intracranial.

laboratories throughout Brazil. Further validated and randomized studies should be performed to define the ideal simulators that could truly fit in every level of Brazil's residency skill training program.

Conclusion

The MERSQI score of the Brazilian studies resembles the international average. The LoE and the degree of recommendation of most of the published articles is still low. New studies should pursue a further validation of the simulators and hold randomized trials with a control group. There is a lot of creativity, simplicity and technology involved in Brazilian simulators. Most of them can be reproduced at the skill training laboratories that are available in the country.

Conflict of Interest
None declared.

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Peripheral Nerve Schwannomas: A Literature Review

Schwannomas de Nervos Periféricos: Revisão da Literatura

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Abstract

Introduction Schwannomas are benign tumors originating from the cells, which wrap around axons that are usually encapsulated and solitary. These tumors usually lead to little or no symptomatology. They are usually the most common peripheral nerve tumors in adults, with their highest incidence between the third and fifth decades of life.

Objective To perform a review about schwannoma of the peripheral nerves, presenting its definition, epidemiology, diagnosis, symptomatology and treatment.

Methodology This is a descriptive work, based on a review of articles available in the PubMed database with the descriptors *schwannoma* and *peripheral nerves*.

Results and Discussion Only papers published between 1981 and 2019, describing studies in humans, and that were available as full articles were selected. A total of 391 articles were included; after reading the titles, we noted that 67 articles fit the topic of the present study. Among the articles selected for reading, 33 fit the objectives of the present work, and were considered for the writing of the present article.

Conclusion Schwannomas are benign myelin sheath tumors that develop with local symptomatology or asymptomatic and present a good surgical prognosis with generally reduced rates of surgical complications.

Keywords
- schwannomas
- peripheral nerves
- neuroanatomy
- neurosurgery

Resumo

Introdução Os Schwannomas são tumores benignos originados das células de Schwann que envolvem os axônios de nervos periféricos. Esses tumores são encapsulados e solitários que geralmente levam a pouca ou nenhuma sintomatologia. Eles são os tumores de nervos periféricos mais comumente encontrados em adultos, com maior incidência entre a terceira e quinta décadas de vida.

Objetivo Realizar uma revisão sobre o schwannoma de nervo periférico, apresentando sua definição, epidemiologia, diagnóstico, sintomatologia e tratamento.

Metodologia Este é um trabalho descritivo, baseado na revisão de artigos disponíveis na Base de dados PubMed, a partir dos descritores: schwannoma e nervos periféricos.

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Resultados e Discussão Somente os artigos publicados entre os anos de 1981 e 2019, estudos envolvendo humanos e que estavam disponíveis como artigos completos, foram selecionados para a revisão. Um total de 391 artigos foram incluídos, após ler os títulos apenas 67 artigos se enquadraram no tópico do presente estudo. Entre os artigos selecionados para leitura, 33 se enquadram nos objetivos do presente trabalho e por isso foram considerados para a redação do presente artigo.

Conclusão Os Schwannomas são tumores benignos da bainha de mielina que se desenvolvem com sintomatologia local ou ausência de sintomas e que apresentam bom prognóstico cirúrgico, com taxas usualmente reduzidas de complicações cirúrgicas.

Palavras-chave
- Schwannomas
- nervos periféricos
- neuroanatomia
- neurocirurgia

Introduction

Most peripheral nerve sheath tumors (PNSTs) correspond to schwannomas, which are also known as neurilemomas or neurinomas. They are benign tumors, usually solitary, which develop and reach sizes between 1.5 cm and 3 cm in diameter; there is also the possibility of presentation as several tumors following the same path of the nerve. In most cases, these tumors consist of well-differentiated Schwann cells, and the occurrence of malignant transformation is rare.[1]

Epidemiologically, they are the most common peripheral nerve tumors in adults; they usually occur when the individual is between 30 and 50 years old, with no significant difference regarding ethnicity or gender. They comprise ~ 8% of all intracranial tumors, and ~ 29% of spinal tumors. About 12 to 19% of the cases of schwannoma occur in the upper extremity of the body, while 13.5 to 17.5% of the cases occur in the lower extremity.[1]

The present work aims to perform a literature review about schwannoma of the peripheral nerves, describing its definition, epidemiology, symptomatology, diagnosis and surgical treatment.

Methodology

The present is a descriptive work, based on review of articles available in the PubMed database with the descriptors *schwannoma* and *peripheral nerves*. Only papers published between 1981 to 2019, focusing the on peripheral nerves, were selected. Studies focusing on the cranial nerves were excluded. Reference books on the subject were also used.

Results

A total of 391 articles were included; after reading the titles, we noticed that 67 fit the topic of the present study. Among the articles selected for reading, 33 fit the objectives of the present work, and were used to support the writing.

Discussion

Definition

Schwannomas are tumors that arise from Schwann cells and are characterized by slow growth, which can create a capsule around the lesion. They are typically composed of well-differentiated Schwann cells.[2,3] (►**Fig. 1**)

Schwannomatosis is a genetic disease characterized by the development of multiple peripheral tumors.[4]

Epidemiology

Less than 5% of the tumors of the extremities are PNSTs.[5] Studies have shown a disproportionately greater incidence of schwannomas in the upper extremities (the head and neck, involving the spinal nerves and the brachial plexus), which is double that of those in the lower extremity; this is in contrast with neurofibromas, which are equally distributed throughout the nervous system.[5,6] Only 1 to 3% of the schwannomas occur in the pelvis. In addition, the involvement of the

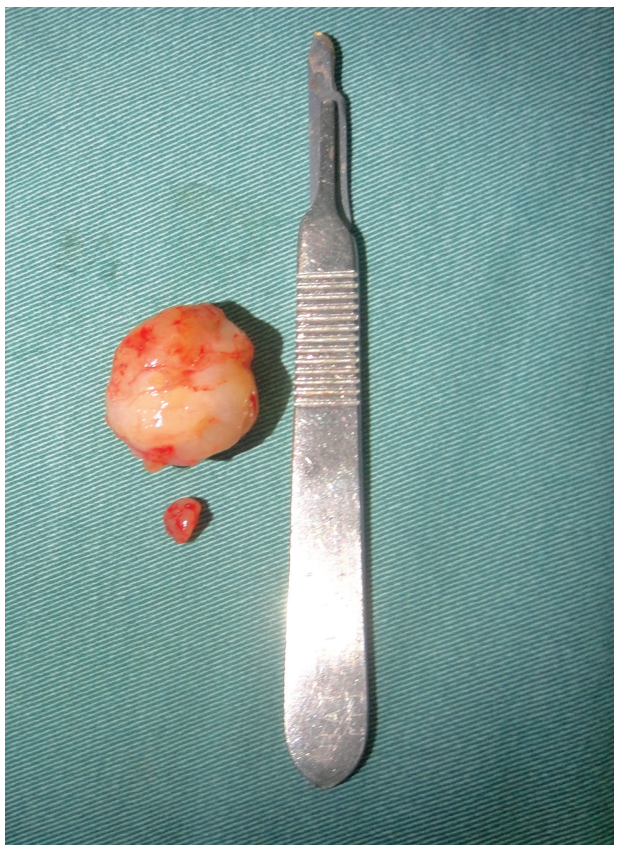

Fig. 1 Macroscopic aspect of the schwannoma.

obturator nerve is extremely rare, with only nine cases reported in the literature in English.[7]

Although all ages can be affected, schwannoma is the most common peripheral nerve tumor in adults, whereas pediatric cases are rare. They have a peak incidence in individuals between 30 and 60 years old, with an incidence of 0.3 to 0.4 cases per 100,000 people per year. Most studies do not show gender preference, but some series show a predominance of female intracranial tumors.[2,5,8]

Schwannomas can be benign or malignant; benign tumors are the most common tumors of the peripheral nerves, and recurrence or malignant transformation rarely occurs. When they occur, recurrences are more common (30–40%) regarding the cellular schwannomas of the intracranial, spinal and sacral regions.[2,3,9]

Clinical Manifestations

The schwannoma originates from the nerve sheath, and can occur anywhere within the peripheral nervous system. It is often asymptomatic, and may occasionally present only as a small palpable tumor mass, with few or no neurological deficits.[5]

It usually becomes symptomatic secondary to nerve compression and local mass effect. The symptoms depend on the location, with radiculopathy being the most frequent initial symptom, followed by paresthesia and limb weakness.[10]

When large nerves are affected, the tumor has characteristically eccentric growth, and the nerve is displaced toward the periphery. Clinically, Schwannomas can mimic a lipoma or a ganglion at the skin level.[3,5,8]

Schwannoma of the tibial nerve or sciatic nerve, for example, can mimic the radicular pain in the legs, which can lead to an erroneous diagnosis of radiculopathy.[11]

Involvement of the brachial plexus is uncommon, and usually presents as a palpable, slow-growing, supraclavicular or axillary mass, usually without pain or neurological signs.[3]

Predictors of malignancy include rapid tumor growth, positive predictive value (PPV) of 95%, and presence of any loss of neurologic function (PPV of 73%), which probably reflects nerve injury. The pain, however, can be observed in 75% of all peripheral nerve sheath tumors, and its PPV for malignancy is between 20% and 30%. Nonetheless, when considering the character of pain, resting pain is more likely to be observed in schwannomas, which are believed to be caused by the release of substances that stimulate pain receptors.[12]

Histopathology

Schwannoma is generally composed primarily of Schwann cells that possess moderate amounts of eosinophilic cytoplasm with no discernible cell borders. Schwann neoplastic cells are arranged in two patterns.

The Antoni A pattern is represented by areas of compact, elongated cells with occasional nuclear palisades. In Antoni A tissue, there are normochromic spindle-shaped or round nuclei similar in size to smooth, tapered rather than closed muscle cells. In this pattern, the tumor cells are very close together, forming nuclear palisades (Verocay bodies), which are alternating parallel lines of tumor cell nuclei with densely-aligned cellular processes.[5] All tumor cells have a pericellular reticulin pattern corresponding to the surface soil membranes.

In Antoni B tissue, tumor cells have smaller nuclei, generally round to ovoid, and are arranged freely. Collections of lipid-loaded cells may be present within the Antoni A or B tissues.[2] It is also noted that the B pattern consists of fewer cells, whose textures are superficial, with indistinct processes and variable lipidization.[2] In contrast to schwannomas, neurofibromas do not contain Antoni A and Antoni B regions, and are less likely to show myelogenous and degenerative areas.[12] Secondary degenerative changes of the tumor can be shown and characterized by the formation of cysts, hyalinization, hemorrhage and calcification. However, degeneration of the ossification is extremely rare.[13] (►**Fig. 2**)

Examples of nuclear pleomorphism such as bizarre forms with cytoplasmic nuclear inclusions ("old schwannoma") and occasional mitotic figures may occur, but should not be considered as indications of malignancy. Malignant transformation rarely occurs in conventional schwannomas.[2]

Schwannomas, immunohistochemically, show strong positivity to proteins, including S-100, vimentin and CD56, and negativity to desmin, smooth muscle myosin, SMA, CD34 and CD117.[5,13] In both histological patterns of Schwannomas, the S-100 protein is positive and essential to establish the diagnosis.[3]

One of the types of these tumors is the schwannoma cell. This variant is hypercellular, composed exclusively or largely by Antoni A tissue, and has no Verocay bodies.[14]

Melanocytic schwannoma consisting of cells with ultrastructure and the immunophenotype of Schwann cells contains melanosomes, reactivity to melanoma markers, heavy melanin deposition, presence of psammoma bodies, nuclear pleomorphism and low mitotic rate.[15,16] Hyperchromasia and macronuclei are common cytological atypia, unlike the reticulin pattern that is generally poor in this subtype.[2]

Melanotic Schwannoma is a rare primary tumor, predominating in spinal and paraspinal nerves, with a global prevalence of less than 1% of primary PNSTs. It is a rare tumor that usually involves roots of the spinal nerves, but may also present in other anatomical sites. The recent publication of the largest series of cases[15] suggested that it was a separate entity from other schwannomas, and that its reclassification to a malignant lesion is considered.

Genetics

Extensive analyses have shown that the *NF2* gene acts as a tumor suppression gene, and is an integral part of the formation of Schwannomas, with the inactivation of the *NF2* gene detected in ~ 60% of these tumors.[17–22] These genetic events are predominantly small frameshift mutations that result in truncated protein products.[23]

In most cases, such mutations are accompanied by the loss of the other allele on chromosome 22q. Still, other cases demonstrate loss of the 22q chromosome in the absence of detectable *NF2* gene mutations. However, loss of expression of the *Merlin* gene, demonstrated by Western blot or immunohistochemistry, appears to be a universal finding in schwannomas, regardless of its mutation or allelic status, suggesting that disruption of the

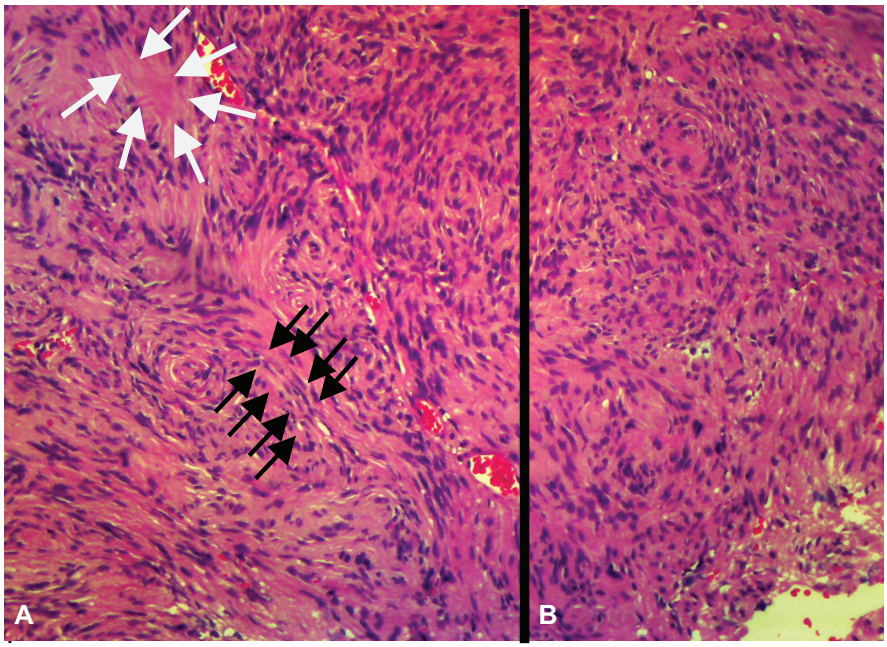

Fig. 2 Schwannoma staining eosin hematoxylin. The white-colored arrows point to a region with less cellularity compatible with a Verocay body. (**A**) An area of Antoni A due to the presence of Verocay body and palisade pointed by black arrow. (**B**) An area of Antoni B in which there is no predominance of palisade area or Verocay body.

Merlin gene function is an essential step in schwannoma oncogenesis.[24–26]

Mutations of the *Merlin* tumor-suppressor gene cause the development of multiple tumors of the nervous system, one being schwannoma. The *Merlin* gene is known to be involved in the regulation of a variety of cell signaling pathways to control cell matrix adhesion, proliferation and survival. The benign nature of tumors deficient in *Merlin* makes them relatively insensitive to conventional chemotherapy, with invasive surgery or radiosurgery being the main therapeutic options.[27]

The Axl, Tyro3 and Mer (TAM family) receptors have a high expression in the TAM family receptors, so that Axl, Tyro3 and Mer are expressed at higher levels in the schwannoma when compared with normal Schwann cells. The expression of the Axl and Tyro3 receptors, but not Mer, was diminished by the reintroduction of the *Merlin* gene.[27]

The relevance of the Axl receptor in tumors deficient in the Merlin *gene* is marked by findings demonstrating that such a receptor is down-regulated by the *Merlin* gene and positively by the E3 ubiquitin ligase CRL4DCAF1. The *Merlin* gene appears to inhibit E3 ubiquitin ligase, which is responsible for changes in tyrosine kinase receptor expression in tumors with this gene.[27]

Other genetic alterations are rare in schwannomas, although a small number of cases with loss of chromosome 1p, gain of 9q34, and gain of 17q have been reported.[28,29]

In patients with type-2 neurofibromatosis, it is important to remember which schwannomas can form along the course of the peripheral nerve and provoke peripheral neuropathies. Nodular subcutaneous schwannomas are identified in ~ 40% of patients, and often cause pain and may produce pain during palpation. In this group of patients, symptomatic lesions of the peripheral nerves are mainly treated by surgical resection.[21]

Diagnostic Imaging

All of the imaging modalities presented here are useful in the preoperative diagnosis of schwannomas; however, each of these methods has limitations in distinguishing the different types of tumors from the nerve sheath and establishing a differentiation between benign and malignant lesions.[11] Although they do not have specificity, they are endowed with a certain diagnostic value, and some radiological characteristics can help doctors differentiate these tumors, helping to guide their approach.[13]

Ultrasonography

On ultrasonography (US), most PNSTs, including schwannomas, are hypoechogenic and have posterior acoustic reinforcement, making them look like a ganglion cyst, which can also be observed in other tumors of uniform cellularity, such as lymphomas.[5,11,12] The presence of blood flow on the Doppler can distinguish a PNST from a cystic lesion.[5]

On US, schwannomas appear as well-defined, ovoid, heterogeneous masses together with cystic degeneration and eccentric location.[11] Although magnetic resonance imaging (MRI) and US can be used to aid in the differentiation between benign and malignant tumors, these techniques are not consistently reliable; however, it is possible to identify signs of degeneration of long-standing tumors by features such as calcifications.[5,12](►**Fig. 3**)

Computed Tomography

On computed tomography (CT), the typical Schwannoma is characterized as an oval-shaped lesion with soft tissue density, heterogeneous, generally with well-defined limits, established by the encapsulation, and they may also present cystic degeneration.[3,13]

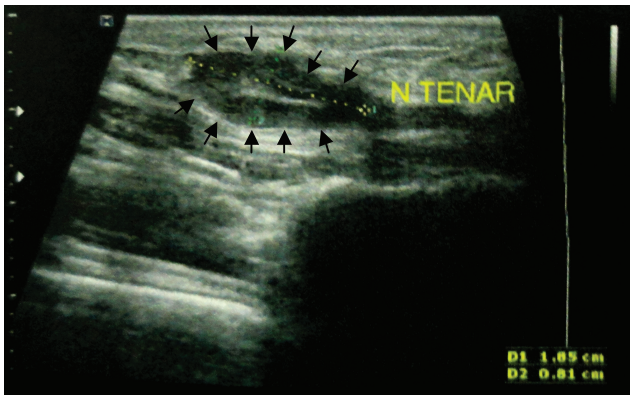

Fig. 3 Note the ultrasonographic aspect of the schwannoma of the median nerve (black arrows). This tumor presents a well-defined limit in this modality of examination. Schwannomas are hypoechoic on ultrasonography.

Some histopathological features of schwannomas may be reflected radiological patterns in tomography images. High cellularity of Antoni A areas produce as inhomogeneous images due to the increased lipid content. On the other hand, Antoni B areas can present cystic/multiseptate components and reveal hypodensity due to loose stroma and low cellularity[13] (►**Fig. 4A** and **4B**).

Magnetic Resonance Imaging

The MRI enables the identification and characterization of lesions with neural involvement, their relation to important anatomical structures, and the extent of intrinsic or extrinsic nerve involvement.[5,11,12] The lesion is typically visualized as a well-defined mass of fusiform shape, located within the nerve, iso- or hypointense in the signal related to the skeletal muscle in T1-weighted images, and with increased signal intensity and slightly heterogeneous in T2-weighted images[11,13] (►**Fig. 5A** and **5B**).

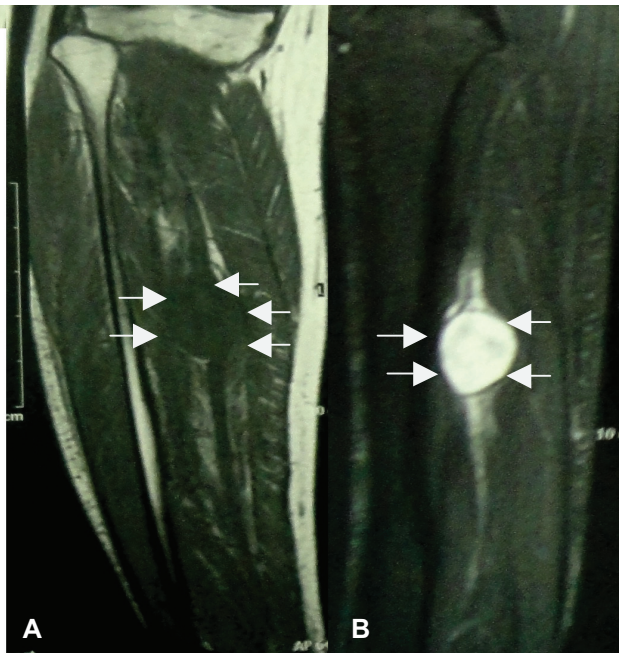

Fig. 5 Magnetic resonance imaging scan of the right lower limb (T1 and T2 respectively). (**A**) Normal tibial nerve (black arrows) and the hypointense tumor (white arrows). (**B**) Enhancement of the tumor with gadolinium.

Postcontrast enhancement in T1-weighted images is considered a defining characteristic of schwannomas. The pattern of this enhancement is characteristically non-homogeneous, with a prominence at the periphery of the lesion. Whether on the MRI or US, cystic changes can be observed and probably represent fluid secretion from tumor cells or areas of the tumor where cell growth has surpassed the blood supply.[3]

Another benefit of the MRI is the possibility of differentiating between neurofibromas and schwannomas based on characteristic findings and an understanding of the intraneural

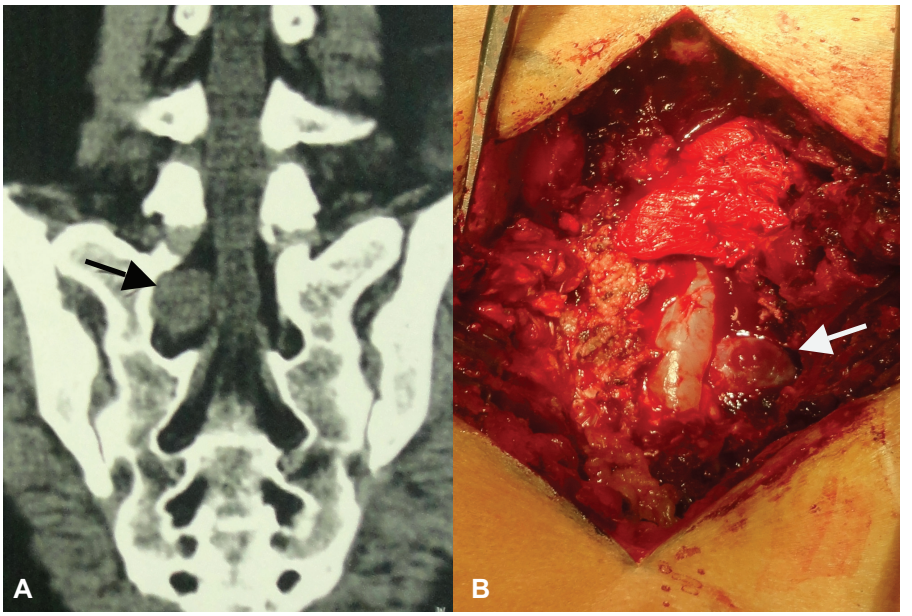

Fig. 4 (**A**) Computed tomography of the lumbosacral spine in a coronal section. The black arrow points to Schwannoma of the spinal nerve S1 on the right. (**B**) Notice the same intraoperative tumor (white arrow).

anatomy. Schwannomas are usually encapsulated and eccentrically located, while neurofibromas are usually located centrally in the nerve sheath and have fascicles that span the tumor, often spreading it in a fusiform fashion. These most commonly demonstrate a target signal, which is a peripheral hyperintense ridge and a central hypointense region in T2-weighted MRI. Schwannomas, more frequently, present a diffuse increase in contrast in the T1 sequence of the MRI.[5]

Although the reliability of imaging techniques in the differentiation of benign and malignant neurogenic tumors is not fully established, certain magnetic resonance characteristics may suggest malignancy, such as large volume tumors, perilesional edema, and intratumoral cystic changes[12] (►**Fig. 5A** and **5B**).

Tractography

The treatment is a technology that enables, through the MRI, the visualization of the cerebral tracts. The construction of the MRI can be performed using conventional anatomical techniques and diffusion-based functional techniques that have the potential to overcome the limitations of the conventional MRI due to its ability to analyze the microstructure of the tissue.[30,31]

An important goal of the surgical treatment is the maintenance of intact limb involvement, with free and tumor-free resection margins, resulting in an oncologically safe preservation of the peripheral nerve. Thus, the treatment represents an extremely valuable tool for the preoperative evaluation of these tumors due to its excellent contrast to soft tissues and its potential to acquire structural image data and to identify where the motor fascicles are passing in the peripheral nerve structure.[31]

The topographic relationship between the peripheral nerve and the tumor can be unequivocally visualized in the treatment, even in the presence of an important alteration of the regional anatomy. In schwannomas, the tumor characteristically originates in the sheath of only one fascicle (main fasciculus or "mother"), leaving the main trunk of the peripheral nerve connected to the mass, and the perception of this topographic relation proves to be particularly important. Thus, a spatial description detailing the location of the motor nerve and the PNST may be extremely valuable to plan the elective surgery for otherwise benign lesions. It is important to state that tractography is a neuroimage exam still restricted to specialized centers, and it presents a practical limitation regarding its use as an elective exam.[31]

Treatment

Surgery

Schwannomas can be resected and evolve with reasonable morbidity, although microscopic enlargement is indicated to avoid damage to nerve fibers. Surgery is successful, with preservation of neurological function in 90% of schwannomas, 80% of neurofibromas, and 66% of neurofibromas in those with type-1 neurofibromatosis.[5]

Patients whose schwannomas are treated by excision with intracapsular enucleation may evolve with sensory and/or motor dysfunction, but few develop long-term neurological deficits. Approximately 80% of patients who have benign tumors experience improvement or complete resolution of pain. Patients who have already undergone biopsy or surgery often have less satisfactory results. Recurrences are quite rare when complete resection is performed. The tumor may be enucleated from the nerve without lesion to the nervous fascicles, except for the one that originated the tumor.[5] (►**Figs. 6A-6D**)

When resection is performed by experienced surgeons, these tumors can be achieved in both superficial and deep sites, including the brachial plexus, lumbosacral plexus, and

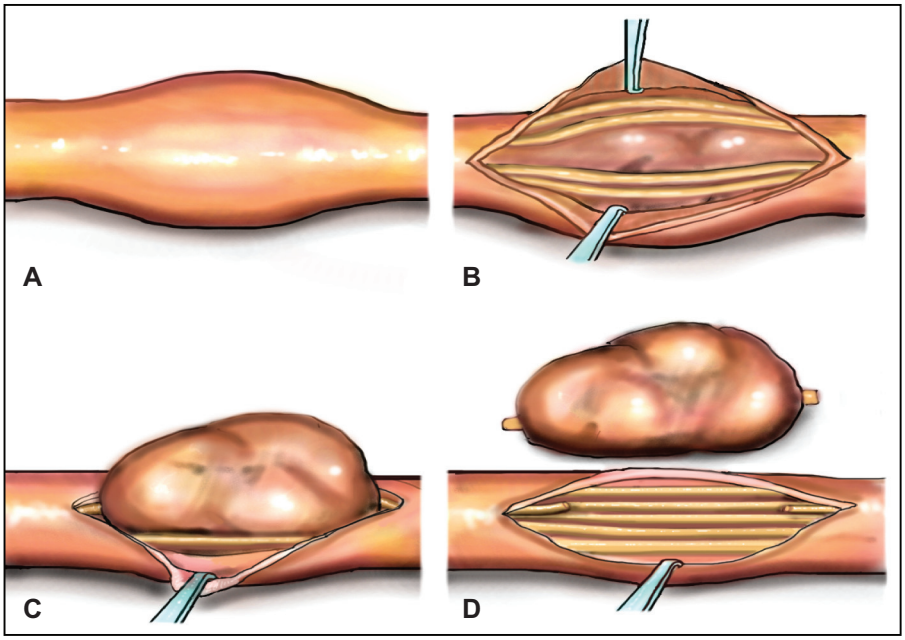

Fig. 6 (**A**) Schwannoma causing bulging in the peripheral nerve. (**B**) After the opening of the epineurium, it is possible to identify the presence of the tumor involved by viable nervous fascicles. (**C**) After the correct dissection of the tumor, the fascicles were removed peripherally to preserve them. (**D**) Complete excision of the Schwannoma is noted with sacrifice only of the bundle that originated it. Source: Marcelo Magalhães and Henrique Oliva.

paraspinal region. Neighborly nervous elements must be mobilized and preserved, and should be identified and protected proximally and distally to the tumor itself before the direct resection attempt. Intraoperative electrophysiology or nerve stimulation may help to identify safe areas in which dissection can be performed, so it assists in the determination of functional and nonfunctional fascicles and facilitates tumor resection.[5,32]

There are already descriptions of the resection of schwannomas through the endoscopic technique for the obturator nerve and sacral spinal nerves.[7,33,34]

Conclusion

Schwannomas are capillary tumors of the myelin sheath, which, for the most part, have benign behavior. They may present asymptomatic or with local symptomatology, evolving with paresthesia, anesthesia and pain, due to nervous compression (mass effect). Imaging tests such as the US and MRI help in the diagnosis. Macroscopically, they present eccentric growth, promoting the centrifugal displacement of the axonal fibers. This feature enables its surgical enucleation without compromising the nerve fibers. When it is approached by experienced professionals and with adequate techniques, the patients do not usually have motor sequelae.

Conflicts of Interest
The authors have none to declare.

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Abducens Nerve Palsy as Initial Manifestation of Chronic Subdural Hematoma: Case Report

Paralisia do nervo abducente como manifestação inicial de hematoma subdural crônico: Relato de caso

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Abstract

Chronic subdural hematoma (CSDH) is a form of progressive intracranial hemorrhage, typically associated with cases of trauma. The manifestation of this comorbidity with abducens palsy is a rare finding. The present work aims to describe the case of an adult patient with abducens nerve palsy as a manifestation of CSDH. Chronic subdural hematoma is most commonly found in elderly patients, with systemic hypertension as a manifestation. The relation with the sixth cranial nerve is unusual and draws attention to the case reported. In addition, the prognosis is positive, since trepanation and drainage surgery was performed, as it is recommended in the literature.

Keywords
- chronic subdural hematoma
- abducens nerve palsy
- cranioencephalic trauma

Resumo

O hematoma subdural crônico (HSDC) é uma forma de hemorragia intracraniana de caráter progressivo, tipicamente associado a casos de traumatismo. A manifestação dessa comorbidade com paralisia do nervo craniano abducente é um achado raro. O presente trabalho visa descrever o caso de um paciente adulto com paralisia do nervo abducente como manifestação do HSDC. O HSDC é mais comumente encontrado em pacientes idosos, com manifestação de hipertensão arterial sistêmica. A relação com o sexto nervo craniano é incomum, e chama a atenção no caso relatado. Além disso, o prognóstico é positivo, uma vez que foi realizada cirurgia com trepanação e dreno, conforme recomendado na literatura.

Palavras-chave
- hematoma subdural crônico
- paralisia do nervo abducente
- traumatismo cranioencefálico

Introduction

Chronic subdural hematoma (CSDH) is characterized as an encapsulated blood collection of different stages of degeneration, with well-defined limits and located between the dura mater and the arachnoid meninges. It is one of the most common forms of intracranial hemorrhage that can present a progressive and chronic character.[1]

The present study aims to describe a rare case of CSDH with initial manifestation of abducent nerve palsy, besides presenting a brief literature review of the topics related to the case herein studied. In order to do so, we used recent

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material made available in virtual libraries, in addition to the analysis of patient records with unusual case presentation.

The study was performed at Hospital Aroldo Tourinho, located in the municipality of Montes Claros, in the state of Minas Gerais, Brazil. A review of the medical records of the patient was first performed to write the case report. Then, we proceeded to the literature search for papers published in the past 35 years and written in Portuguese, English and Spanish. The inclusion criteria for the studies searched were: use of the appropriate methodology; current studies; and studies that shared any similarities with the present case. The exclusion criteria were: low relevance; articles not approaching the area of interest; and lack of essential information.

The following descriptors were used: *chronic subdural hematoma*, *abducens nerve palsy* and *cranioencephalic trauma*. The databases accessed were the Scientific Electronic Library Online (SciELO) and the Virtual Health Library (VHL). The minhaUFMG web portal was also used to access paid articles on topics pertinent to the present research.

Case Report

Patient S.M.O., 35 years old, male and farmer, presented with mild cranioencephalic trauma that had occurred approximately in the preceding 2 months, due to a motorcycle crash while wearing a helmet. He sought outpatient medical care due to diplopia and persistent headache, which resolved $\sim$ 30 days after the accident. A magnetic resonance imaging (MRI) scan of the skull evidenced the presence of a bulky chronic subdural hematoma in the right frontoparietal convexity, with a hypersignal aspect in T1 and heterogeneous isosignal in T2. This hematoma caused a mean line deviation of 1.1 cm and presented the following dimensions: 12.0 $\times$ 6.4 $\times$ 2.0 cm (length x width x depth), totaling 65 mL (►**Figs. 1a** and **1b**). Upon neurological examination, we identified the presence of paresis of the abducens nerve on the left (►**Fig. 2**) side. On the right side, the consensual pupillary reflex was present. There were no alterations in the cerebellar evidence. On the motricity examination, the presence of hemiparesis of degrees 4/5 was observed in the left dimidium. Fundoscopy showed the presence of bilateral optic papilla edema. Conscious alert, oriented and euphasic. After the examination, the patient was urgently hospitalized, , and surgical risk exams were requested. He was submitted to neurosurgical treatment through the trepanation technique in the frontal and parietal bones using a surgical drain. The drain was removed after 24 hours of the surgical procedure, and the patient was discharged 48 hours after surgery. In a return consultation, performed 30 days after the surgical procedure, the patient presented complete recovery of the paresis of the oculomotor nerve.

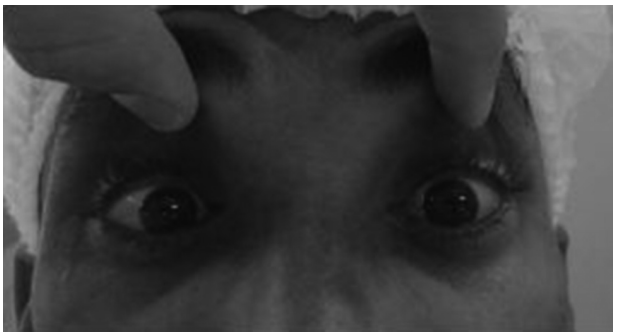

Fig. 2 Photo of the patient moments before the surgical procedure. Observe the presence of convergent strabismus due to the paresis of the abducens nerve to the right.

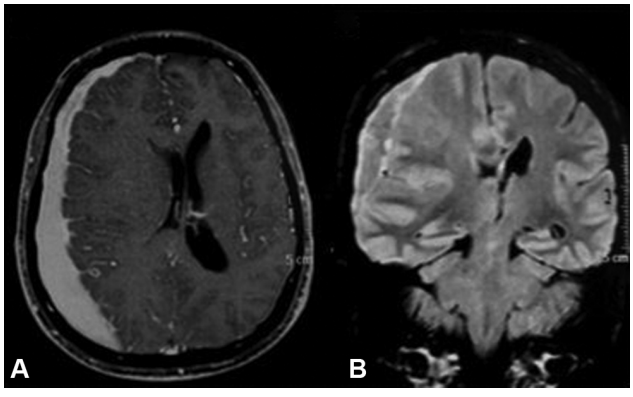

Fig. 1 (**A**) T1-weighted magnetic resonance imaging (MRI) scan of the skull in axial section following contrast with gadolinium. Note the presence of bulky subdural hematoma in the right convexity causing mass effect. (**B**) T1-weighted sequence of MRI of the skull in coronal section revealing a bulky subdural hematoma in the right convexity. Observe the mass effect with evidence of herniation of the cingulate gyrus.

Discussion

The first case of CSDH was reported in 1657 by Johannes Wepfer. A blood-filled cyst was found in the subdural space in a patient who died after a vascular accident. About 9 years later, Morgagni reported a similar finding in a patient who had also died after a vascular accident. In 1817, Houssard described this cyst as a clot wrapped in a membrane. Bayle, in 1826, described CSDH physiopathology as a chronic rebleeding. Chronic subdural hematoma was considered a type of cerebrovascular accident (CVA) in the 17th century, an inflammatory disease in the 19th century, and, in the 20th century, the consequence of a traumatic injury. Only in the end of the 20th century there was a consensus on the current theory of CSDH, which consists of a chronification of an asymptomatic acute subdural hematoma, in which there are microhemorrhages in the external region of the formed membrane, which are responsible for the growth of what would become the CSDH mechanism that Markwalder[2] commented in his review of the subject.[3]

Two theories have been proposed to clarify the development of CSDH: the osmotic theory and the theory of recurrent bleeding in an encapsulated hematoma.[4] The osmotic theory is basically explained by coagulation and posterior degradation of extravasated blood into the subdural space. This degradation would generate a greater number of proteins, increasing osmotic pressure and creating a greater difference in the concentration gradient that would attract fluids of adjacent blood vessels to the hematoma cavity.[5]

However, the most well-accepted and proven theory is the recurrent bleeding theory, which describes the abnormality and dilation of the blood vessels of the hematoma capsule as a source of recurrent bleeding.[1,4]

The most frequent cause of CSDH is trauma, characterized by a sudden process of acceleration and deceleration of the skull, to the point of generating a displacement of the encephalon and rupture of the bridge veins.[6–8]

Chronic subdural hematoma is commonly found in the elderly, and it is usually bilateral, especially in those older than 75 years of age. In young adults, CSDHs are relatively infrequent and, unlike those in the elderly, are almost always unilateral.[9] Since one of the risk factors is age, which is not modifiable, its incidence may reach 58 cases for every 100,000 people per year in age groups of people older than 70 years, while in the general population it is of $\sim$ 5 cases for every 100,000 people per year.[1]

The most used exams for CSDH evaluation are computed tomography (CT) and MRI of the skull, since they detect various characteristics of the hematoma, such as the intensity of the lesion, presence of recurrence, and the patient's hematocrit status.[9,10]

Computed tomography is the least innocuous imaging method, but it is faster and has a lower cost. Some cranial CT findings are the deviations of structures in the median line and cerebral herniations. The blood collection usually presents as homogeneous and hypoattenuating in the CT; if there is any new bleeding, the new collection will present as hyperdense.[11]

The MRI provides more accurate information about the location and extent of the hematoma and its effect on adjacent structures. In cases of isodense and bilateral hematomas, if small collections at the base of the skull and in the posterior fossa are found, the MRI is even more advantageous.[10]

The signs and symptoms of the patient may be diverse, as they depend on certain factors such as: size and location of the hematoma, age of the patient, and whether it is unilateral or bilateral. Some of the most recurrent symptoms of this disease are: hemiparesis, sudden hemiplegia, and progressive headache without improvement with the use of simple analgesia.[12] In a study[13] conducted between 1971 and 1987 with 96 surgical cases of CSDH, the following symptoms were present in order of prevalence: headache (69.8%), focal motor deficit (62.5%), dementia syndrome (38.5%), torpor (28%), urinary incontinence (19.8%), coma (14.5%), ataxia (11.5%), convulsive crises (5%) and aphasia (5%).[13]

Oculomotor nerve palsy as one of the initial clinical manifestations of CSDH is rare, but some cases are found in the literature. This paralysis is responsible for causing palpebral ptosis on the affected side and diplopia. In the case of unilateral lesions of the third cranial nerve, a differential diagnosis of microvascular infarction and intracranial aneurysm should be performed.[14]

The abducens nerve is the sixth pair of cranial nerves, responsible for innervating only the lateral rectus, for abduction of the ocular globe.[15] Motoneurons originate in the abducens nucleus, which is located in the caudal and dorsal regions of the bridge, and leave the nucleus ventrally to form the abducens nerve fibers in the brainstem. This cranial nerve leaves the brainstem at the junction between the bridge and the bulb to enter the subarachnoid space. It is noted that the nerve then makes an acute angle before turning and ascending over the clivus at the petrous apex. It passes under the petroclinoid ligament and penetrates the Dorello canal, where the dural connection makes it vulnerable to the change in intracranial pressure and trauma. Then, this nerve crosses the cavernous sinus, adjacent to the internal carotid artery.[15,16] Abducens nerve lesions result in unilateral involvement of the eye abduction, in addition to horizontal diplopia and deviation of the eye toward the nose, being worse in the direction of action of the affected lateral rectus.[15] In addition, abducens nerve palsy is reported as the most common cranial neuropathy to occur in isolation.[17] The main etiologies are: trauma, neoplasia, cerebrovascular disease and cerebral aneurysms.[15]

There are other cases of abducent nerve palsy reported in the literature with favorable prognosis. There is a good margin of recovery of the physiological activity of the sixth cranial nerve, and the total recovery rate can reach up to 73% within 6 months, when the CSDH is unilateral, and the mean recovery time is 3 months.[18]

There are several possibilities of conservative treatment described in the medical literature for CSDH: extreme rest, corticoids and hypertonic solutions.[1,9] However, clinical treatment is not the best indication, since the surgical procedure has been accepted worldwide as a more efficient method.[1]

There are several types of surgical treatment for CSDH, such as craniotomy, trepanation and endoscopy. Craniotomy is indicated when the blood collection membrane is calcified, and not liquefied, ossified, organized or multiloculated. Trepanation is one of the most efficient choices when the CSDH will not be removed; one or two trepanations can also be performed, and the performance of two is associated with a better postoperative evolution. The endoscopic treatment is a safer way to perform the removal of the CSDH, and it is indicated when the blood collection is solid, organized and multiloculated, because it guarantees a direct view of it.[19]

The use of drains in the trepanation orifice in the postoperative period is associated with a reduction in the number of recurrences of the subdural hematoma. In a randomized study conducted in the United Kingdom with 269 patients older than 18 years of age, the recurrence rate in patients with drains was of 9.3%, while in patients without drains it was of 18.1%.[20]

Conclusion

When compared with other cases found in the neurosurgery routine practice, CSDH is a disease associated with significant rates of morbidity and mortality. As described, the most frequent clinical alterations are systemic arterial hypertension and altered consciousness. The case is especially rare when it presents involvement of the abducens nerve, even when the cause is not uncommon, that is, trauma. Trepanation with double orifices and drainage confirmed the effectiveness reported in the literature, and it is the most indicated technique,

which did not involve complications in the present case. The patient presented a good prognosis, with improvement of the symptoms 1 month after the surgical intervention.

Conflict of Interests

The authors have none to declare.

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Lhermitte-Duclos Disease and Cowden Syndrome: A Case Report and Literature Review

Doença de Lhermitte-Duclos e Síndrome de Cowden: relato de caso e revisão da literatura

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Abstract

Lhermitte-Duclos disease (LDD), also known as dysplastic gangliocytoma of the cerebellum, is a rare, usually benign, slow-growing tumor, that commonly affects patients aged 30 to 50 years-old. The manifestations of dysplastic cerebellar gangliocytoma are nonspecific and are related both to the mass effect produced by its growth and to the location of the lesion. Cerebellar symptoms such as ataxia are often present. In 40% of cases, the tumor is associated with Cowden syndrome, which is part of a group of genetic disorders called polypoid hamartoma complex. In this case report, the patient presented expansive lesion in the posterior fossa, compatible with LDD, associated with macrocephaly. These findings are considered major criteria for Cowden syndrome. When together, they confirm the diagnoses. To our knowledge, this is the first report of the association of LDD and Cowden syndrome in Brazil.

Keywords
- Lhermitte-Duclos disease
- Cowden syndrome
- hamartoma syndrome
- cerebellum

Resumo

A doença de Lhermitte-Duclos (DLD), também conhecida como gangliocitoma displásico do cerebelo, é um tumor raro, geralmente benigno e de lento crescimento, que geralmente afeta pacientes entre 30 e 50 anos. Suas manifestações são inespecíficas e se relacionam ao efeito de massa produzido por seu crescimento e pela localização da lesão. Comumente, observam-se sintomas cerebelares, como ataxia, dismetria e disdiadococinesia. Em 40% dos casos, a doença encontra-se associada à síndrome de Cowden, a qual faz parte de um grupo de enfermidades genéticas chamado complexo do hamartoma polipoide. No caso relatado, o paciente apresentou lesão expansiva em fossa posterior compatível com DLD, associada à macrocefalia. Esses achados constituem dois critérios maiores, os quais, em conjunto, determinam o diagnóstico de Síndrome de Cowden. Este é o primeiro relato da associação entre DLD e Síndrome de Cowden no Brasil.

Palavras-chave
- doença de Lhermitte-Duclos
- doença de Cowden
- síndrome do hamartoma múltiplo
- cerebelo

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Introduction

Lhermitte-Duclos disease (LDD), also known as dysplastic gangliocytoma of the cerebellum, is a rare condition. Only ~ 300 cases have been reported in the literature since its description in 1920.[1–3] This tumor, which is composed by atypical ganglion cells, is considered benign and slow-growing.[4,5] It usually presents in patients aged between 30 and 50 years. The non-specific clinical picture is related to the location of the tumor and to the mass effect produced by its growth. Therefore, the most common symptoms result from cerebellar involvement. Headache, motor disorders, intracranial hypertension, and ataxia, as well as others, are frequently observed.

The crucial point of LDD is the possibility of association with Cowden syndrome (CS), which participates in a group of genetic syndromes called polypoid hamartoma syndrome.[6] This rare and autosomal dominant disorder is characterized by the presence of multiple hamartomas, which confers an increased risk to developing other neoplasms. The features of CS include benign mucocutaneous lesions, such as trichilemmomas, acral keratoses, and papillomatous lesions, in addition to LDD—which was recognized as a major criterion for Cowden syndrome by the International Cowden Consortium Criteria, in 2004.[7,8]

As far as we know, there is no report of LDD associated with Cowden syndrome in Brazil. In the present work, we not only report this condition but also present the findings of our systematic review of the literature.

Case Report

A 26-year-old male, living in Manaus, Amazonas, presented at our hospital with progressive unsteadiness. At the moment of admission, he was unable to walk. The patient also reported persistent and gradually increasing headache. Neurological examination revealed preserved motor strength, as well as an ataxic gait, dysdiadochokinesia, hypermetria, and dysarthria. A left nystagmus was further noticed.

Computed tomography (CT) of the skull showed a hypodense lesion in the posterior fossa on the right cerebellar hemisphere. A T1 gadolinium-enhanced magnetic resonance imaging (MRI) demonstrated a lobulated non-enhanced mass lesion, characterized by alternated linear hyposignal and isosignal areas.

In T2-weighted sequences, the hyposignal and hypersignal bands formed a "tiger-striped" pattern, an aspect classically described in cases of LDD. The lesion compressed the fourth ventricle but did not determine hydrocephalus **(►Fig. 1).**

In light of the suspected diagnosis, it became valid to investigate the possibility of CS. A thorough physical examination revealed macrocephaly (62 cm of circumference, 95th percentile), as well as asymptomatic papillomatous lesions on the penis glans. Sexually transmitted diseases were discarded.

After diagnosis, surgical excision of the tumor through right suboccipital craniotomy was performed. Following dural opening, the cerebrospinal fluid was drained next to the cisterna magna, and we performed a small corticectomy. The non-bleeding hardened lesion resection was subtotal,

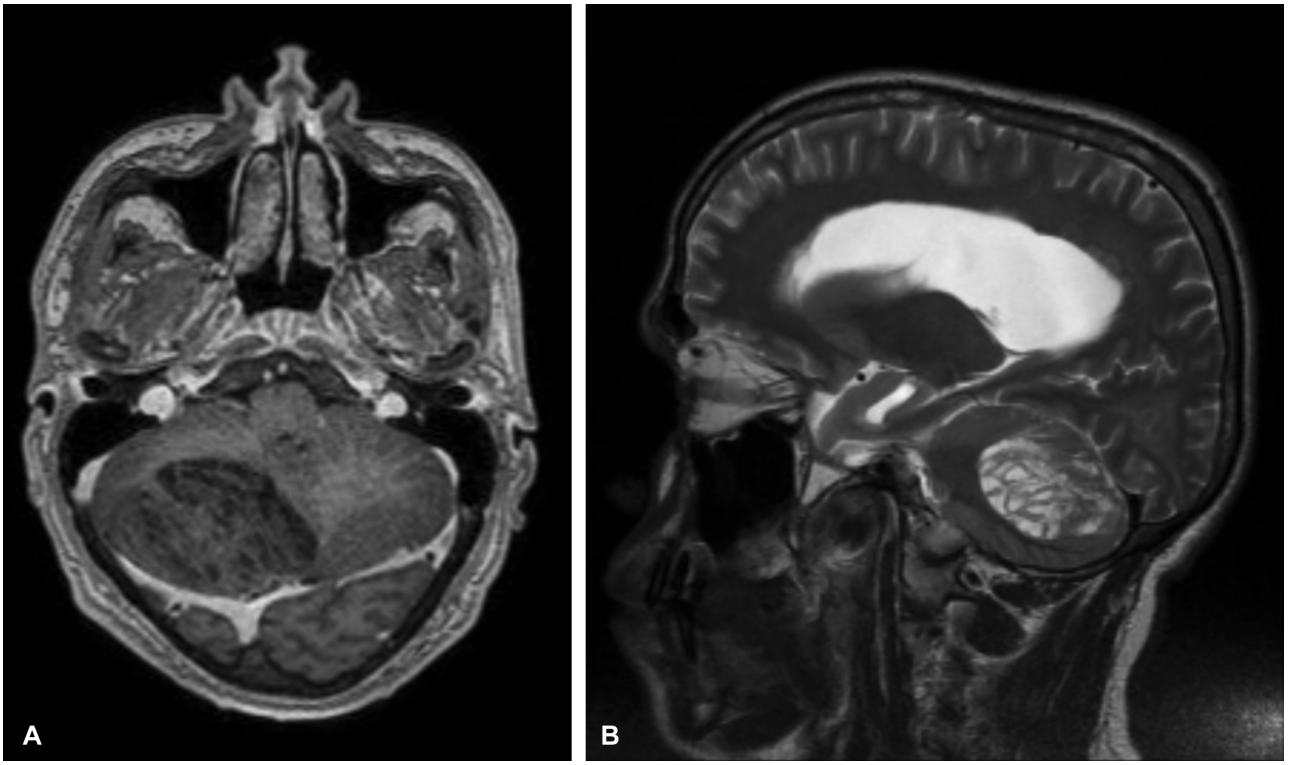

Fig. 1 Magnetic resonance imaging shows a non-contrasting expansive lesion in the right cerebellar hemisphere, with lamellar areas of intense hyposignal and isosignal in T1 with gadolinium (A). In T2 (B), the hyposignal and hypersignal bands reveal the striated pattern, referred to as "tiger-striped" sign, which is classically described in the cases of Lhermitte-Duclos disease.

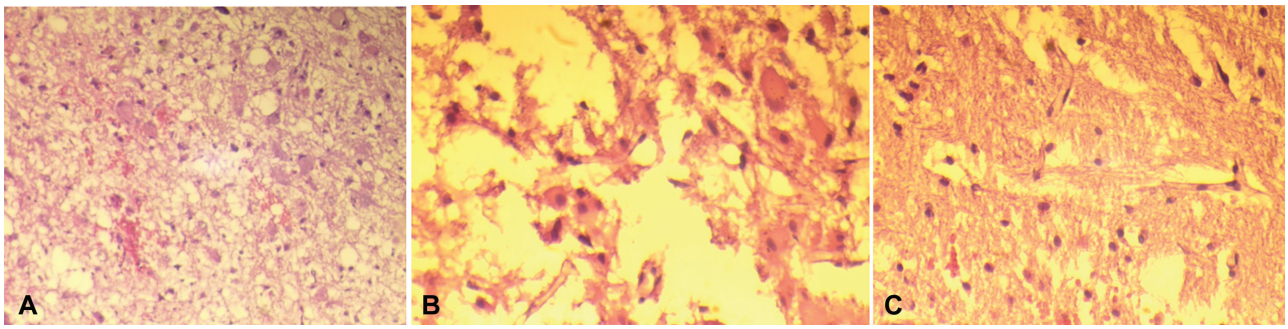

Fig. 2 Histopathological examination of the tumor (hematoxylin and eosin staining, original magnification of 200x). A and B: Polygonal cells with pleomorphic and cytoplasmic broad, eosinophilic nuclei, placed diffusely associated with vacuoles. C: normal glial cells of the same patient.

due to the absence of cleavage plane and difficult differentiation from the normal tissue.

In the histopathological study, proliferation of polygonal cells with pleomorphic nuclei, and broad and eosinophilic cytoplasm associated with vacuoles was observed. Hypertrophy of the cerebellar granular layer compatible with the diagnosis of dysplastic gangliocytoma of the cerebellum was further noticed. (►**Fig. 2**)

After treatment, the patient presented significant clinical improvement, with no cerebellar complaints and reduction of the headache. He has now completed 12 months of postoperative follow-up.

Discussion

For the literature review, we used the Medline and Lilacs databases to search relevant articles from the last review of the literature on the subject from 2006 until March 2019. We use the terms *Lhermitte-Duclos disease*, *Lhermitte Duclos disease*, *Dysplastic gangliocytoma Cowden Disease*, *Dysplastic Gangliocytoma of the Cerebellum*, and *Cowden Syndrome*. We identified 136 articles, and, of these, most were case reports (77 articles), and 2 articles were case series. So far, there are ~300 cases published in the literature. Of these, 5 reports are Brazilian.[9–14] Therefore, this article is the 6th report of LDD and the first to report the association with CS in Brazil.

First described in the 1920s, there still is considerable controversy concerning the origin of LDD. It is known, however, that LDD is considered a major criterion of CS, an autosomal dominant genetic disorder.

Lhermitte-Duclos disease, or dysplastic gangliocytoma of the cerebellum, is a slow growing lesion of the cerebellum cortex, and it is usually diagnosed between the third and fourth decade of life, as identified in the present case, with no gender predominance. The expansive effect, associated with obstruction of cerebrospinal fluid flow, may result in noncommunicating hydrocephalus and intracranial hypertension. In addition, cerebellar symptoms, as in the case described, and cranial nerves involvement may occur.

The imaging examination is of great value during the diagnostic investigation of LDD. Although CT has significant limitations—showing a hypodense image without contrast enhancement—, the MRI associated with diffusion sequence and spectroscopy, shows a classic expansive lesion with hypo-signal on T1 and hypersignal on T2-weighted sequences.[15] Another feature observed in T2-sequences is the characteristic "tiger-striped" pattern. These changes result from both the white matter atrophy and the granular cell layer thickening.

The preoperative diagnosis is given by the tiger striped pattern present in T2-weighted MRI scans, associated with expansive cerebellar lesion affecting a single hemisphere. The lesion is characterized by hyperdense parallel grooves that occur due to cerebellar foliation thickening secondary to cortical cell enlargement, as well as groove dysplasia, which are considered to be practically pathognomonic radiological signs of LDD.[16,17]

Cowden syndrome, characterized by Lloyd and Dennis in 1963, should be investigated in patients diagnosed with LDD.[18] The syndrome is a genetic disorder due to a mutation in the phosphatase and homologous tensin (PTEN) gene or in its promoter region. The disorder affects the PTEN gene in the 10q23.2 locus in 80% of the patients. In addition, most LDD patients have a deletion-type mutation of the PTEN gene, resulting in abnormal growth of granular cells.[8,18] The clinical diagnosis of this condition is based on the major and minor criteria described below (►**Table 1**). The pathognomonic CS criteria are: mucocutaneous lesions (facial trichilemmomas, papillomatous lesions, acral keratosis and mucosal lesions). The major criteria include: breast cancer, thyroid carcinoma (especially follicular type), macrocephaly (occipital-frontal circumference $\geq$ 97th percentile), endometrial carcinoma and LDD. Minor criteria include: other thyroid lesions, decreased intellectual capacity (IQ $\leq$75), hamartomatous intestinal polyps, fibrocystic breast disease, lipomas, fibroids, tumors of the genitourinary tract (mainly renal cell carcinoma), genitourinary malformation, and uterine myoma. Therefore, the patient reported in the present case presents CS since it has 2 major criteria (LDD and macrocephaly), which define the diagnosis. The importance of the association relies on the fact that this disease determines a high risk of both benign and malignant neoplasms development. The thyroid, breast and endometrium are the main organs affected by the aforementioned neoplasms. Therefore, those patients should be closely monitored by a multidisciplinary team for surveillance of possible neoplasms that may occur.

The definitive treatment of LDD is surgical resection with decompression of the posterior fossa by total or subtotal tumor removal. Complete resection of the tumor is difficult due to the

Table 1 Diagnosis criteria of Cowden syndrome

Pathognomonic criteria	Major criteria	Minor criteria
Mucocutaneous lesions: - Facial trichilemmomas - Acral keratoses - Papillomatous papules - Mucosal lesions	Breast cancer Non-medullary thyroid cancer Macrocephaly Endometrial Cancer Lhermitte-Duclos disease	Benign thyroid lesions (goiter/nodules) Mental retardation Hamartomatous intestinal polyps Lipomas Fibrocystic breast disease Fibromas Genitourinary tumors or malformations
Operational clinical diagnostic criteria for an individual: 1) Pathognomonic mucocutaneous lesions alone if: a. Six or more facial papules, at least three of which are biopsy-confirmed trichilemmomas, or b. Cutaneous facial papules plus oral mucosal papillomatosis, or c. Oral mucosal papillomatosis plus acral keratoses, or d. Six or more palmoplantar keratoses 2) Two or more major criteria, one of which must be macrocephaly or Lhermitte-Duclos disease 3) One major plus three minor criteria 4) Four minor criteria		

Adapted from MESTER, 2014.

impossibility of clearly defining its margins.[19,20] In the largest series published to date, Jiang et al[19] evaluated 18 patients with LDD. Complete resection was possible in 9 of the 17 operated patients, and there was no recurrence in the late follow-up. Cowden syndrome was diagnosed in 11 of these 18 patients. Despite the degree of resection (partial or subtotal), the outcome is favorable, and recurrence is rare.[19,20]

In the second largest published series, Wang et al[20] evaluated 12 patients, and a complete resection was achieved in 3 patients. Only one recurrence was reported. In cases of asymptomatic patients incidentally diagnosed by MRI, conservative management may also be assumed.[21,22] The real effectiveness of posterior fossa irradiation therapy is unknown. However, assuming the non-neoplastic etiology of LDD, irradiation is unlikely beneficial, and, therefore, it is not recommended—even in subtotal resections.[19,23]

Moreover, in the histopathological examination, which is the gold standard for diagnosis, the white mass atrophy and the granular cell layer thickening can be observed.[2,6] The absence of the Purkinje, the laminar cytoarchitecture destruction of the cerebellar cortex, and the presence of hypertrophic and dysplastic neurons in the internal granular layer are common findings. On the other hand, the absence of mitotic activity, necrosis, and endothelial proliferation indicate the benign nature of the lesion.

Conclusion

Lhermitte-Duclos disease is considered a rare cause of progressive headache, associated with cerebellar symptoms. When it comes to preoperative diagnosis, the T2-weightened MRI, which can demonstrate the classical "tiger-striped" pattern, is the preferential exam. The definitive diagnosis, nonetheless, is histopathological, and it results from the demonstration of a laminar cytoarchitecture destruction, as well as from the presence of hypertrophic and dysplastic neurons in the internal granular layer, and the absence of the Purkinje cell layer. The treatment can be either surgical or not. While tumor resection is recommended for all symptomatic patients, a conservative management may be considered for incidentally diagnosed asymptomatic patients. Physicians must remember to search the association with CS, which justifies a regular follow-up of the patient due to the risk of developing malignant lesions in other organs, such as the breast, the colon, and the thyroid.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Large Vertex Epidural Hematoma: Case Report and Review of Surgical Approaches

Volumoso hematoma epidural do vértex: relato de caso e revisão de estratégias cirúrgicas

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Abstract

Vertex epidural hematomas (VEHs) are a special clinical entity due to their clinical presentation, vascular etiology and options of surgical approach. The clinical suspicion involves recognizing the mechanism of the injury and the correct visualization of the hematoma in computed tomography (CT) coronal sequences. In the present article, we describe a case of a very large (146 mL) VEH with central brain herniation, and provide a technical note on the surgical planning and treatment. A 34-year-old male patient was admitted to the hospital after an injury on the left superior parietal region. The Glasgow coma scale score was 6, and the left pupil of the patient was dilated. The CT scan showed a large epidural hematoma on the vertex between the coronal e lambdoid sutures, and a fracture over the sagittal suture. During the surgery, multiple burr holes were made laterally to the sagittal suture, and after inspection and no visualization of bleeding in the superior sagittal sinus (SSS), we performed a standard biparietal craniotomy. The patient was discharged three days after the surgery without any deficits. Currently, with the improvement in imaging modalities, more cases of VEH are being identified. Identifying the etiology prior to the craniotomy is challenging in severe cases. Tears in the SSS can bleed profusely, and they demand strategies during the craniotomy. With multiple burr holes parallel to the sagittal suture, we can visualize whether there is bleeding in the SSS and design a craniotomy with or without a central osseous bridge to anchor the dura. Neurosurgeons must be prepared to plan a surgical strategy in cases of large VEHs. Due to its rare frequency and bleeding risks, VEHs are considered challenging.

Keywords

- vertex epidural hematoma
- traumatic brain injury
- craniotomy

Resumo

O hematoma epidural do vértex (HEV) é uma entidade clínica especial particularmente por sua sintomatologia, etiologia vascular e tratamento. A suspeita clínica envolve o reconhecimento do mecanismo do trauma e a correta visualização de sequências

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coronais na tomografia. Descrevemos no presente artigo um paciente com volumoso HEV (146 mL) com herniação central e detalhes do planejamento cirúrgico. Paciente de 34 anos, do sexo masculino, deu entrada no hospital após agressão na região parietal esquerda superior. A escala de coma de Glasgow foi de 6 pontos, com dilatação pupilar esquerda. A tomografia demonstrou grande HEV entre as suturas coronal e sagital associado a fratura. Na cirurgia, realizamos múltiplas trepanações lateralmente à sutura sagital e, após inspeção do seio sagital superior (SSS), fizemos uma ampla craniotomia biparietal. Após 3 dias, o paciente recebeu alta sem déficits. Atualmente, mais casos de HEV são identificados radiologicamente por conta de melhoras nas modalidades de exames radiológicos. Identificar a etiologia antes de realizar a craniotomia é desafiador em casos graves. Lesões no SSS podem apresentar sangramento volumoso, o que exige o uso de estratégias durante a craniotomia. Com múltiplas trepanações paralelas à sutura sagital, podemos antecipar se há ou não sangramento ativo do SSS e desenhar uma craniotomia com ou sem ponte óssea central de ancoramento dural. Neurocirurgiões devem estar preparados para planejar uma estratégia cirúrgica em casos de HEV. Por sua raridade e potencial de sangramento, os HEVs são considerados desafiadores.

Palavras-chave
- hematoma epidural do vértex
- traumatismos craniocerebrais
- craniotomia

Introduction

Vertex epidural hematomas (VEHs) are extremely rare. They comprise ~ 1 to 8% of all traumatic epidural hematomas.[1] The diagnosis is difficult, and it is based on cases of inadequacy of orientation in axial head CT scans; therefore, the identification of this type of hematoma is challenging.[2,3] In many cases, the superior sagittal sinus (SSS) is the main structure involved in the origin of the bleeding.[4]

There are a lot of reported cases of VEH.[1,5–7] We describe in the present article a rare and extremely large VEH with central brain herniation, and provide a technical note on the surgical planning and treatment.

Case Report

A 34-year-old male patient was admitted to our hospital after a traumatic aggression on the left superior parietal region by a Wood stick during a discussion. He immediately lost his consciousness, and was intubated and transferred by helicopter to our facility. After 80 minutes, upon admission at the emergency room, a physical examination revealed a dilated left pupil with no reaction to light. He had a Glasgow coma scale (GCS) score of 6 and a subcutaneous hematoma on the vertex scalp. The best motor response was obtained in the arms, which made us investigate traumatic spinal cord injury. Clinically, he presented arterial pressure of 140/95 mmHg, heart rate of 88 beats/minute, and blood oxygen level (SpO_2) of 98%, and received 2,000 mL of crystalloid fluid. A non-contrast brain computed tomography (CT) scan showed a large epidural hematoma on the vertex between the coronal e lambdoid sutures, bilaterally (►**Fig. 1**). The volume of the hematoma was of approximately 146 mL. A three-dimensional (3D) CT reconstruction revealed a straight fracture over the sagittal suture extending to the frontal bone (►**Fig. 2**). No spinal fracture or dislocation was found on the routine CT of the spine. Due to the evident brain herniation in progress and intracranial hypertension, the patient was transferred immediately to the operating room without being submitted to a more accurate study of the vascular damage in the SSS

Surgical procedure: The patient was placed in supine position with a slight flexion of the head. An incision was planned bilaterally at a point between the coronal and lambdoid sutures. After a subperiosteal plane dissection, the parietal bone was exposed, showing a diastatic fracture aligned with the sagittal suture (►**Fig. 2**). A large bilateral parietal bone flap was made by two anterior burr holes, close to the coronal suture, and close to the midline. The flap was taken out, and the clot was identified and evacuated carefully from the lateral to the medial parts to prevent bleeding from the SSS. There was no injury in the outer surface of the SSS. Dural anchoring sutures were applied around the lateral edges of the craniotomy. The subdural space was inspected to exclude the presence of subdural hematoma, and, at the same time, we inserted saline solution to facilitate dural adhesion to the bone. The flap was secured with sutures, and subgaleal drains were placed.

Postoperative Course

Recovery was good, with a GCS score of 15 after 24h. A CT scan of the head after surgery showed a good result and no evidence of mass effect, with minimal residual hematoma (►**Fig. 2**). By day 5, the patient was discharged successfully, with no additional deficits.

Discussion

Vertex epidural hematomas are rare and frequently associated to bleeding from the venous sinus, bone fracture or dural diffuse bleeding (arterioles).[7] They must be considered a special clinical entity because of their presentation and vascular etiology.[1] Clinical suspicion relies on the symptoms of the

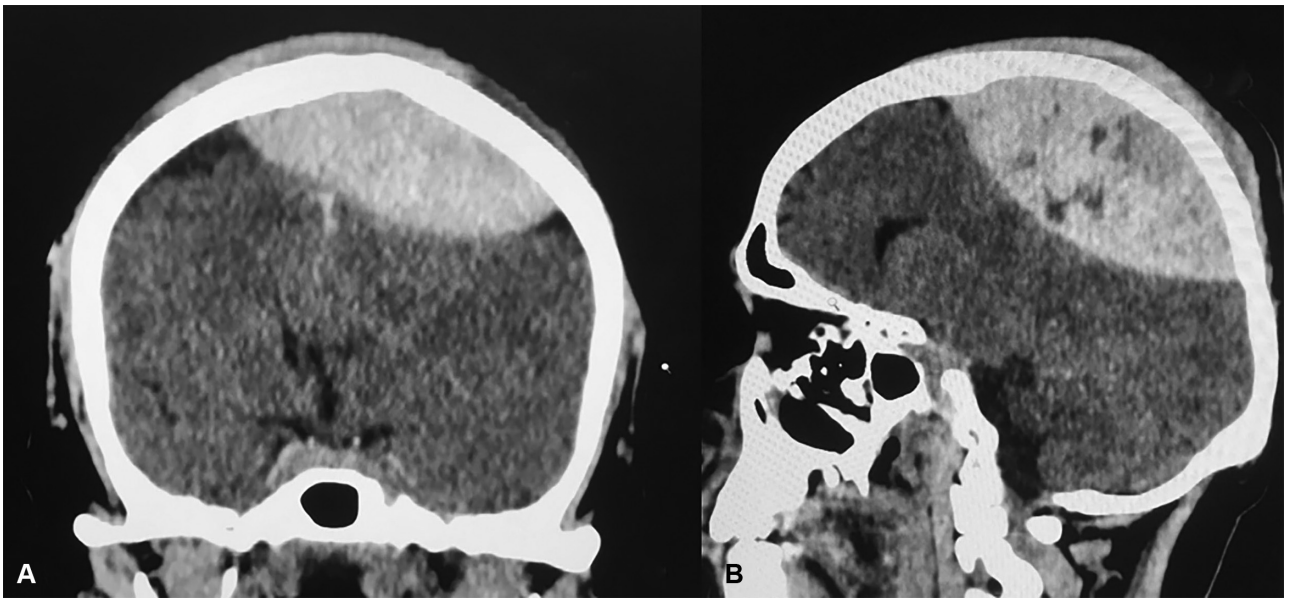

Fig. 1 Large vertex epidural hematoma with central brain herniation and compression of the diencephalic structures. (**A**) Coronal and (**B**) sagittal computed tomography (CT) scan sequences.

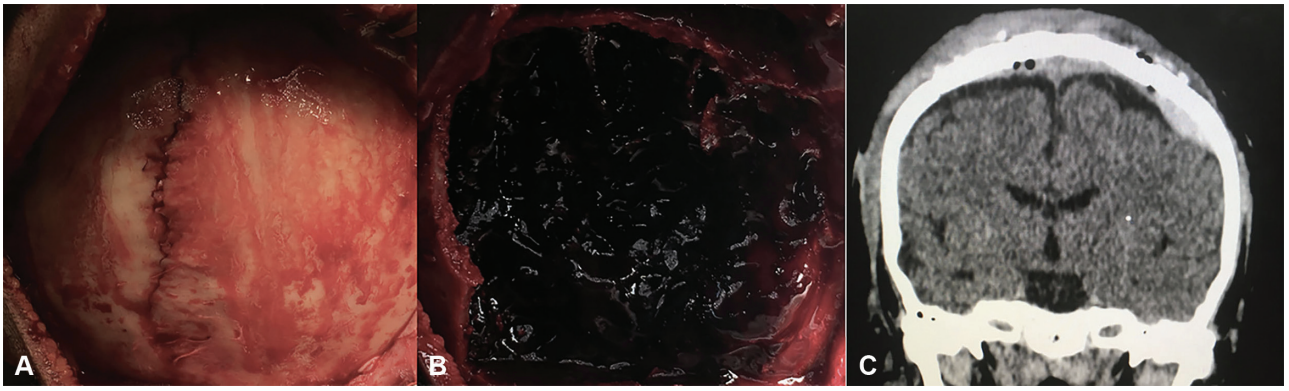

Fig. 2 (**A**) Intraoperative view of a diastatic fracture of the sagittal suture. (**B**) After the biparietal craniotomy with visualization of a large epidural hematoma; (**C**) Coronal CT scan one day after surgery.

patient and on the mechanism of the injury. In cases in which the SSS is damaged, the clinical course is more acute, with elevation of intracranial pressure (ICP) and brain herniation.[7,8] When the bleeding comes from other sources, the clinical symptoms and the evolution are more indolent.

A wide variety of symptoms can occur in cases of VEH. In the emergency room, weakness in the lower extremities can lead the physicians to mistake the clinical picture for spinal cord injury. In cases of paraplegia after a traumatic brain injury, the possibility of occurrence of VEHs must be considered. If the patient is conscious, awake, a critical volume of 40 to 50 mL can be treated conservatively.[9] About 30% of VEHs reported have a chronic course of symptoms. The block of the cerebrospinal fluid and disruption of the venous drainage can explain the chronic presentation, even with VEHs with small volumes.[10]

Due to its location, VEH can cause compression of the rolandic cortex, with special involvement of the motor control of the lower limbs.[5] This presentation is usually noted when the course of the hematoma expansion is more subtle and slow. Even if it is secondary to venous structures, VEH can present a large and quick expansion and be restrained by the coronal and lambdoid sutures. In this situation, a pressure vector toward the diencephalon contributes to the depression of the consciousness level.

Coronal CT scan sequences are the ideal method to investigate VEHs. Depending on the orientation of the axis in axial CT scans of the brain, a large VEH may not be visualized, and be masked by surround bone.[3] This is a particular problem when the patient is studied in sequential (horizontal) scans instead of spiral (helical) scans, and the more cephalic scan planned be out of VEH.[2] This interface between these two structures with grossly differing density is known to be problematic. When the trauma is on the skull vertex and reveals strong forces, repeating a normal CT scan and finding no evidence of hematoma is a secure option to identify or rule out VEH.

Some authors recommend the use of CT venous angiography before craniotomy to prevent a large bleeding from the SSS

and thus program a surgical strategy. Cerebral arteriography has been mentioned as an option in cases of chronic evolution due to the rare possibility of occurrence of an arteriovenous fistula.[10] Before the existence of the CT, finding a dislocation of the SSS from the inner skull table was an evidence of VEH.[2] Slow blood flow on the SSS is another evidence. In pediatric patients with open fontanels, treatment with aspiration by direct puncture is an alternative approach.[2]

Many authors have described surgical techniques in which a bone bridge is left over the SSS to avoid potential bleeding.[1,4] That is a consideration if we realize the risks of dealing with the second third of the SSS. Tears over the SSS may complicate the surgery and result in higher morbidity and mortality.[1,8] Another option that has been mentioned is the interposition of sutures using Teflon pledgets to control profuse SSS bleeding.[5] In our case, we planned a straight incision over a line between the coronal and lambdoid sutures. A biparietal craniotomy was performed with multiples burr holes beside the sagittal suture. At this point, we didn't see active bleeding coming from the sinus, and we ended up performing a craniotomy without a bridge bar. In our opinion, this strategy can be followed carefully before planning the craniotomy, leaving only a strip of bone over the SSS if active bleeding is visualized under the fractured bone.

We emphasize in the present article that the use of saline infusion for the expansion and elevation of dural gaps has some risks that include infections and the creation of hypertensive subdural collections. Central and peripheral anchoring are still the main options to prevent the accumulation of a new hematoma. When no anchoring point is possible to obtain, the direct repair of the SSS bleeding can be performed by direct pressure with cottonoids, muscle and Gelfoam (Pfizer, New York, NY, US). Even digital pressure is a temporary option. Putting the head in the reverse Trendelenburg position helps prevent air embolism. In rare cases with large sinus lacerations, the use of a Fogarty catheter, sinoraphy with continuous suture, or even grafts can control this problem.

Conclusion

Neurosurgeons must be prepared to plan a surgical strategy in cases of large VEHs. Due to their rare frequency and bleeding risks, they represent a challenge in cases of emergency surgery.

Conflicts of Interest
The authors have none to declare.

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Bilateral Accessory C1 and C2 Facet Joints; Clinical, Neuroradiological and Peroperative Findings in an Adult with Quadriparesis

Acessórios faciais bilaterais C1 e C2; Achados clínicos, neurorradiológicos e peroperatórios em um adulto com quadriparesia

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Abstract

Objectives Accessory C1 and C2 facet joints are very rare. Only few cases were reported in the literature. We report a case of bilateral accessory facets in an adult with special attention to clinical, neuroradiological, as well as peroperative findings.

Case report A 37-year-old male presented with progressive quadriparesis. Radiology revealed bilateral posterior accessory C1 and C2 facet joints compressing the spinal cord with craniovertebral junction (CVJ) instability. Both accessory C1 and C2 facets with the posterior arch of the C1 were removed. Lateral mass screws and plates fixation at the C1 and C2 level, as well as fusion, were performed. Postoperatively, the patient recovered well.

Conclusion In accessory C1 and C2 facet joints, when symptomatic, neuroradiological findings can guide to the proper diagnosis, to pathological understanding, and, ultimately, to management strategy.

Keywords
- accessory atlantoaxial facet joint
- C1 and C2 accessory facets
- craniovertebral junction
- instability
- quadriparesis
- adult

Introduction

Common craniovertebral junction (CVJ) skeletal deformities are basilar invagination, occipital assimilation of the C1, platybasia, os odontoideum, foramen magnum stenosis, and skeletal deformities associated with Chiari malformations, among others.[1] Accessory facet joints or supernumerary facets between the C1 and the C2 is a very rare anomaly, and only a few cases of this condition have been reported in the literature. The origin, anatomical descriptions, functions and pathological associations of these joints still remain to be defined. In the present work, we report a case of bilateral accessory facets in which an adult patient presented with quadriparesis (due to C1 and C2 instability and spinal cord compression by the accessory facet joints from back), where special attention was given to clinical, neuroradiological, as well as peroperative findings.

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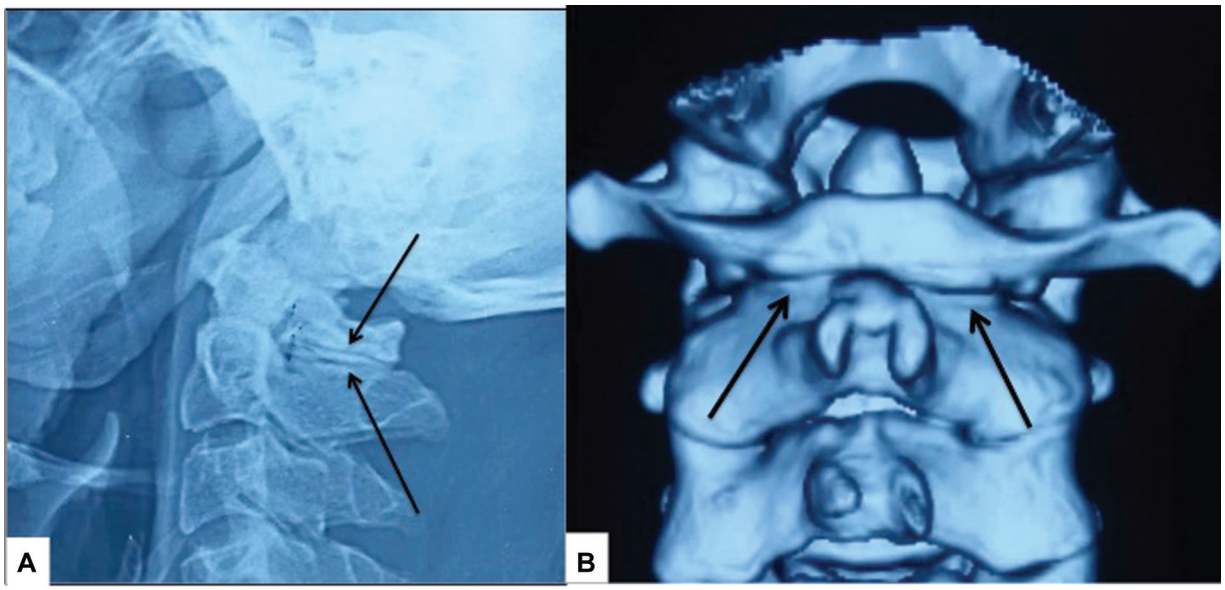

Fig. 1 A – X-ray of the cervical spine (lateral view) showing the C1 and C2 accessory facet joint (arrow marked); B- 3D computed tomography scans of the craniovertebral junction (posterior view) showing bilateral C1 and C2 accessory facet joints (arrow marked).

Case Report

A 37-year-old male presented with neck pain and weakness of all limbs for 15 days. The weakness was progressive in nature, due to which he was unable to stand and walk for the last few days of his complaints. He had no history of trauma. His neck movements were restricted and painful, especially in the upper cervical spine. There was tenderness at the CVJ. His muscle power was Medical Research Council (MRC) grade 3^{-}/5 in all limbs. The Hoffman sign was bilaterally positive and the planter reflex was extensor on both sides. All of the tendon jerks were exaggerated. All of the modalities of sensation were reduced 40% bilaterally up to the C2 dermatome.

Neuro-Radiology

An X-ray of the CVJ seemed to be normal at first, but a careful observation of the lateral view showed a joint between the C1 arch and the C2 lamina, characterized by two articular surfaces and a joint space. The C1 posterior arch and the C2 neural arch seemed to be bigger and heavier than usual (►**Fig. 1A**).

Computed tomography (CT) scans of the CVJ showed that the C1 posterior arch and that the C2 neural arch were bigger and heavier than usual. There was a knob-like elongation of the lateral part of the posterior arch of the C1 just posterior to the lateral mass on both sides. The same type of knob-like bony formations were also found at the laminopedicular junction of the C2 bilaterally. Together, these bony elongations formed accessory facets joints on both sides that compromised the spinal canal from the back. Odontoid was shifted to left as seen in axial films indicate atlantodental joint instability. The vertebral foramina and the vertebral arteries seemed to be normal (►**Figs. 1B**, **2**, & **3**).

Magnetic resonance imaging (MRI) of the CVJ showed compression of the spinal cord at the C1 and C2 level from

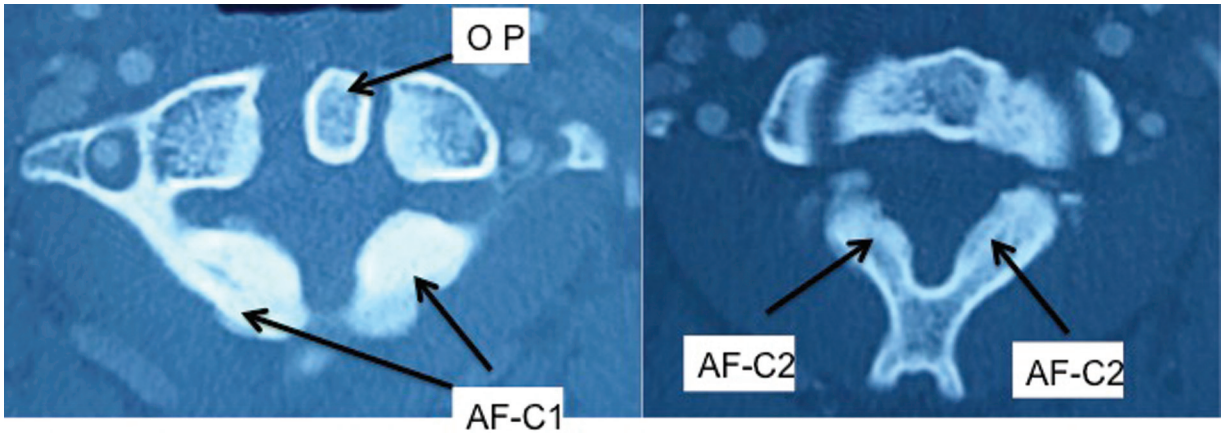

Fig. 2 Computed tomography scan axial views of the craniovertebral junction showing accessory articular facets of the C1 and C2, respectively (left and right). The left side also shows atlantodental joint dislocation. Abbreviations: AF-C1: accessory facet C1; AF-C2: accessory facet C2; OP: odontoid process.

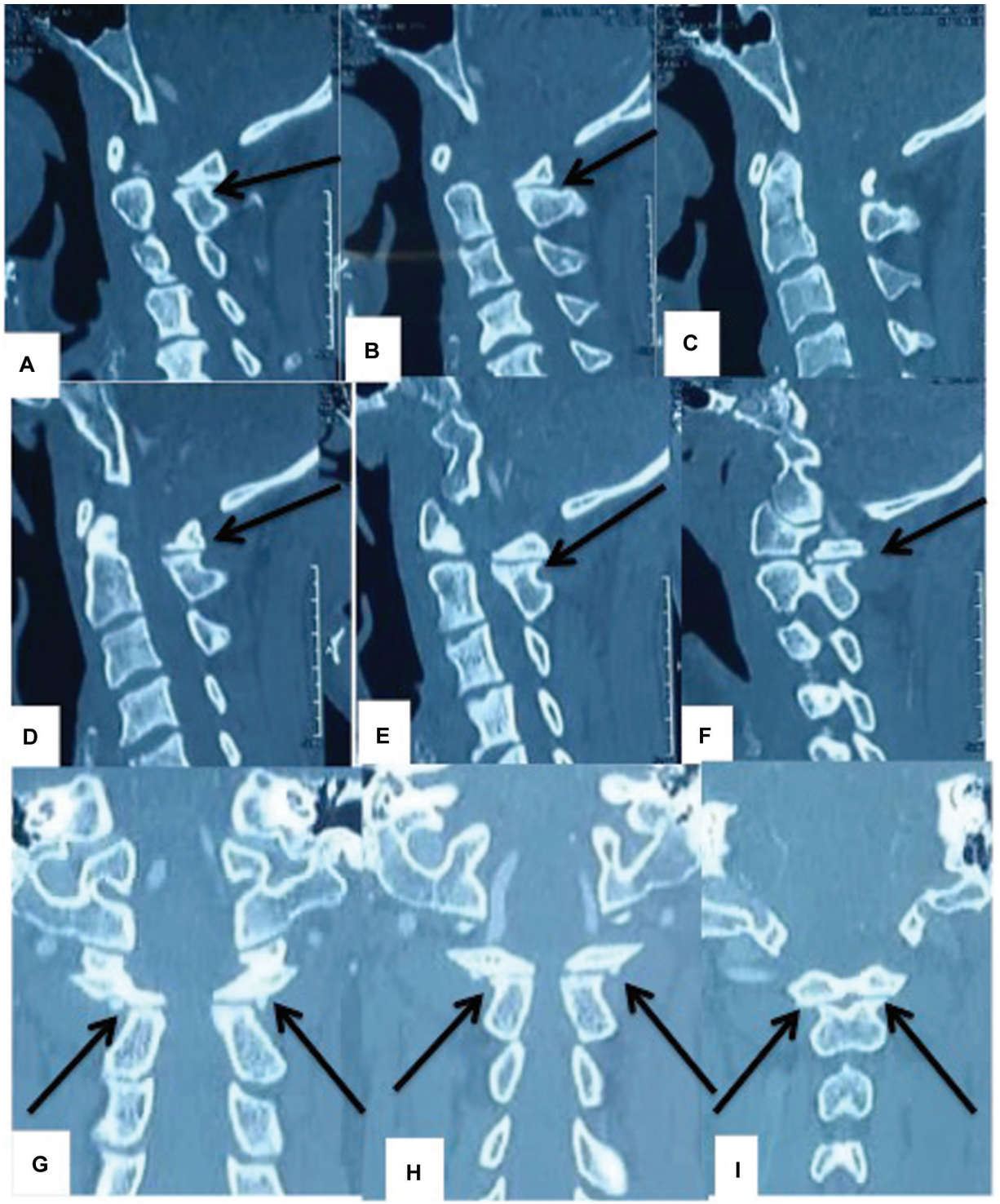

Fig. 3 Computed tomography scan (bony windows) of the craniovertebral junction. A, B, C, D, E, and F: serial sagittal sections (left to right) showing bilateral accessory facet joints between the C1 and the C2 (arrow marked); G, H and I: serial coronal sections A, B, C and D: Showing bilateral accessory facet joints between the C1 and C2 (arrow marked)

back with spinal cord signal changes from the C4 to the medulla oblongata. Careful observation also showed two more facet joints posterior to the regular facet joint that were compressing the spinal cord from back (►**Fig. 4**). Paramedian sagittal cuts in T2-weighted MRI showed heavy accessory facets that were easily identified with linear joint space (that is, linear hyperintensity). Spinal cord compression and signal changes indicated instability in the regular C1 and C2 facet joints (►**Fig. 5**).

Dynamic X-ray or dynamic CT scan were not performed since the spinal cord was already compressed with signal changes and the accessory facets narrowed the spinal canal. (In the CT scan and MRI images, there were signs of C1 and C2 instability.)

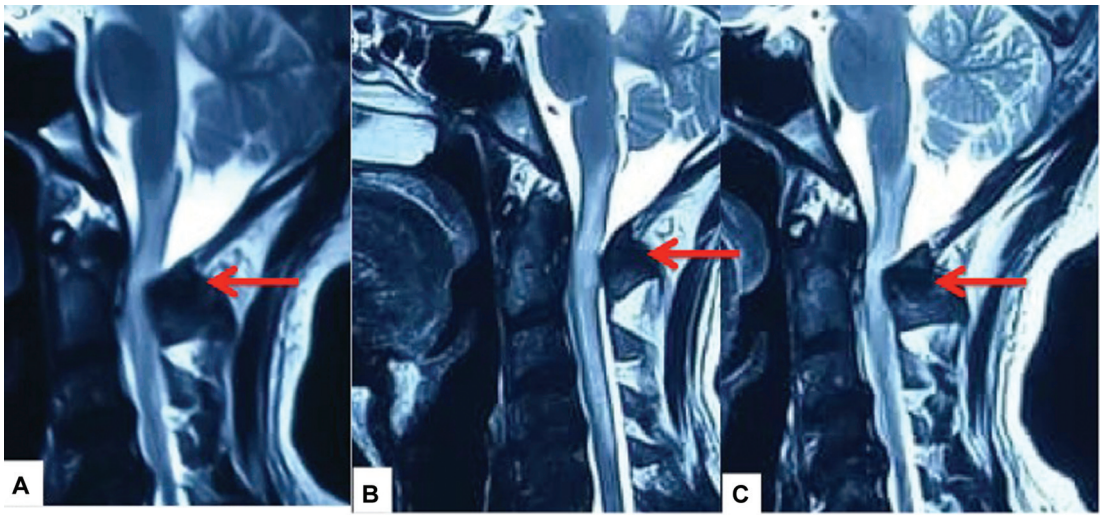

Fig. 4 T2-weighted magnetic resonance imaging of the craniovertebral junction, sagittal images . A, B, and C: Compression of the spinal cord from the back (arrow marked) with signal changes in the spinal cord.

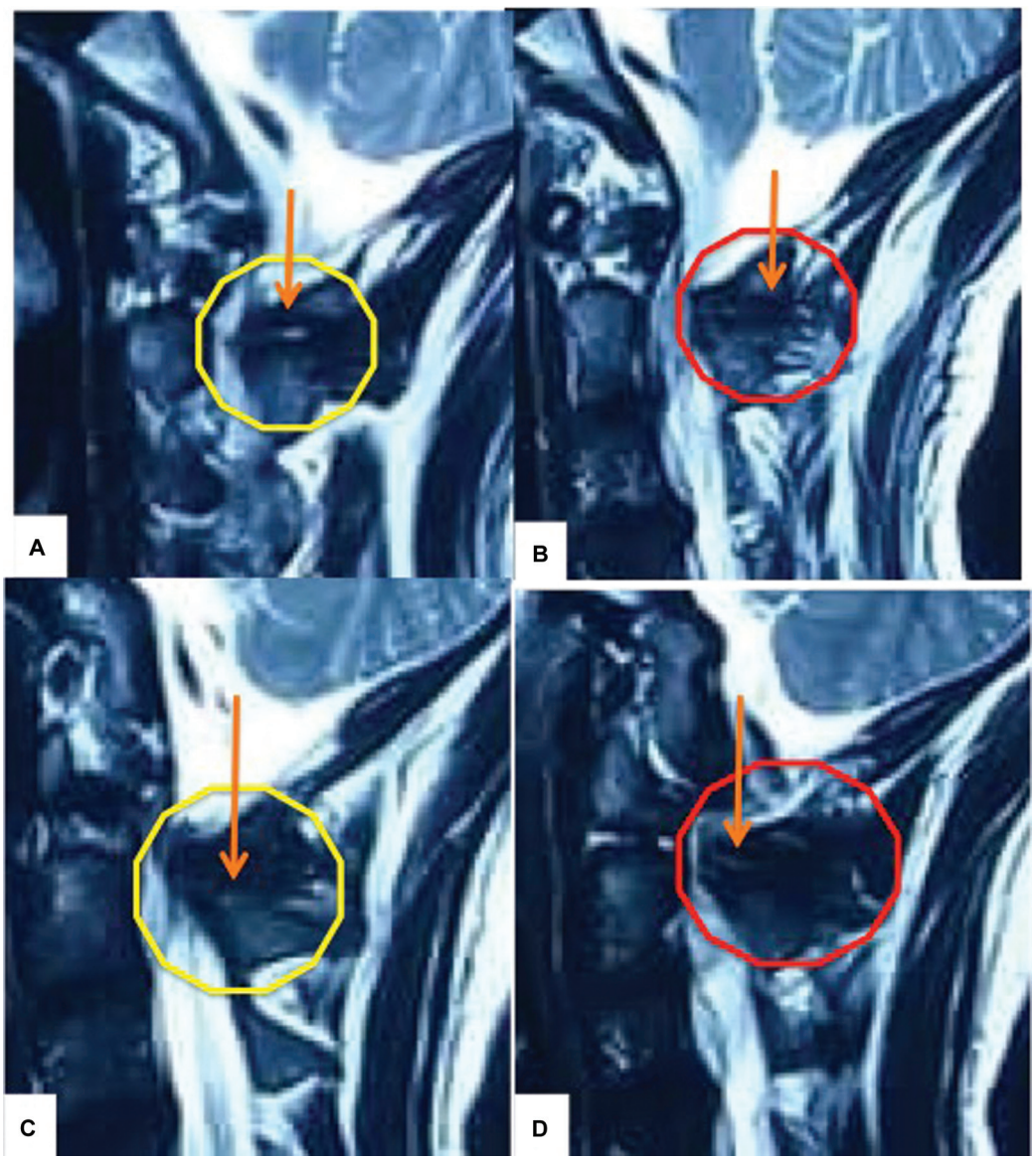

Fig. 5 Magnetic resonance imaging of the craniovertebral junction. A and B: left-sided paramedian; C and D: right paramedian sagittal T2-weighted images showing accessory facets (within the circle) and linear hyperintense joint cavity (arrow marked).

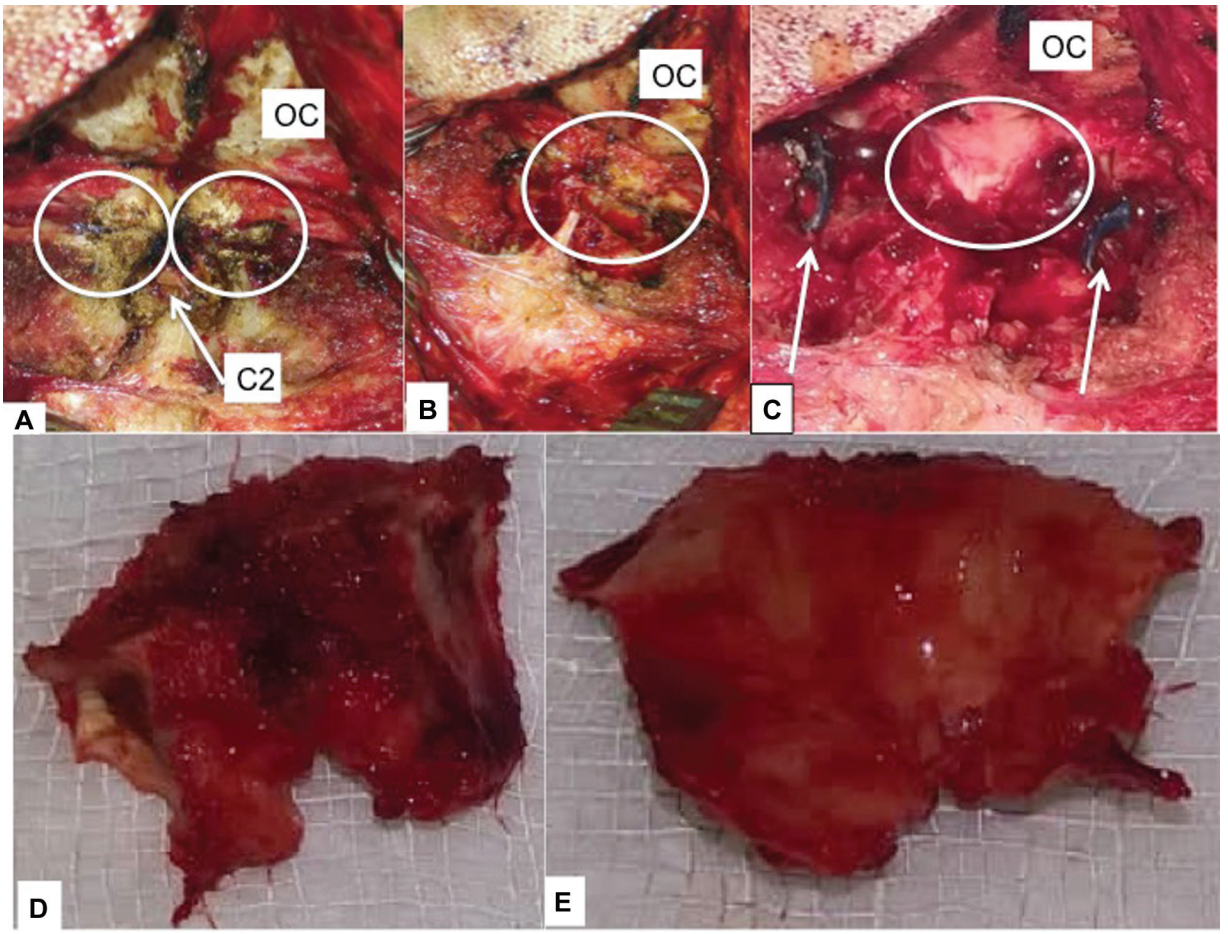

Fig. 6 Peroperative pictures after the exposure of the craniovertebral junction, A: showing both accessory facet joints within the circle and the C2 spinous process (arrow marked),; B: after the removal of both accessory facets with the C1 posterior arch (circle marked area); C: after the removal of both accessory facets with the C1 posterior arch and after the removal of the posterior atlanto-occipital and atlantoaxial ligaments (circle marked area). Fixation of the lateral mass screws and of the plate are also seen (arrow marked). OC-occiput; D and E: after the removal of both C1 accessory facets and of the C1 posterior arch as a single piece. interior surface & exterior surface respectively

Planning

After counseling with the patient party, decompression of the spinal cord by removing both accessory facet joints along with the C1 posterior arch, as well as C1 and C2 lateral mass screws and plate fixation and fusion were planned.

Operation and Operative Findings

The patient underwent the operation under general anesthesia with endotracheal intubation in the prone position. Skull traction was set to keep the neck in the neutral position and the head end was elevated to counteract the skeletal traction and also to ease venous drainage of the head and the neck. The occiput, the posterior arch of the C1, the spinous process, the lamina of the C2, and both the C1 and C2 facet joints (that is, the CVJ) were exposed completely from the back. Two extra facet joints were found between the C1and the C2 posterior to the normal facet joints. The C2 nerve root and ganglion came out laterally between the regular and accessory facets bilaterally. The C2 accessory facets were smaller than the C1 accessory facets. The right and left accessory facet joints were asymmetric and unequal (►**Fig. 6A**). The C2 part of the accessory facets were removed by using a high-speed drill under a microscope. Then, the C1 part of the accessory facets were also removed by drilling along with the C1 posterior arch in a single piece (►**Figs. 6B, C, D & E**). After the removal of both accessory facets and of the C1 posterior arch, spinal cord pulsation returned. The C1 accessory facets compressed the spinal cord more than the C2 accessory facets. In both accessory facets, there were articular cartilage and a pannus-like synovial membrane. After the decompression of the spinal cord, both regular C1 and C2 facet joints were checked and found to be unstable. The regular C1 and C2 facet joints were opened and the articular cartilages were denuded. Joint fusion and jamming[2] were performed with autologous bone chips from the C2 spinous process and the C1 posterior arch. The C1 and C2 lateral mass screw and plate fixation was performed on both sides (►**Fig. 8C**). Then, the wound was closed without drain.

Postoperative Period

Postoperatively, the neurological recovery of the patient was rapid. By the end of 2 weeks he could walk without support.

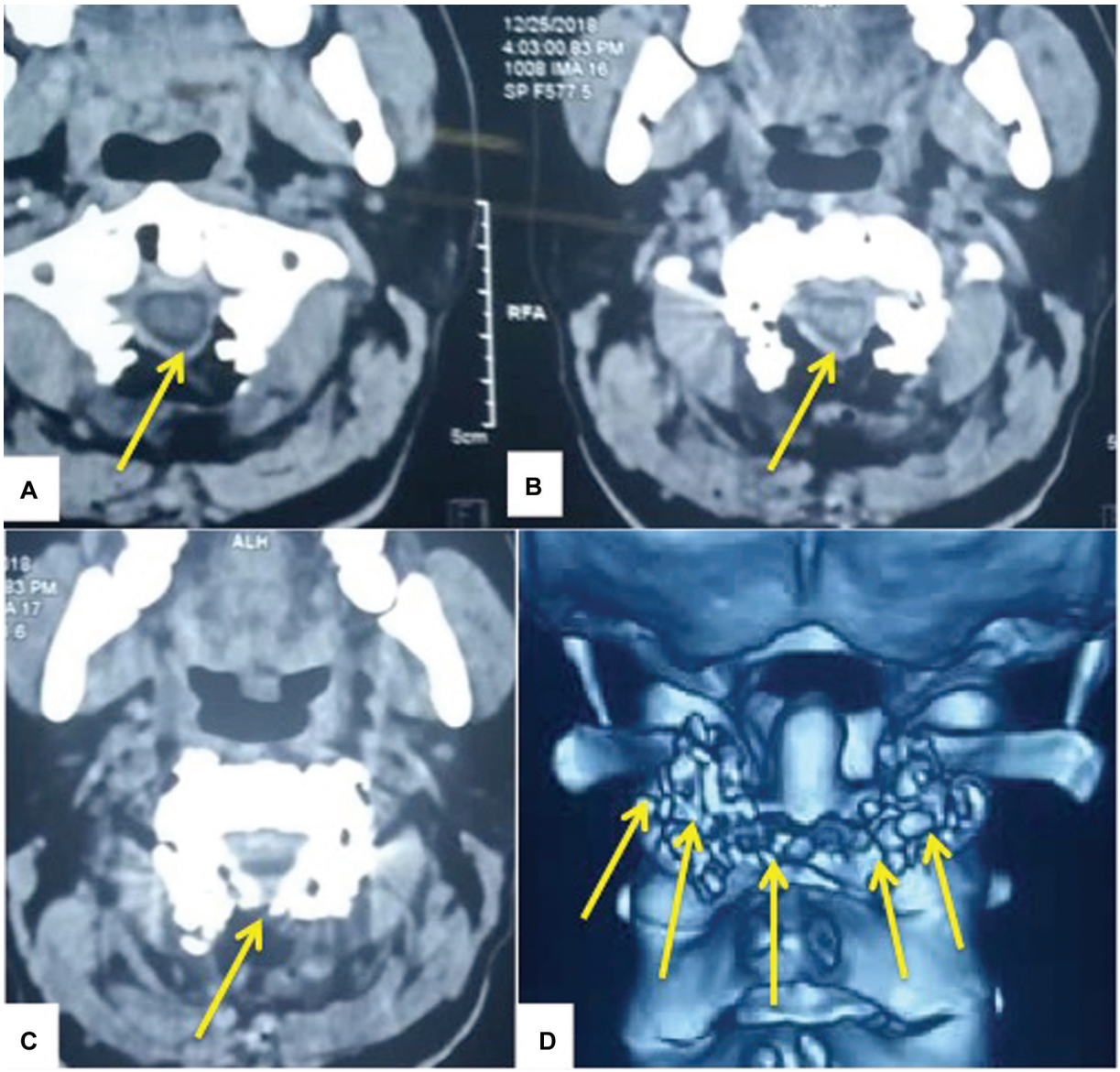

Fig. 7 Postoperative computed tomography scans of the craniovertebral junction, axial views. A, B and C: showing decompression of the spinal cord by removing the C1 and C2 accessory facet joints with the C1 posterior arch (arrow marked); D: 3D computed tomography scans of the craniovertebral junction showing the removal of the C1 and C2 accessory facet joints with the C1 posterior arch, as well as the fixation of the C1 and C2 screws and plates and fusion with bone chips (arrow marked).

Six weeks after the operation, he recovered completely. Postoperative CT scans of the CVJ showed C1 and C2 fixation with screws and plates with absence of accessory facets and of the C1 posterior arch (►**Fig. 7** & **8**).

Discussion

Unilateral C1 and C2 accessory facet joint was first reported in 2011 by Riesenburger et al.[3] Bilateral accessory facet joint was first reported by Salunke et al in 2013.[4] The origin of C1 and C2 accessory facet is not exactly known. The formation of such a dysmorphic joint suggests an aberration of *HOX* genes determining articulation.[4] During the embryological development of the C1 and C2, sclerotomes may fuse abnormally posteriorly, followed by the initiation of events at this site that eventually lead to the formation of a morphologically normal synovial joint in an abnormal location.[3] These are seen posteriorly to the true facets and resemble partially formed joints. The C2 facet was acutely bent over its isthmus in these patients.[5] These joints are dysmorphic and partially formed, as evidenced by the absence of the synovial membrane and capsule. However, in our case, peroperatively, the articular cartilage, along with a pannus type of synovial membrane, were seen, although these were not confirmed by the histopathological examination. The function and physiological aspects of these joints are not exactly known.[4]

The first 'unilateral accessory facet' case presented at the age of 35 years old,[3] and the first 'bilateral accessory facets' case presented at the age of 17 years old.[4] Their clinical presentation includes neck pain, headaches, and tingling sensation, spasticity and quadriparesis.[3–5]

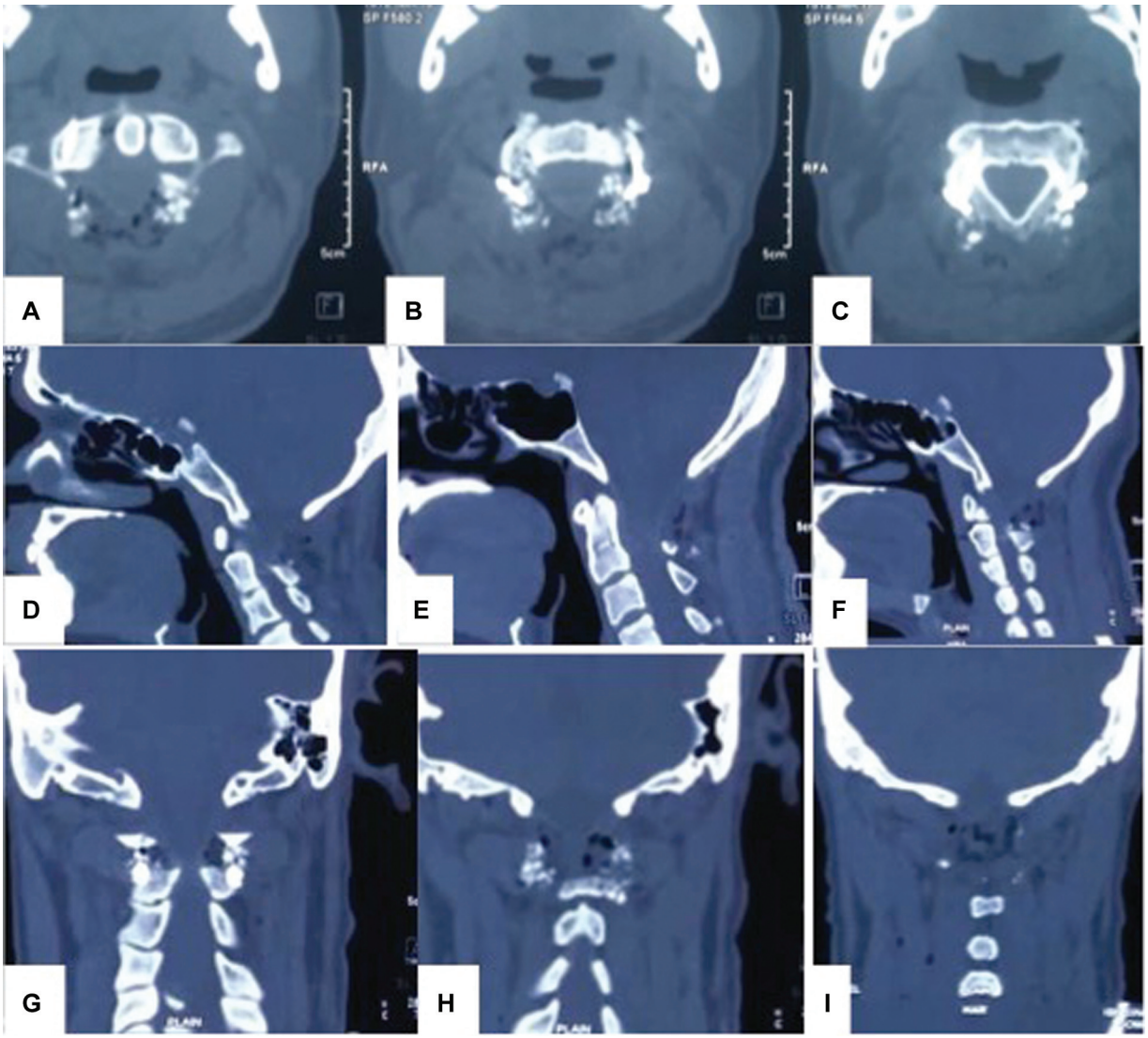

Fig. 8 Computed tomography scans of the craniovertebral junction. A, B and C: axial views; D, E and F: sagittal views; G, H and I: coronal views showing the removal of both accessory C1 and C2 facets with the posterior C1 arch, as well as fixation and fusion.

Plain X-rays may be normal, but sometimes can give very useful information in symptomatic cases like the presented case. Computed tomography scan is used to identify the accessory joint and C1 and C2 instability. Magnetic resonance imaging is used to identify the cord compression. In our case, the accessory facets were also seen in the MRI. In the cases reported in the literature, the accessory facets were associated with C1 and C2 congenital instability.[5] Therefore, atlantoaxial regular facets may be congenitally weak when associated with accessory facet joints, and these facets may provide some stability. The direction of these pseudofacets appeared to counter the abnormal mobility at the C1 and C2 true facets.[5]

When symptomatic, the treatment of this condition is the excision of the accessory joint or joints along with fixation and fusion of the C1 and C2.[3,4] During the operation, there is a visual hindrance to reach up to the true facets for the placement of spacers and lateral mass screws, requiring extensive drilling.[5] We think that, peroperatively, the C2 nerve root and ganglion should be identified by removing the accessory facets completely, and then the surgeon can comfortably and safely manipulate the regular C1 and C2 facets for fusion and fixation. More drilling of bone is needed on the C2 for the proper placement of screws and plates. Area for C2 screw placement is much more than usual. In our case, it seemed that the accessory facets were true synovial joints.

Conflicts of Interests

The authors have no conflicts of interests to declare.

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Delayed Cerebral Metastasis of Breast Cancer: Case Report and Molecular Review

Mestástase cerebral tardia de cancêr de mama: Relato de caso e revisão molecular

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Abstract

Breast cancer (BC) is a prevalent disease, and its incidence of brain metastasis (BM) varies from 5 to 30% according to the literature. We present the case of a delayed isolated cerebral metastasis in a female patient following a period of 16 years after the diagnosis and first treatment. During this time, there was no other recurrence. We also review the literature concerning central nervous system spread and the molecular subtypes of such late tumors.

Keywords
- breast cancer
- neuro-oncology
- delayed metastasis

Resumo

O câncer de mama é uma doença prevalente e sua incidência de metástase cerebral varia de 5 a 30%, de acordo com a literatura. Apresentamos um caso de metástase cerebral tardia isolada em uma paciente do sexo feminino após um período de 16 anos do diagnóstico e tratamento. Durante esse período, não houve outra recorrência. Também é feita uma breve revisão da literatura sobre metástases de câncer de mama no sistema nervoso central e suas características moleculares.

Palavras-chave
- câncer de mama
- neuro-oncologia
- metástase tardia

Introduction

According to recent data, around 1,7 million new cases of breast cancer (BC) are diagnosed each year in women worldwide. It represents 25% of new cancer diagnoses in women. Only non-melanoma skin cancer has a greater prevalence. Between 5 and 30% of the patients with BC have seeding in the central nervous system (CNS).[1–3] Therefore, the presence of patients with BC metastases in the neurosurgical centers is a common occurrence.

This report presents a patient who developed multiple cerebral metastases 16 years after the initial diagnosis, without any prior evidence of systemic disease. Such a delayed metastatic presentation in the CNS is unusual.[3] We found only one case with longer time between primary diagnosis and secondary brain metastasis (BM).[4] Here, we also review the involvement of the CNS in breast cancer, as well as its molecular profile and prognosis.

Case Report

A 54-year-old female reported difficulty with manual dexterity in her right hand for 3 months. Neurological examination revealed no motor deficit in her arms. There was also postural instability and progressive worsening of gait, associated with headache and vomiting. She had cerebellar ataxia and dysmetria of the right upper limb. Brain magnetic resonance imaging (MRI) showed multiple supra and infratentorial expansive

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lesions (►**Fig. 1**). The largest one was located in the right cerebellar hemisphere. Oncological screening excluded any other site of primary tumor or metastatic lesions.

The patient had been diagnosed with breast cancer in May 2001. A radical mastectomy was performed then, with axillary node clearance. In addition, she received radiotherapy and adjuvant chemotherapy. The histological study evidenced ductal adenocarcinoma, positive for estrogen receptors (ERs), progesterone receptors (PRs), and human epidermal growth factor receptor type 2 (HER 2)—a "triple positive". In the following year, she underwent prophylactic bilateral oophorectomy and was treated for 5 years with tamoxifen.

The neurosurgical and oncological team opted for immediate operative resection of the largest infratentorial lesion due to risk of hydrocephalus. Four days after the first MRI, the patient underwent cerebellar tumor resection in May 2017—192 months after the first diagnosis—with total resection of the lesion, and she recovered postoperatively without complications (►**Figure 2**). She had significant improvement of

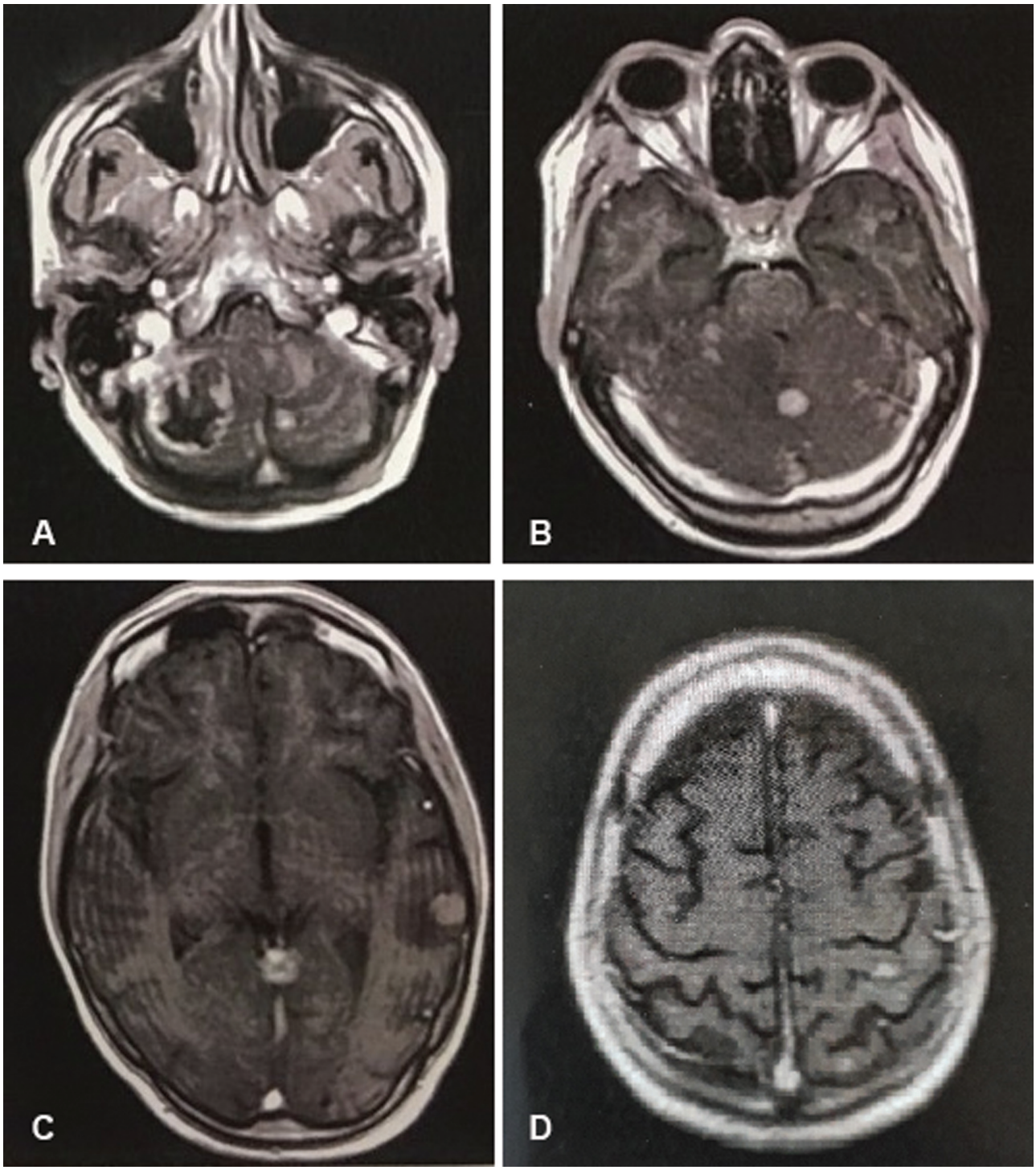

Fig. 1 Symptomatic cerebellar metastasis (A) Multiple metastases, infra and supratentorial (B, C, and D).

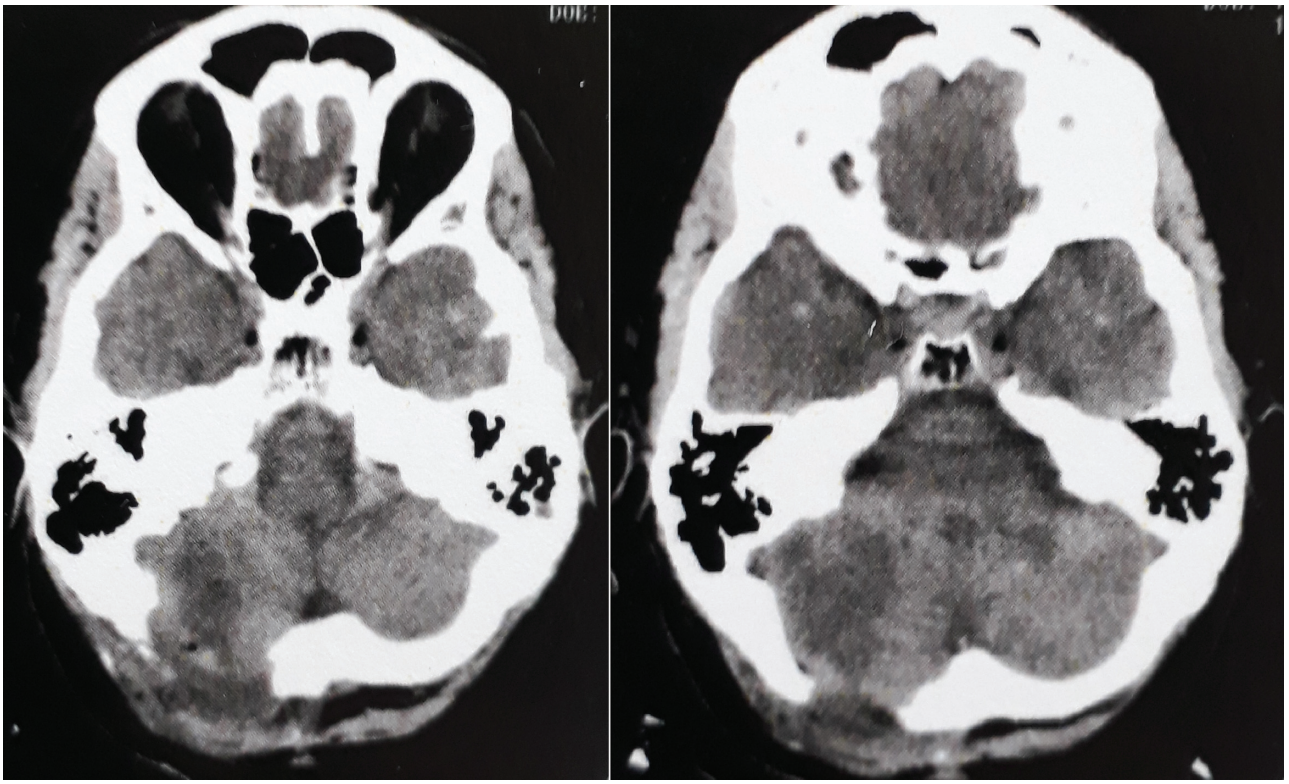

Fig. 2 Postoperative computed tomography.

symptoms and recovered capacity for all daily activities. Immunohistochemistry confirmed breast metastasis, with 10% of the neoplastic cells being progesterone receptor (PR)-positive and Ki 67-positive.

Oncological treatment followed with adjuvant radiotherapy and chemotherapy. No more neurosurgical intervention was necessary in the follow-up of 12 months. An MRI and a positron emission tomography (PET)-scan exam 1 year later showed satisfactory control of brain lesions and absence of others metastases (►**Figure 3** and **4**).

Discussion

In Brazil, 57,960 new cases of BC were diagnosed in 2016, and 14,000 deaths were attributable to this disease.[5] It is the second most prevalent type of tumor to cause metastasis to the CNS, following lung implants. Recent numbers in the literature indicate that up to 30% of metastatic presence in the nervous system in autopsy analysis.[3] Modern methods of imaging, like MRI, and the longer survival time of these patients have contributed to a greater prevalence in recent years.

In a recent review, the mean age of patients at diagnosis of the brain metastases was 48.8 years. Multiple metastases are present in 54% of the cases, with cerebellum and frontal lobe being the most frequent locations. In addition, the mean time between diagnosis of the underlying disease and the BM was 32 months.[6]

In a cohort study, the 5-year follow-up of 802 BC patients showed an incidence of 5% (42) of BM.[1] Another study that followed more than 9,000 patients showed incidence of 3.3% in 5 years and 5.2% in 10.[2]

We searched for late metastasis in the literature. A comprehensive review with more than 14,000 patients showed the diagnosis of BM varying from 1 to 97 months after detection of the primary disease.[6] In another review study, only 0.1% of cases present a CNS involvement as 1st site after 10 years.[2] The longest reported case of late CNS metastases from BC was at 193 months of the 1st diagnosis.[4]

Analyzing biomarkers characteristics, Altundag et al described a relation of estrogen receptor (ER)-negative and HER-2 positive tumors to patients presenting CNS spread. Although, among the 420 patients evaluated by the group a better prognosis was observed in the ones with ER-positive tumors. Patients younger than 50 years old have longer survival too. Trastuzumab, a monoclonal antibody therapy used for HER-2 positive patients, is related to better disease control. Other risk factors were positive sentinel lymph node, younger patients, and tumor grade. Of note, these factors are described to increase not only CNS spread, but also systemic.[3]

Moreover, Shen et al showed HER-2 expression as an independent predictor of better survival in patients treated with craniotomy for BM stemming from BC. In this same analysis, patients with positive ER and PR, presented longer survival after cerebral metastatic diagnosis compared to one or two negative receptors.[7]

Lin et al discussed the epidemiology and prognosis of HER-2 status in BM. They supported the biomarker as a risk factor for CNS spread, because of its inherent behavior and also because of longer survival of patients treated with

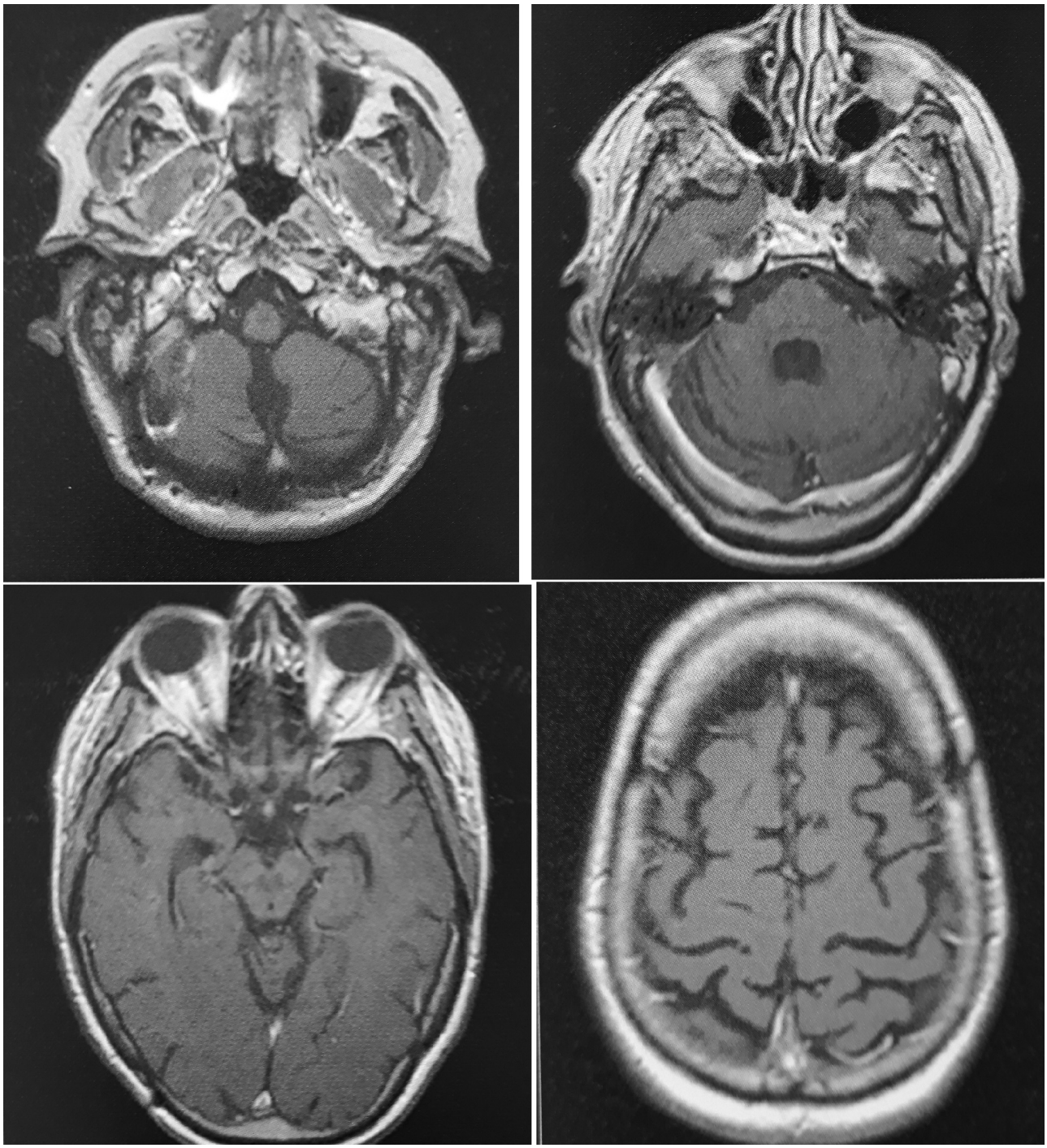

Fig. 3 Control magnetic resonance imaging after surgery, chemotherapy and adjuvant radiotherapy.

monoclonal therapy.[8] Similar data was found by others authors.[9,10]

Overall, the prognosis of these patients is associated with the presence of implantation in different organs, size and degree of the primary lesion in breast, negative hormone receptors, clinical performance at the time of diagnosis, and progression-free survival. Karnofsky performance status was also important for overall survival.[11] The mean life expectancy after the identification of BM is 17 months.[6] A study that exclusively examined patients who underwent craniotomy for treatment of the BM presented a mean survival of 1.3 years.[12]

These patients benefit from multimodal approaches, with adjuvant radiotherapy and chemotherapy. In fact, more than half of the patients undergo whole brain radiation, and up to 20% have an indication of stereotactic treatment.[6]

The improvement of survival in patients with positive HER-2 BC, and the advances in diagnostic option, allowed for such a delayed CNS BM.

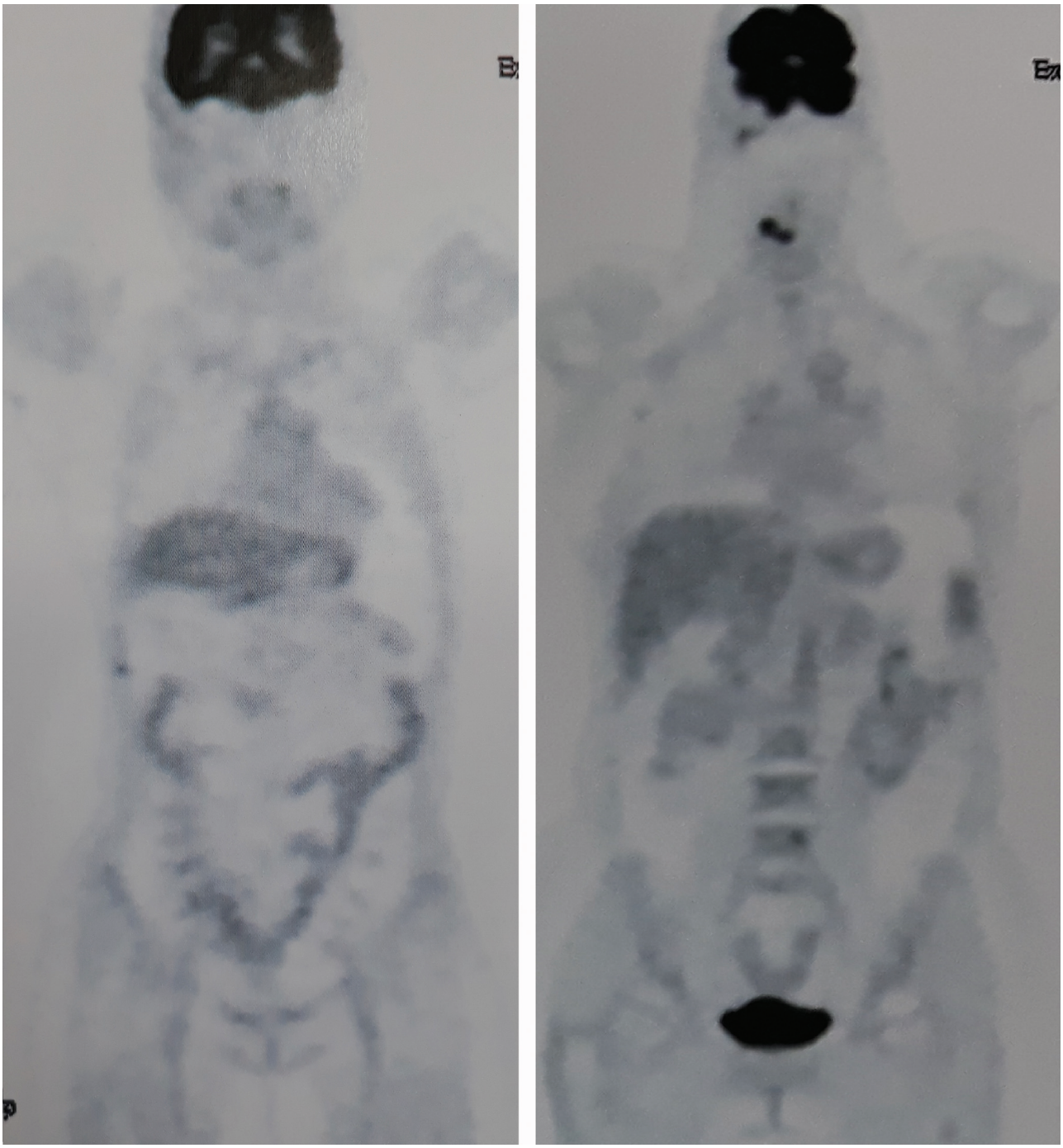

Fig. 4 Positron Emission Tomography-computed tomography confirms patient with no other implant.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Ependymoma with Intraorbital Extracerebral Recurrence: Case Report

Ependimoma com recidiva extracerebral intraorbital: relato de caso

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Abstract

Ependymomas are rare neuroepithelial tumors that originate from a type of glial cell called ependymal cell. In general, they correspond to ~ 1.2 to 7.8% of all intracranial neoplasms, and to ~ 2 to 6% of all gliomas. Although it corresponds only to ~2 to 3% of all primary brain tumors, ependymoma is the fourth most common cerebral neoplasm in children, especially in children younger than 3 years of age.[1,2] In patients younger than 20 years of age, the majority (90%) of ependymomas are infratentorial, more precisely from the IV ventricle. In spite of this, in adults, medullary ependymomas are more frequent (60%). In this context, supratentorial and extraventricular ependymomas, as in the case reported in the present article, are infrequent in both adults and children.[1,2] Both sexes are equally affected.[3] Recurrence of intracranial ependymomas occurs in almost 50% of the cases, and the follow-up outcome is not favorable.[4] In another perspective, the recurrence of extracerebral ependymomas is extremely rare, and even more unusual in the intraorbital site, as it occurred in the case in question.

Keywords
- ependymoma
- ependymal cell
- anaplastic ependymoma
- supratentorial glioma

Resumo

Ependimomas são raros tumores neuroepiteliais originados de um tipo de célula glial chamada célula ependimária. Em geral, correspondem a cerca de 1,2 a7,8% de todas as neoplasias intracraniais, e a cerca de 2 a 6% de todos os gliomas. Embora corresponda apenas a cerca de 2 a 3% de todos os tumores cerebrais primários, o ependimoma é a quarta neoplasia cerebral mais comum em crianças, principalmente nas menores de 3 anos.[1,2] Em pacientes com menos de 20 anos, a maioria (90%) dos ependimomas são infratentoriais, mais precisamente oriundos do IV ventrículo. A despeito disso, nos adultos são mais frequentes (60%) os ependimomas medulares. Nesse contexto,

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Palavras-chave
- ependimoma
- célula ependimária
- ependimoma anaplástico

ependimomas supratentoriais e extraventriculares, como o do caso relatado no presente artigo, são infrequentes tanto em adultos quanto em crianças.[1,2] Ambos os sexos são afetados igualmente.[3] A recorrência de ependimomas intracraniais ocorre em quase 50% dos casos, sendo o resultado de seu seguimento não muito favorável.[4] Em outra perspectiva, a recorrência extracerebral dos ependimomas é extremamente rara, sendo ainda mais incomum o sítio intraorbital do caso em questão.

Introduction

Ependymomas are rare neuroepithelial tumors that originate from a type of glial cell called ependymal cell. Found in the ventricular system, the choroid plexus, the terminal filament and the central canal of the spinal cord, these ciliated cells have a role in the production and circulation of cerebrospinal fluid (CSF). Such are the most common sites for the development of this type of glioma, and the ventricle is the most frequent location.[1–3]

The etiology of the onset of ependymomas, as well as of other tumors, is still unknown. However, a possible infectious etiology has been reported by Bergsagel et al[4] (1992) and Lednicky et al[5] (1995), who demonstrated, using the polymerase chain reaction (PCR) technique, the probable involvement of the simian virus 40 (SV40) in the origin of ependymomas.[4,5] However, further epidemiological studies are needed to clarify this hypothesis. Also regarding the etiology of these tumors, the role of genes is important, since it is remarkable in some studies that the most common chromosomal alteration found in ependymomas is the loss of an allele of chromosome 22, a fact that probably entails the loss of a suppressor gene of the tumor other than the already known *neurofibromin 2* (*NF-2*) and *hSNF5/INI1* genes.[3,6]

It is also important to inform that endocrine factors can help in the mechanism of origin of this neoplasia, since the presence of sex hormone receptors in an anaplastic variant of the ependymoma has already been found, and the other types may share this characteristic.[7] According to the epidemiological observation, it is important in the clinical practice to emphasize that ependymomas occur more in neurofibromatosis patients than in the general population.[7]

According to WHO histological classification in 2007, ependymoma can be divided into four types: (1) subependymal (WHO I grade); (2) myxopapillary ependymoma (WHO I grade); (3) ependymoma (WHO II grade), including cellular leiomyoma, clear cell type, papilla cell type and tanycyte; (4) anaplastic ependymoma (WHO III grade), belonging to a malignant tumor.

Recurrent intracranial ependymomas occur in almost 50% of the cases; however, extracerebral recurrence is extremely rare. In the present article, a rare case of extracerebral recurrence of an ependymoma is described.[8–10]

Case Report

G.S.B., 15 years old, female, from the city of Bertolínea, state of Piauí, Brazil, came to the medical service in 2011 presenting persistent headache, painful supraorbital bulge on the right side, with progressively growing and without acuity visual alteration. In the anamnesis, we verified that the patient had undergone a microsurgery for resection of a right frontal anaplastic ependymoma, in another service in 2001, without any degree of differentiation and with a mitotic index of 3 per 10 high-power fields (HPFs), being submitted to adjuvant treatment with radiotherapy located in the right hemisphere at the same time. At the neurological examination, the patient presented palpebral ptosis due to the involvement of the third pair on the right, had no motor deficit, and the deep reflexes were alive. In the imaging tests, we verified that this was a case of recurrence in the parenchyma and at the base of the skull. Then, the patient was submitted to a microsurgery for the resection of the recurrent tumor in the parenchyma and skull base, compromising the right orbit ceiling, and a reconstruction was performed with a pericranial flap. In spite of that, in the magnetic resonance imaging (MRI) control exam after the microsurgery, a residual lesion in the right orbit was observed. The evolution of oncology was then demanded. In the histopathology, we found that it was a neoplasia with a clear-cell pattern, with diffuse expression of the S-100 protein and focal perivascular expression of the glial fibrillary acidic protein (GFAP), with anaplastic ependymoma as the main hypothesis (►**Fig. 1**).

After 5 months of outpatient follow-up, the patient returned to the service presenting with a rapid and progressive increase of the orbital and supraorbital regions to the right, local hyperalgesia, exophthalmos, and a significant decrease in visual acuity (►**Fig. 2**). In the complementary examination, there was an injury with invasion of the right orbit and of the periorbital musculature (►**Figs. 3** and **4**).

An image-guided tumor resection was performed in the right orbital cavity in a block with the eyelids, as well as orbital exenteration and resection of the lateral wall of the orbit. In the postoperative histopathological analysis, the diagnosis of anaplastic ependymoma, with the periorbital soft tissues and orbital bone tissue compromised by the neoplasia, and with the ocular globe and optic nerve free of neoplasia, the extracerebral recurrence of this type of glial tumor, which is quite rare, was confirmed. ►**Fig. 5** and **6** show the postoperative control of this procedure. Adjuvant chemotherapy was performed.

Discussion

Ependymomas were considered an independent entity for the first time by Bailey and Cushing[31] in their first classification of brain tumors (1926). Over the course of the

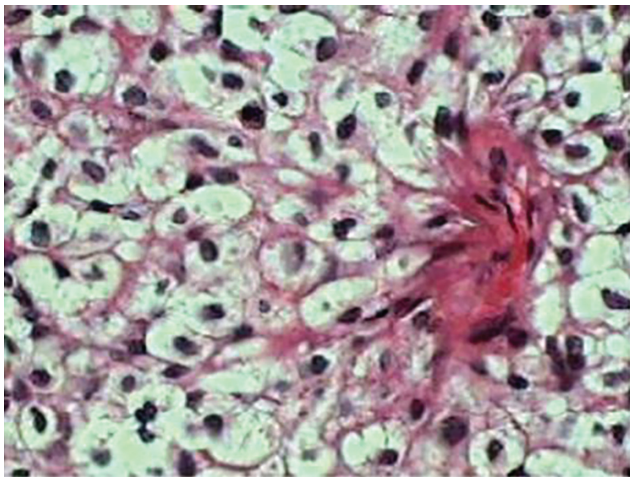

Fig. 1 Hypercellular neoplasm with clear cytoplasmic cells with tendency to perivascular disposition – clear-cell ependymoma.

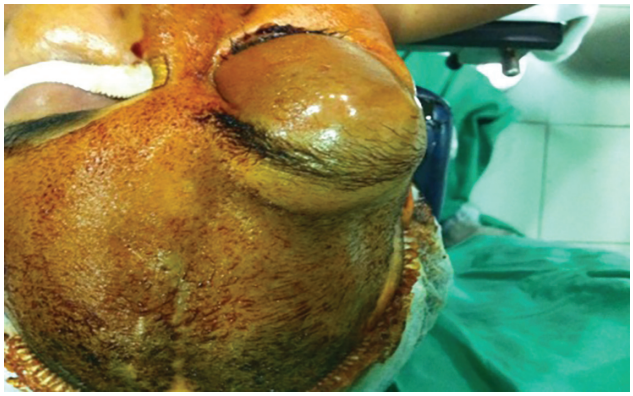

Fig. 2 Preoperative period for tumor resection and orbital exenteration.

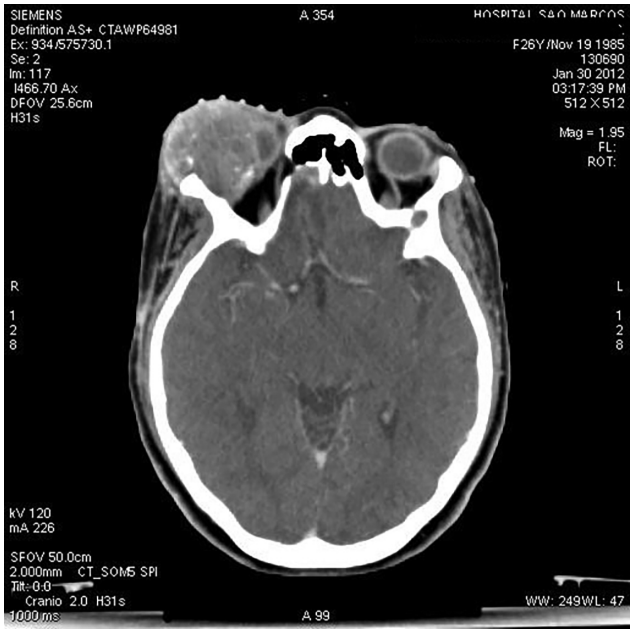

Fig. 3 Tumor mass in the right orbit and invasion of the periorbital musculature.

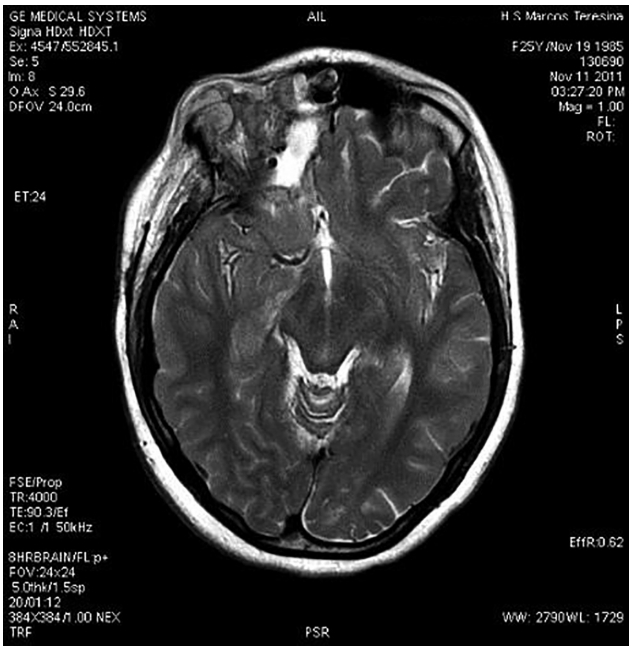

Fig. 4 Tumor mass on the right side of the base of the skull.

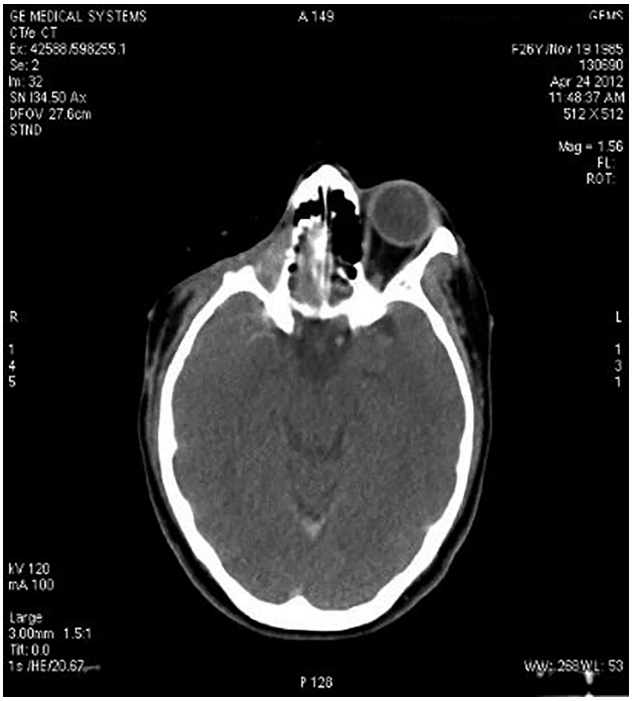

Fig. 5 Postsurgical control image.

years since the first classification, the variants of ependymomas were defined. In 1932, Kernohan[32] defined the myxopapillary variant, and, in 1945, Scheinker[33] described the subependymoma. Only in 1978, Friede and Pollack[11] described the tanycytic variant, and in 1989 Kawano et al[34] identified clear-cell ependymomas. The 2007 World Health Organization[16] (WHO) classification considers the subdivision of ependymomas into these 4 histological variants (cell, papillary, tanycytic and clear cells) in addition to the degree of malignancy, including in grade I tumors the

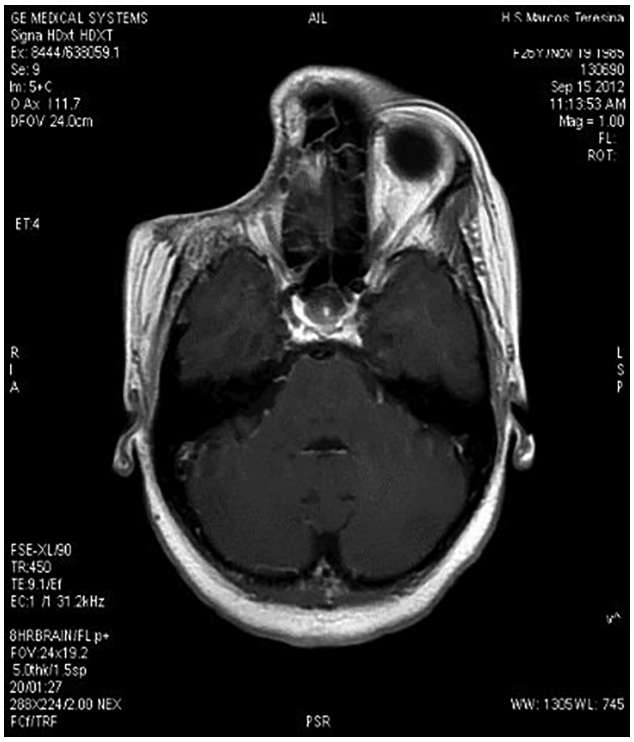

Fig. 6 Postsurgical control image.

subependimoma and the myopopapillary ependymoma; in grade II the ependymoma; and grade III anaplastic ependymoma.[11–14]

In general, some histological structures are characteristic of ependymomas, and are important for their identification, such as perivascular rosettes, which consist of a perivascular anuclear zone of ependymal cells distributed radially close to the blood vessels. Another peculiar structure is the ependymal rosettes, which, although very characteristic of ependymomas, are extremely rare, consisting of tumor cells distributed concentrically around the lumen, forming a canal.[11,13]

Clear-cell ependymomas are generally grade II tumors, predominantly supratentorial, affecting more adolescents and young adults, as in the case reported in the present article. As a histological parameter, they have oval cells with dense chromatin, surrounded by light halos, similar to oligodendroglioma, but differing from it because the latter has no intraventricular location. Central neurocytoma is a differential diagnosis, and it should be confirmed by an immunohistochemical exam if there is doubt concerning the diagnosis. When proliferation and mitoses of endothelial cells are found, they are considered grade III tumors, as was the case of the patient described in the present article.[11,13]

The clinical manifestations triggered by ependymomas are variable, depending on the size of the tumor and its location. Those located in the posterior fossa are often related to obstruction of the IV ventricle and obstructive hydrocephalus. Because it is located near the vomit center, the presence of nausea and emesis followed by headache is common. Moreover, due to the compression effect on the posterior fossa structures, ependymomas can occur with ataxia, hemiparesis, vertigo, visual disturbance and neck pain. In supratentorial ependymomas, it is common to see an increase in intracranial pressure, which manifests as headache, nausea, vomiting, cognitive impairment, and lowering of the consciousness level, as was the case of the patient in question. When located in the spinal cord, the first symptom is dysesthesia, due to the neoplasm that originates in the central canal of the spinal cord, which is similar to what occurs in syringomyelia.[3,13]

For the diagnosis of ependymomas, as well as of other clinical situations of suspicion of mass effect, computed tomography (CT) and the MRI are essential.[6,15,16] The CT is effective in the diagnosis of infratentorial ependymomas, usually presenting isointense to the brain parenchyma and with calcifications. In the MRI, the tumor image is hypointense in T1 and hyperintense in T2 in relation to the encephalic parenchyma. In both T1 and T2, the tumor is heterogeneous. Spinal-cord MRI is still used in cases of suspicion of cauda equina and terminal filament tumors. Because of the neuroepithelial tumors that affect mostly the spinal cord and in 11% of the cases they are classified as CSF, it is necessary to perform a spinal-cord MRI and an analysis of the CSF by lumbar puncture (without contraindications) in every case.[3,15,16]

The treatment consists of total surgical resection, which is not always possible due to the infiltrative character of the tumor, which can occur in noble areas of the brain. The MRI should be performed in the immediate postoperative period (the first 48 hours) to evaluate the residual disease, while hemoglobin degradation artifacts and local inflammatory reactions in the surgical site are not yet present. The surgical treatment can be complemented by radiotherapy, which should be applied to the spinal cord in a smaller dose if there is confirmation of tumor cells in the CSF or confirmation of the tumor by a spinal-cord MRI. In spite of this, there are no studies with a high degree of clinico-epidemiological evidence that justifies the use of adjuvant radiotherapy, which is contraindicated for children under 3 years of age and in cases in which there was total resection of the tumor, since the risk of side effects in the long term outweighs the benefits of the procedure. For recurrent ependymomas, if the patient has not yet undergone radiotherapy, it should be the recommended therapy; however, if the therapy has already been performed, then chemotherapy, radiation therapy or palliative care should be adopted.[10] The role of chemotherapy has not yet been well established, but it should only be performed in cases of tumor recurrence, as in the case reported in the present article.[3,6,7,14,15,17]

Recurrent intracranial ependymomas occur in almost 50% of the cases, but the extracerebral recurrence of ependymomas is extremely rare.[8–10] It is known that intracranial gliomas may occasionally develop extraneural metastases.[18] However, this event is determined in virtually all instances by prior operative decompression, and a similar thing occurred in the case reported in the present article (Russell and Rubinstein, 1963, p. 219;[19] Smith et al, 1969).[24] Examples of this extracerebral complication in ependymomas remain very uncommon, and when they occur, the cervix, the thorax and the lumbar spine are more common sites.[20,21] Some cases of extracerebral metastasis of ependymomas have been reported in the literature. Regarding the cases of euthymic

metastasis of cauda equine tumors verified at necropsy, we highlight the ones reported by Weiss, 1955;[27] Sharma, 1965;[22] Patterson et al, 1961;[10] and Rubinstein and Logan, 1970.[20] Other cases of extraneural metastases of ependymomas have been reported, such as the propagation into the internal auditory canal by a spinal myxopapillary ependymoma, described by Kittel et al, 2001;[17] a case of metastasis to the lungs and regional lymph nodes, described by MacMahon and Urista in 1964[13], at a time when only 5 cases of extraneural ependymoma metastasis had been reported. In 1984, Andoh et al[26] also described a case of multiple pulmonary, pleural and lymph node metastases, which were supraclavicular and paraortic. A case similar to the one reported in the present article was described by Rutka et al[21] in 1985: the extracerebral extension of a cystic ependymoma, due to the fact that the third ventricle, in the pre-chiasmatic cistern, compressed the right optic nerve, causing progressive monocular visual loss. Still according to Rutka et al,[21] the extracerebral growth of primary intracerebral gliomas can cause optic neuropathy, and it is indistinguishable from other compressive neuropathies. Intraorbital recurrence, as presented in the case reported in the present article, is a very rare event, with only a few cases reported in the literature. It is presumed that, in most cases, the route of distant dissemination of ependymomas is the hematogenic route.[29] This idea is reinforced because of very exceptional cases in which the extraneural deposits developed in the absence of a previous craniectomy (Rubinstein, 1967).[18] As for the metastatic route of propagation, the venous route has a greater permeability, playing an important role in the origin of extracerebral glioma metastases, which has already been demonstrated in previous studies.[30]

Conclusion

The case described in the present article is uncommon due to the intraorbital extracerebral recurrence of the anaplastic ependymoma. As for the procedure performed, the expected success was obtained. Because of the periorbital soft tissue and orbital bone involvement by the neoplasia, the therapeutic option for tumor resection with orbital exenteration was successful.

Conflicts of Interest

The authors have none to disclose.

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The Role of Neurophysiological Monitoring during Complex Aneurysm Surgery: Report of Two Cases and Review of the Literature

O papel do monitoramento neurofisiológico durante cirurgia de aneurisma complexo: relato de dois casos e revisão da literatura

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Abstract

The surgical treatment of intracranial aneurysms is a routine operation in the neurosurgeon practice. Complex aneurysms are those with morphological irregularities, usually large or giant; thrombosed, partially thrombosed or calcified; with aberrant fundus/neck ratio and near eloquent neurological structures. These cases demand special skills by the surgical team. The present article is a report of two cases of complex aneurysms successfully treated, with a discussion on the role of neurophysiological monitoring. In these two cases of supra- and infratentorial complex giant aneurysms, intraoperative monitoring was extremely relevant. Thus, we believe that treating complex and giant aneurysms carries several pitfalls, and the use of multimodal intraoperative monitoring is mandatory to mitigate risks and deliver the best result to the patient.

Keywords

- intracranial aneurysm
- surgery
- neurophysiological monitoring
- intraoperative angiography

Resumo

O tratamento cirúrgico de aneurismas intracranianos é uma cirurgia de rotina na prática neurocirúrgica. Aneurismas complexos são caracterizados por terem irregularidades morfológicas; serem grandes ou gigantes; parcialmente trombosados ou calcificados; com uma razão fundo/colo desfavorável ou aqueles próximos a estruturas neurológicas eloquentes.

Esses casos demandam habilidades específicas do time cirúrgico. Este estudo relata dois casos de tratamento bem sucedido de aneurismas complexos, discutindo o uso da monitorização neurofisológica intraoperatória. Em ambos casos, sendo um supratentorial e outro infratentorial, o uso de monitorização neurofisiológica intraoperatória foi essencial para avaliar a qualidade da clipagem dos aneurismas e eventualmente reposicionamento dos clipes para evitar déficits neurológicos.

Dessa forma, devido ao alto risco potencial de tratamento cirúrgico de aneurismas complexos, acreditamos que a monitorização intraoperatória neurofisiológica multimodal se faz mandatória para mitigar os riscos e alcançar o melhor resultado cirúrgico e funcional.

Palavras-chave

- aneurisma intracraniano
- cirurgia
- monitorização neurofisiológica
- angiografia intraoperatória

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Introduction

The surgical treatment of intracranial aneurysms is a routine operation in the neurosurgeon practice. They may be unruptured or ruptured, and surgical clipping enables mass effect control and the avoidance of further bleeding or rebleeding. The majority of intracranial aneurysms is located near the skull base, and are related to branching sites of large vessels of the anterior or posterior circulation. Morphologically, aneurysms may be small, large or giant, and saccular or fusiform. They may also be classified according to the fundus/neck ratio and their content (thrombosed, partially thrombosed or calcified).[1–15]

Complex aneurysms are those with morphological irregularities, usually large or giant; thrombosed, partially thrombosed or calcified; with aberrant fundus/neck ratio, and near eloquent neurological structures. These cases demand special skills by the surgical team. A preoperative complete investigation associated with the correct intraoperative planning is essential for maximum success. Currently, these cases need special technology application, including navigation, neurophysiological monitoring, and intraoperative real-time angiographic evaluations by immunofluorescence.[10–18]

In the present report, we describe two cases of complex aneurysms successfully treated, and discuss the role of neurophysiological monitoring. In these two cases of supra- and infratentorial complex giant aneurysms, intraoperative monitoring was extremely relevant because the aneurysms were closely related to eloquent brain structures such as: the medulla, the cerebellum, the lower cranial nerves (IX, X, XI, XII), the posterior inferior cerebellar artery (PICA), the vertebral artery, the internal carotid artery, and the perforating arteries of these vessels.

Case Descriptions

Case 1

The first case was of a 36-year-old male patient with a history of left holocranial pulsatile headache with irradiation to the cervical region. It was persistent, relieving with usual analgesic use. There were no other complaints and/or neurological deficits. The neurological examination was normal. His previous medical history was unremarkable.

The patient was submitted to cerebral angiography, which disclosed a fusiform lesion of the left internal carotid artery (ICA), reaching the bifurcation of the ICA, the M1 segment of the middle cerebral artery (MCA), and segment A1 of the anterior cerebral artery (ACA). There was no subarachnoid hemorrhage (SAH) associated (►**Fig. 1**).

The patient underwent microsurgical clipping of the aneurysm and vessel reconstruction by a pterional approach with adjunct use of neurophysiological monitoring (►**Fig. 2**). Additionally, we used indocyanine green to address the

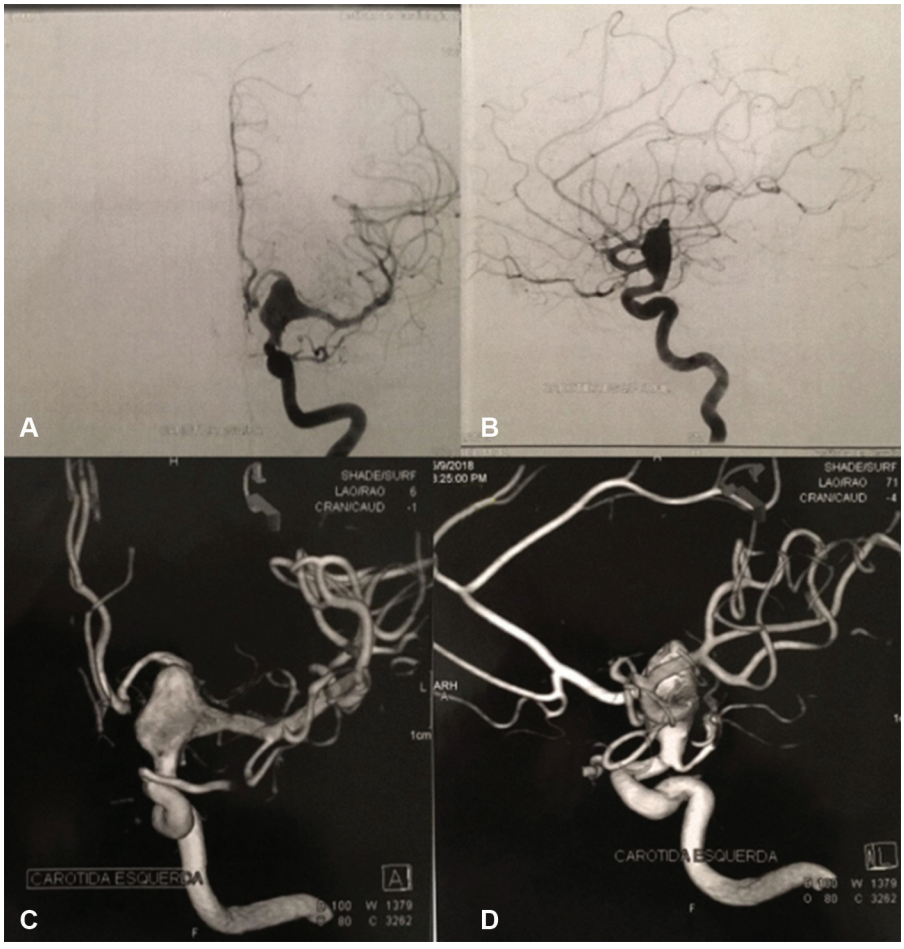

Fig. 1 Complex and fusiform internal carotid artery (ICA) bifurcation aneurysm reaching the proximal M1 and A1 segments.

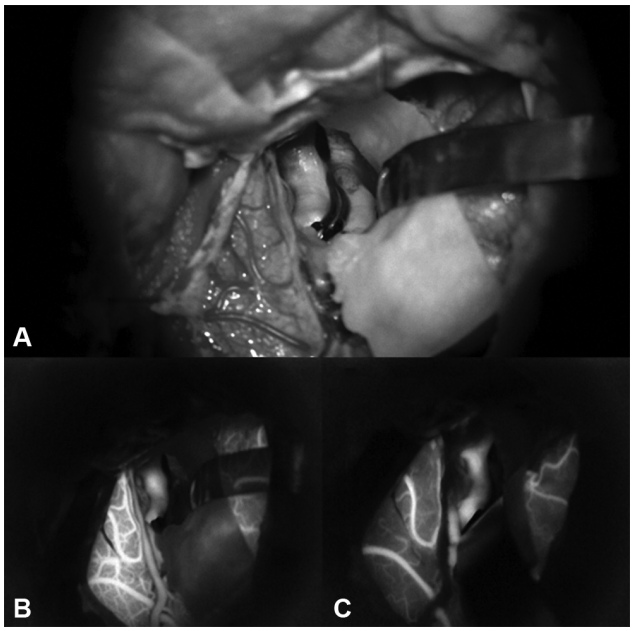

Fig. 2 Aneurysmal clipping and vessel reconstruction. Intraoperative angiography with indocyanine green (ICG) revealing good blood flow.

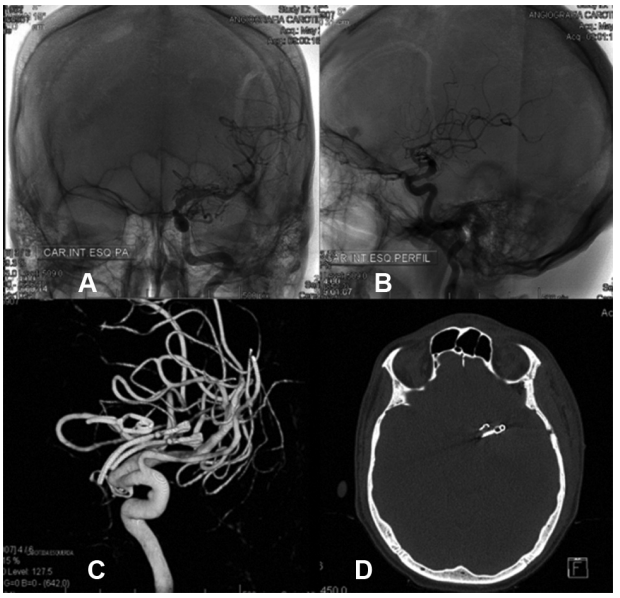

Fig. 4 Postoperative images disclosing total aneurysmal exclusion and preservation of blood flow.

intraoperative flowmetry after clipping. Multimodal neurophysiological monitoring was performed from the beginning to the end of the procedure, with the following techniques (►**Fig. 3**):

(a) Somatosensory-evoked potentials (SEPs) by stimuli in the upper and lower limbs.
(b) Motor-evoked potentials (MEPs) by transcranial electrical stimuli, with registration in muscles of the upper and lower limbs.
(c) Electroencephalogram (EEG) with ten channels for depth assessment anesthesia and train-of-four (TOF) to evaluate neuromuscular blockade.

The reconstruction was accomplished by clipping the proximal ACA and reconstructing bifurcation walls with clips.[3] During surgery, neurophysiological monitoring was unremarkable, and the postoperative neuroimage and clinical picture were adequate (►**Fig. 4**). The patient was discharged in the fifth postoperative day, without neurological impairment.

Case 2

A 54-year-old female patient presented with a history of dizziness and nausea for weeks, which was associated with moderate to severe pulsatile persistent holocranial headache relieved by analgesics. After a few days, the patient evolved

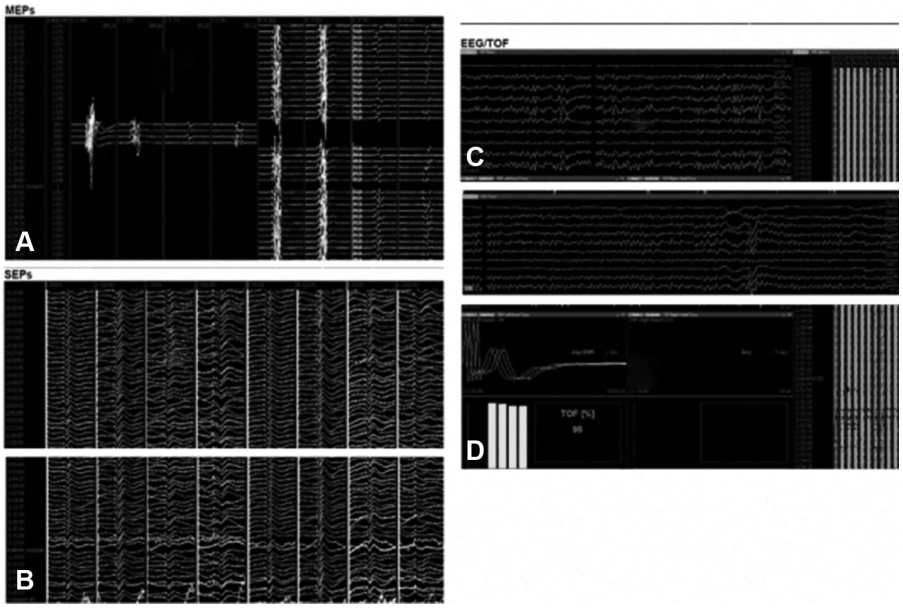

Fig. 3 Intraoperative neurophysiological monitoring revealing no disturbances during clipping.

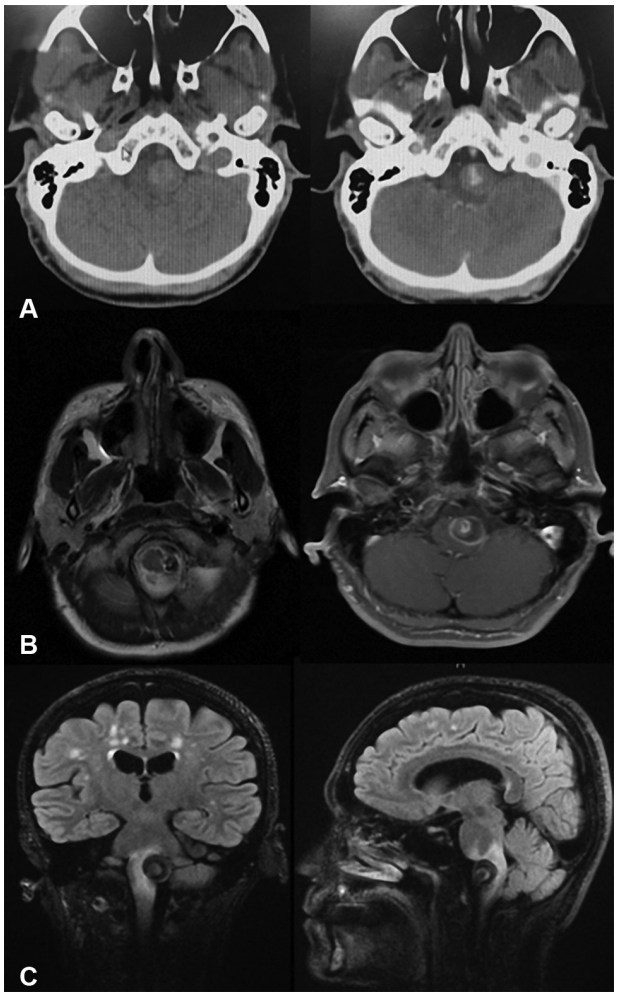

Fig. 5 Large, complex and partially thrombosed aneurysm near the medulla. Inside the aneurysm there were also different phases of intramural bleeding.

with left hemiparesis (grade IV), with gait disturbances and falling, as well as alteration of the lower cranial nerves (X, XII) on the left (dysphagia, dysphonia).

She underwent cranial tomography and magnetic resonance, which revealed an extra-axial nodular lesion on the left side of the medulla measuring 2 cm in diameter, heterogeneous, hypodense in the periphery and hyperdense in the center, closely related to the left vertebral artery, and deforming the medulla. The hypothesis of a vascular lesion was raised, and she underwent a vascular study (►**Fig. 5**).

The images of the cerebral angiography showed a communication of the vascular lesion with the left vertebral artery through a narrow, saccular lesion (►**Fig. 6**). The patient was submitted to a left far lateral approach with partial resection of the occipital condyle and the C1 left arch, to better approach the lesion, which had an intimate contact with the vertebral artery and ipsilateral brainstem (►**Fig. 7**). Additionally, we used indocyanine green to address the intraoperative flowmetry after clipping.

Then, the artery remained for 20 minutes with a provisional straight clip, which caused a decrease in the potential of the ipsilateral XII cranial nerve in this period, with a return after the clip was repositioned (►**Fig. 8**). The patient was discharged in the seventh postoperative day, without neurological impairment.

Discussion

Complex aneurysms are difficult lesions to treat. Their irregular morphology and atypical location and characteristics make surgery attempts potentially harmful and challenging. On the other hand, due to such peculiarities, treatment by endovascular means is not ideal, or may be used just in the context of a staged or partial procedure. Therefore, developing a surgical strategy and additional intraoperative information is key in these cases.[1–10]

Complex and giant aneurysms of the ICA (diameter $>$ 2.5 cm) are sometimes associated with life-threatening complications such as a mass effect, thromboembolic ischemic stroke, and hemorrhage. Patients can deteriorate rapidly, with neurological deficits that can lead to death after the rupture of the aneurysm. The risk of injury to perforating arteries is high, resulting in neurological deficits.[11–18]

In the first case herein presented, the major concern was the injury to ICA perforators. The reconstruction was accomplished by clipping the proximal ACA and reconstructing bifurcation walls with clips without changes in neurophysiology parameters. This technique was previously described,[3] and may be used in complex aneurysms of the ICA bifurcation when the communicating complex is functional and able to provide collateral flow to the ipsilateral ACA territory.[3]

The decision of when to perform the clipping and bypass remains controversial. There are advantages and disadvantages to each technique. Data from the literature shows that 95% of patients with extracranial to intracranial (EC-IC) bypass and ICA occlusion had relatively good results, as

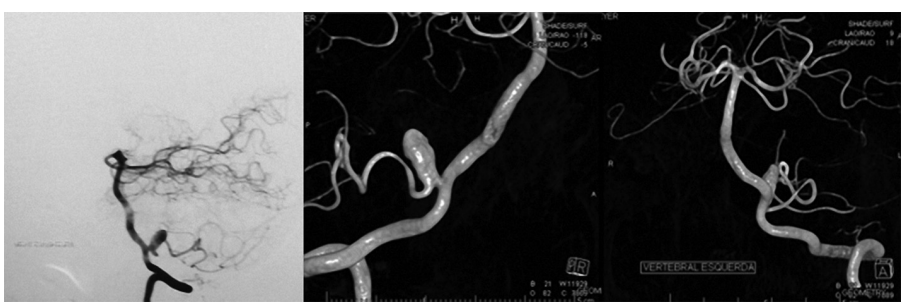

Fig. 6 Posterior inferior cerebellar artery (PICA) aneurysm arising together with the PICA and measuring 10 × 6 mm.

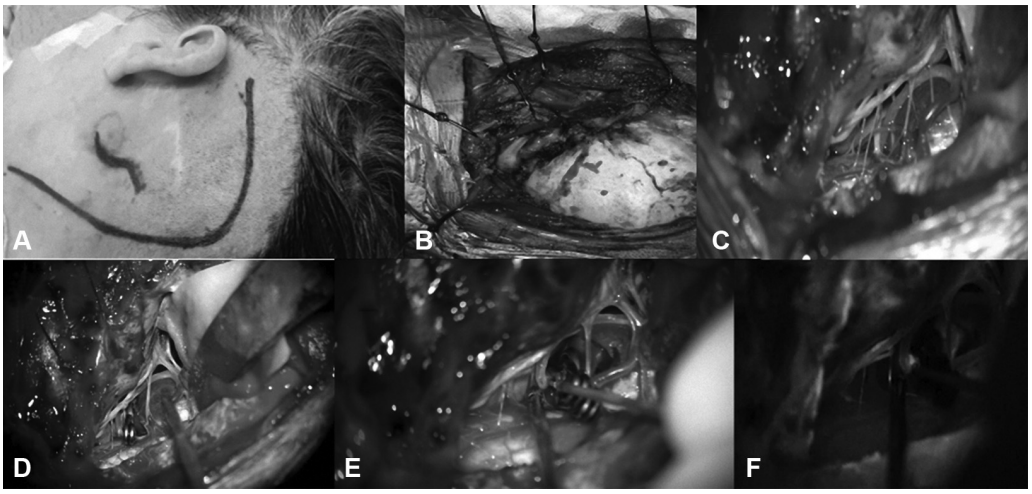

Fig. 7 Surgery by a far lateral approach to enable the manipulation of the anterior and lateral lower medullas. Clipping of the aneurysm and postclipping with indocyanine green (ICG).

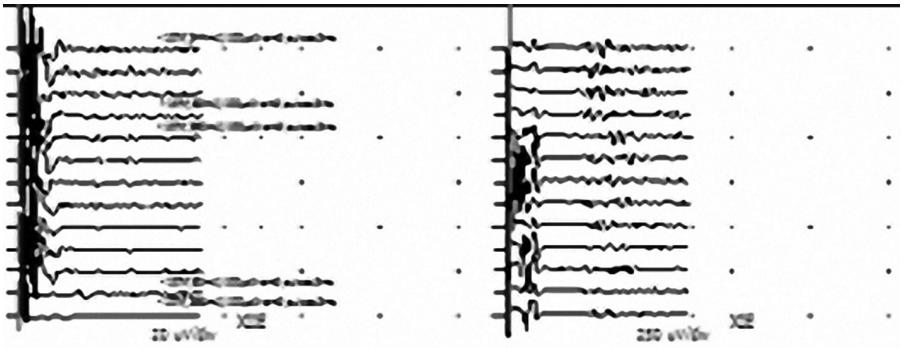

Fig. 8 Loss of motor potential of the XI and XII nerves after initial clipping, demanding repositioning, after which the potentials became normal.

indicated by the Glasgow coma scale (GCS) after 3 to 64 months of follow-up, but those cases were also associated with an incidence of 10% of postoperative obstruction with the bypass technique.[6–15] This finding indicates that, for patients with anastomotic obstruction, bypass surgery may be unnecessary. Then, the clipping technique can be the best choice to protect the main vessel (ICA). Moreover, the ideal technique depends on the expertise of the surgical team, and may change also depending on intraoperative findings.

Temporary occlusion is required during the clipping and bypass procedures. Collateral circulation and tolerance to brain ischemia while the ICA is temporarily occluded is generally assessed according to the preoperative occlusion test. Under general anesthesia, however, this preoperative analysis may be unreliable, because the metabolic demand of the anesthetized brain is lower than that of the waking brain.

The second case (giant aneurysm located in the infratentorial region) originated in the left vertebral artery, and caused mass effect in the brainstem, in addition to having the PICA originating along the neck of the lesion. Clamping of this artery to empty the complex aneurysm was unavoidable. Then, it remained for 20 minutes with a provisional straight clip, which caused a decrease in the potential of the ipsilateral XII cranial nerve in this period, with a return after the clip was repositioned.

Motor-evoked potentials appear to be more sensitive than SEPs for cerebral blood flow deficit, for they can detect subcortical ischemia or infarction during the operation in less than 1 minute, especially pure motor deficits caused by perforating arteries or large branches. In our cases, the MEPs correlated with the postoperative neurological status.[2–6]

Some reports highlight the use of other intraoperative strategies to address functional status during surgery. Some studies emphasize the use of micro Doppler probes to make real-time evaluations of arterial blood flow.[2–6] They are useful to analyze blood flow inside the aneurysm and especially after clipping, to evaluate the patency of the vessel.[5] In the case of the performance of a bypass, it is also useful to analyze the patency of the bypass. Other groups reported the application of awake craniotomies to perform complex aneurysm clipping.[4] Similarly to functional neurological tumor surgery, awake craniotomies would enable a better visualization of functional impairment during surgery, with higher accuracy compared with routine neurophysiological monitoring.[4] Although we recognize the potential benefits of both strategies, we did not apply them in our cases.

Another peculiarity of our cases was that we did not use endovascular means. Had we chosen to use the endovascular treatment, we would not have intraoperative monitoring in our favor, and, due to the morphology of the lesions, we

would have faced an increased risk of obstruction, and, consequently, morbidity and mortality in the postoperative period of these complex lesions. Additionally, ours were cases of unruptured aneurysms. Surely, we managed them rapidly, but had time to make the best preoperative planning. In the scenario of ruptured aneurysms, especially depending on the severity of the clinical profile, there is no time to adequately plan surgery and use all the multimodal neuromonitoring modalities available.

Thus, we believe that treating small or large aneurysms in usual presentations may be performed with safety in the routine neurosurgical set up. Nevertheless, cases of complex and giant aneurysms carry several pitfalls, and the use of multimodal intraoperative monitoring is mandatory to mitigate risks and deliver the best result to the patient.

Conflict of Interests

The authors have none to declare.

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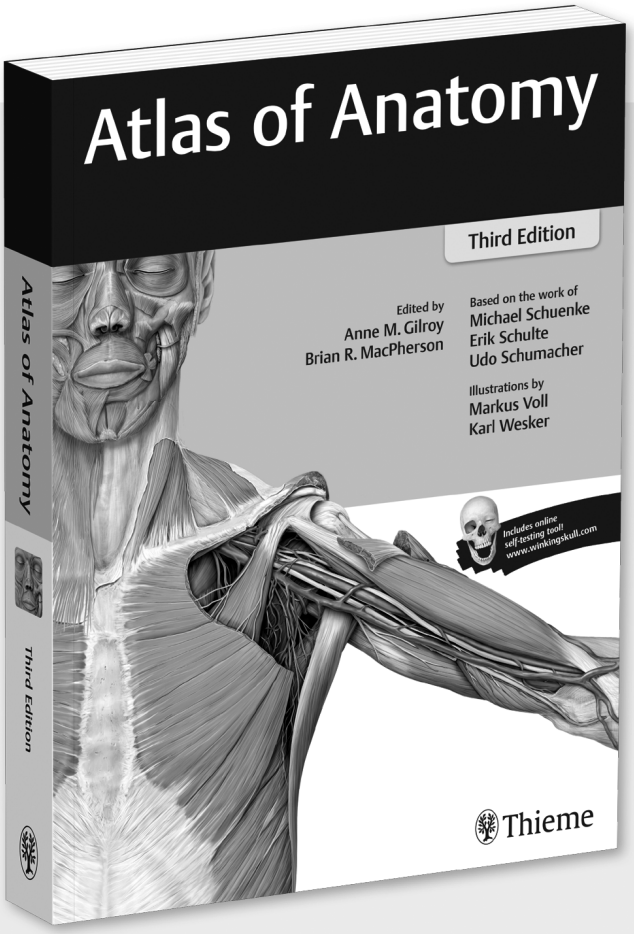

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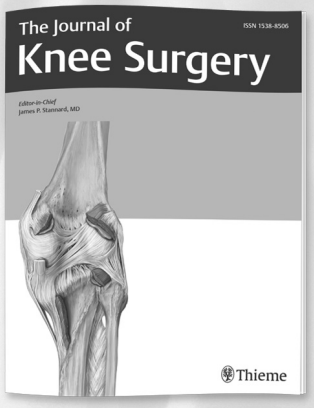

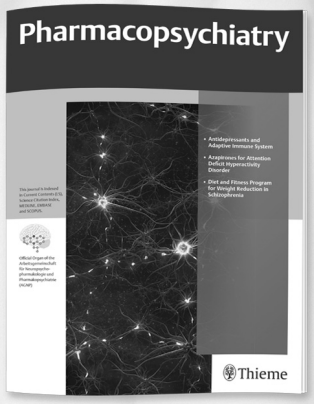

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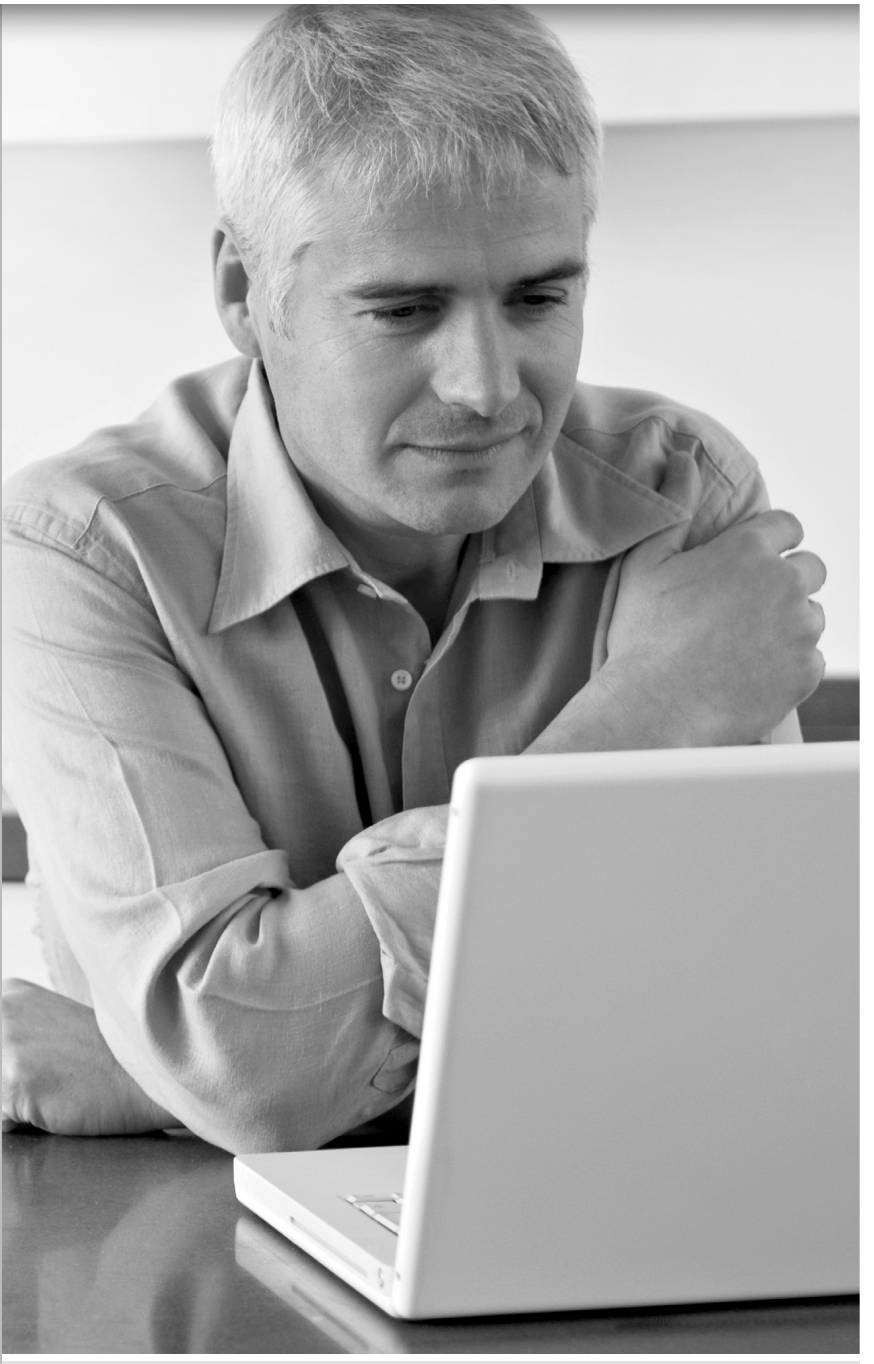

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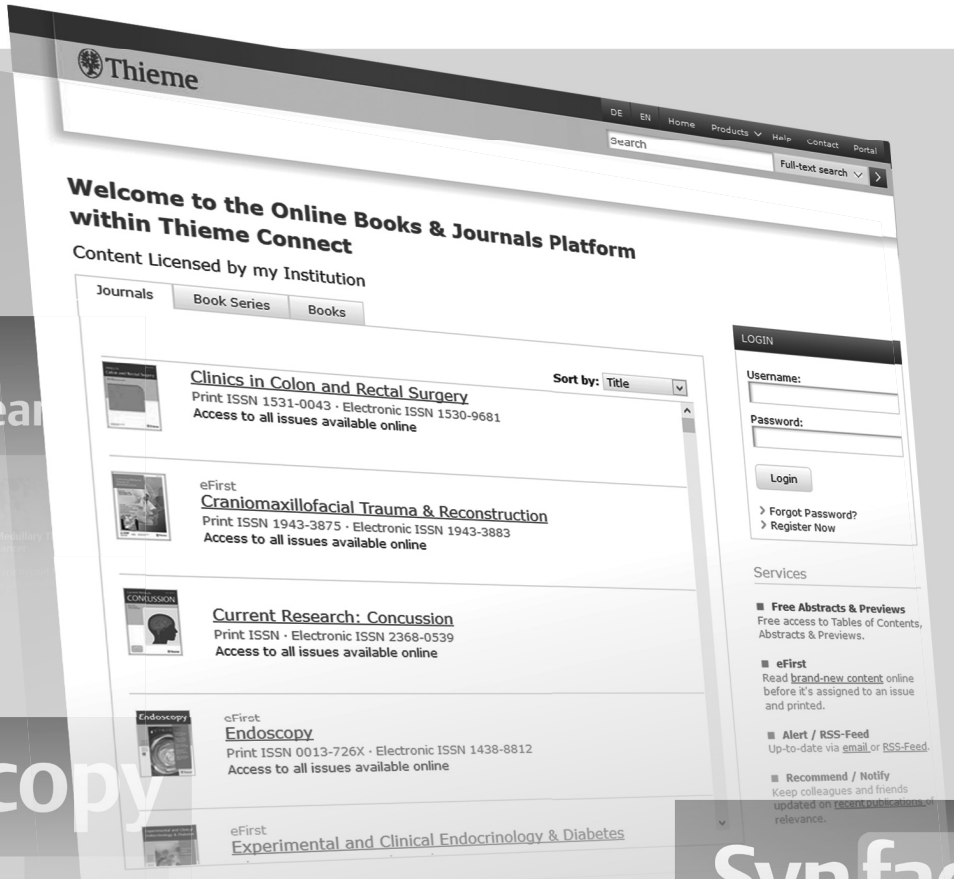

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