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EDITORIAL

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EDITORIAL

Artificial intelligence in medicine

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Artificial intelligence (AI) in medicine began as a special branch of computational science that allows the complex analysis of data in the diagnosis, treatment, and prognosis of different illnesses. Alan Turing proposed the name of AI in 1950[1]. In 1955, John McCarthy named AI the science of making an intelligent machine[2]. In 1976, Gunn applied AI in an algorithm for the first time to diagnose abdominal pain[1].

Nowadays, AI is part of the robots used in medicine. The term robot comes from the Czech word "robota," a biosynthetic machine used for forced work[2]. The possibility of using computational models like an imitation of human behavior is increasing rapidly.

Today, AI in medicine has two branches. One of them is the virtual part, which is in charge of the informatic approach; the specific name is Machine Learning with a core called Deep Learning. Both are directed to analyze the DATA that is comprised of the clinic records, the laboratory results, the histopathologic reports, the information supplied by the pharmacologic industry, the scientific information of different sources, and the monitoring records of patients by Internet of Medical Things (Fig. 1)[1-4]. Machine Learning aims to analyze, classify, and judge a huge digital information to help formulate algorithms for diagnosis and therapy. The main idea is that the computer can learn by itself. This branch of AI utilizes three kinds of algorithms. The first is the unsupervised mode drive to find patterns (K-means, K-methods, Fuzzy C-means, Hierarchical, Gaussian Mixture, Hidden Markov Mode, and Neuronal Network). The second one is the supervised mode aimed at the classification of data (Support Vector Machine, Discriminant Analysis, Naïve Bayes, Nearest Neighbor, and Neuronal Network) and prediction of algorithms with prior knowledge (Linear Regression, Ensemble methods, Decision tree, Neuronal Network). The last mode is called "reinforcement learning," where reward-punishment sequences in specific tasks or missions[3,4].

The physics branch includes the robots charged with rehabilitation (Lokomat) and robots to assist geriatric patients in Japan. Robots assist in surgery, too, such as D'Vinci in general surgery or ROSE ONE for stereotactic neurosurgery.

A specific example of AI application in medicine is designing new therapeutic drugs. Machin learning is used in peptide synthesis, a virtual search of receptors and ligands, predictions of toxicity, monitoring and delivery functions, modeling of pharmacophores, qualitative relation-ship of structure-activity, re-uptake of drugs, polypharmacy, and physicochemical activity[3].

AI has developed several tools such as[4-6]:

- Viewing Machine Learning (human and machine rather than human versus machine),
- Natural Language Processing (the ability of a computer to understand a human language as unprecise, ambiguous, and sometimes unstructured),
- Fuzzy Logic (a multi-valued logic in a solution of problems) and
- Data mining (interaction between database technology, modeling techniques, statistical analysis, pattern recognition, and machine learning).

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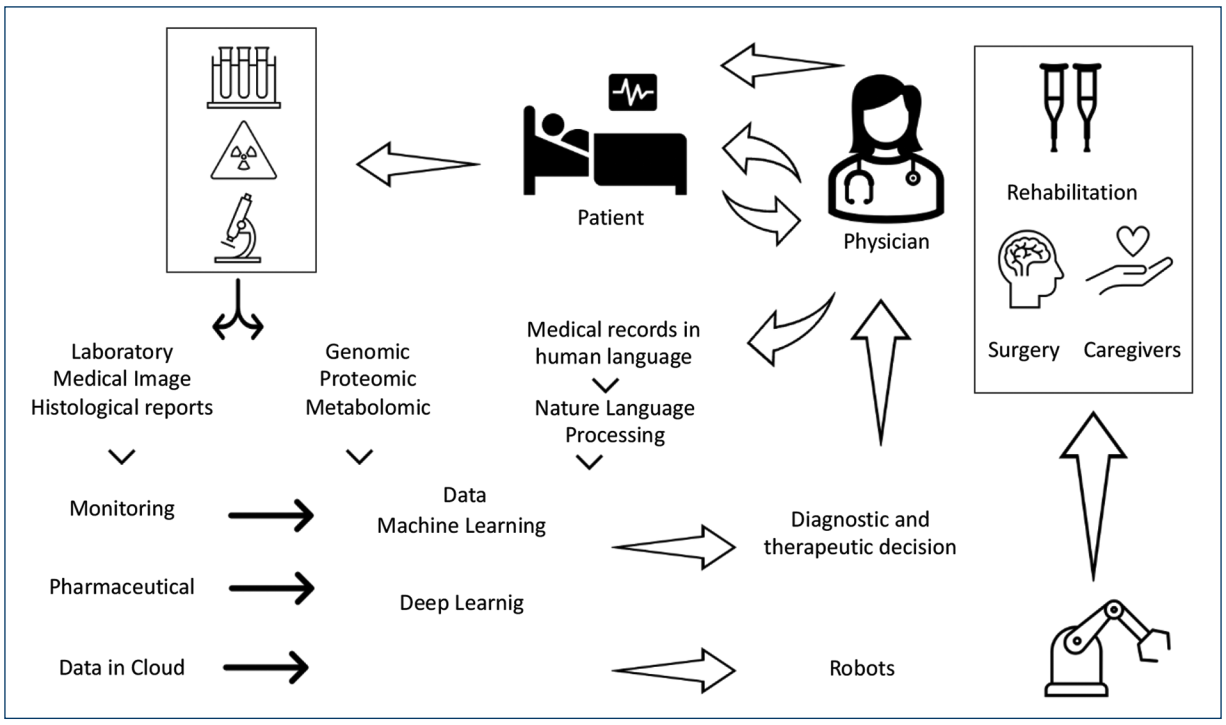

Figure 1. This diagram shows a schema about how Machine Learning (Deep Learning) received information of many sources and allows a computer to learn without previous programming and the analysis move to elaborated algorithms of decision. Two final outputs one of them is robotic solution (rehabilitation, surgery, and caregivers) the other is the physician.

In neurology, AI has shown important advances. AI can produce predictive risk models for stroke, growth of brain tumors, suicide ideation, triggers to seizures, and early diagnosis for Alzheimer's and Parkinson's diseases. The massive analysis of exome, RNA, proteins, and the metabolism mechanism also helps predict the clinical effect of anticancer or antiepileptic drugs[5]. In neurosurgery, the robots have applications for guiding the resection of tumors, detection of the epileptic focus, and directing screws in spine surgery. In rehabilitation or prosthetic surgery, robots make the main contribution. The recent advance in deep brain stimulation allows the delivery of a specific electric energy program in a very restricted anatomical area. In addition, this new system can recognize pathologic patterns of local field potentials and respond with a specific schedule of electric pulse trains[7].

However, AI in medicine must solve several issues like the cost of implementation, the adjustment to the health systems, opposition to change by healthy personnel, and the limits of AI in human activity as medicine. The eventual consolidation of AI in preventing and maintaining health does not see two main functions of medicine: the knowledge of pain and the medic-patient relationship. AI has an advantage over humans in managing a large amount of data. Combining scientific journals with clinical records with lab and paraclinical results information with sociomedical and environmental conditions is very hard for any health professional. AI is now the instrument that gives us an alternative. Despite the concept of the health-disease process, it is a subjective process. Medical thought is naturally rational but involves heuristic knowledge and ethical considerations. The understanding of human suffering is essentially a human act that is not limited to nosology or therapy. Empathy is immanent in medicine and many neurologic aspects and philosophic thought. Machine learning and deep learning cannot reproduce a human mind. It is still waiting and talking about considering a machine as a human being. The human is a subject that means to possess a consciousness. Has AI in a machine consciousness itself?

In addition, the human mind shows a special phenomenon named auto-conscient metacognition, which is the ability to think in the autonomy of the thought. The human is aware of his property thought. On the

other hand, the experience of qualia is the transition from the sensation originated by the external stimulus to the perception-filling, to the emotion, and finally to the interpretation of this stimulus.

How does a patient perceive the painful sensation? How does he or she interpret this feeling? How can other subjects be empathic with a suffering subject? Can AI offer answers to these questions? I recommend additional lectures by Searle on Functionalism[8] and Chalmers on the experience[9]. AI is just a part of the function of the mind. We must remember that the natural human condition needs fillings, emotions, and ethical-moral thoughts combined with rational knowledge. Finally, Bartra proposed an extensive and important extracerebral function on social networks[10]. AI will come to stay, but the human condition is beyond its limits.

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Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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ORIGINAL ARTICLE

Pediatric extreme hydrocephalus after shunting: preliminary findings of long-term follow-up

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Abstract

Introduction: *Pediatric extreme hydrocephalus (PEH) is a complex condition with uncertain prognostic outcomes.* **Objectives:** *In this study, we analyze the long-term change in cerebral parenchymal thickness of pediatric patients with extreme hydrocephalus after shunting.* **Methods:** *A retrospective observational study was conducted on patients with PEH treated at the General Hospital of Mexico from 2009 to 2016. Cerebral parenchymal thickness was measured in computed tomography studies before surgical intervention, at 5 months, and 4 years post-surgery. The average change in thickness in millimeters was analyzed, and its normalized value was assessed using the Wilcoxon test and the R^2 of a linear function.* **Results:** *Twelve patients, including 5 females and 7 males, were studied. Nine cases were congenital, while the remaining 3 cases were 6 months, 7, and 10-years-old. At 5.2 months PostOp., patients showed an average increase of 160% in cerebral parenchymal thickness, which increased to 270% at 4.3 years. However, 4 cases (33.3%) had an increase of < 10% from the original thickness. One patient at 4.3 years exhibited a 594% increase compared to the baseline. In the congenital cases, pre-operative thickness had a good correlation (R^2 = 0.70) with post-operative thickness, but pre-operative age of patients did not correlate with post-operative thickness (R^2 = 0.03).* **Conclusions:** *In this study, 3 out of 12 cases of PEH showed a long-term increase of > 200% compared to preoperative thickness. Even in cases of extreme hydrocephalus, significant long-term improvement can occur. Rapid treatment of these cases is crucial to increase the likelihood of improvement.*

Keywords: *Extreme hydrocephalus. Pediatric hydrocephalus. Structural neuroplasticity.*

Introduction

Hydrocephalus is one of the most frequent and relevant neurosurgical disorders in both adult and pediatric patients. In the pediatric population, hydrocephalus ranks as the third leading cause of admission to the Neurosurgery Department at the National Institute of Pediatrics in Mexico[1]. Similarly, at the General Hospital of Mexico, congenital hydrocephalus has been one of the leading causes of birth abnormalities[2]. In most cases of pediatric hydrocephalus, there is a moderate to significant accumulation of cerebrospinal fluid (CSF). However, in certain cases, there is a massive accumulation of CSF[3-6]. The compression exerted by the excessive amount of CSF on the brain parenchyma can severely affect brain development. In fact, a greater amount of CSF is expected to have a more severe impact on neuronal tissue, sometimes leading to the absence of cortical tissue in extensive areas[3,7].

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Our research problem statement is that these cases of extreme hydrocephalus pose a unique and complex challenge, especially concerning the management and progression of these patients. Interestingly, to date, there are no descriptions of the long-term effects of surgical treatment on parenchymal thickness in pediatric patients with extreme hydrocephalus. In this study, we examine the chronic changes in brain thickness in pediatric patients with extreme hydrocephalus after undergoing ventriculoperitoneal shunt placement at the Hospital General de México.

Materials and methods

A retrospective, observational, and longitudinal study was conducted using the records of pediatric patients treated at the Hospital General de México "Dr. Eduardo Liceaga."

Subjects

The study included patients of both sexes, aged between 0 (newborns) and 18 years, diagnosed with extreme hydrocephalus and treated with ventriculoperitoneal shunt placement in the pediatric neurosurgery department of the General Hospital of Mexico. Patients with hydrocephalus secondary to tumor-related causes and those without long-term imaging studies (> 3 months post-surgery) were excluded from the study. The study period ranged from September 1, 2009, to January 30, 2016. The present study protocol was submitted for registration to the Research Committee of our hospital.

Retrospective measurements

In cranial computed tomography studies, the axial section at the approximate level of the foramen of Monro was identified; in this section, the transition from the frontal horn to the atrium of the left lateral ventricle was identified. Then, the thickness of the cerebral parenchyma was measured from the pial surface to the ventricular surface (Fig. 1A: dashed line), and the distance between both inner tables was also measured at the same level (Fig. 1: solid double-head line).

Data analysis

The post-surgery parenchymal thickness in each patient's studies was adjusted as a ratio relative to the diameter between the inner tables (Fig. 1A, blue line) and normalized to the pre-surgery thickness. Values were expressed as a percentage relative to the pre-surgical baseline thickness. These normalized percentage data were grouped into two time points (5.2 months and 4.3 years), corresponding to the average times at which control imaging studies were conducted for operated patients. In cases of congenital hydrocephalus, the normalized parenchymal thickness data at 5.2 months were plotted against the age at treatment. In these same cases, parenchymal thickness in millimeters was also plotted against pre-surgery thickness in millimeters. In both cases, the R^2 value of a linear function was calculated to assess the degree of correlation. Grouped data were expressed as a percentage or as mean ± standard deviation. The Wilcoxon test was used to determine if the average normalized values at 5.2 months and 4.3 years differed. A $p < 0.05$ was considered statistically significant. Data collection and analysis were conducted in Excel program.

Results

The present study included 12 cases, 7 male and 5 female patients. Nine cases had congenital hydrocephalus (average age at diagnosis: 11.0 ± 7.6 days), while the remaining three cases were aged 6.9 months, 7.1 years, and 10.7 years, respectively (Fig. 1). The thickness of the cerebral parenchyma in the motor/perimotor region of the left hemisphere was measured in all cases before surgery and after ventriculoperitoneal shunting, at 5-6 months (average: 5.2) and 4-5 years (average: 4.3) post-surgery. At the time of diagnosis, prior to shunting, the cerebral parenchymal thickness was 18.48 ± 12.66 mm. However, when considering only cases of congenital hydrocephalus, the parenchymal thickness was 14.11 ± 10.45 mm. Given the considerable intrinsic variation found in the cases, data were adjusted relative to the diameter between the inner tables and normalized to the pre-surgical baseline for temporal comparison. In the follow-up studies, the cases showed an increase in normalized cerebral parenchymal thickness of 160 ± 61% and 270 ± 128% at 5.3 months and 4.3 years of follow-up, respectively (Figs. 1 and 2). At 5.2 months, 5 patients (41%) exhibited an increase in cerebral parenchymal thickness of > 200%, while in 4 cases (33.3%), there was no significant improvement (< 10% increase). One patient at 4.3 years showed an increase of 594% compared to the initial pre-surgical thickness (Fig. 2).

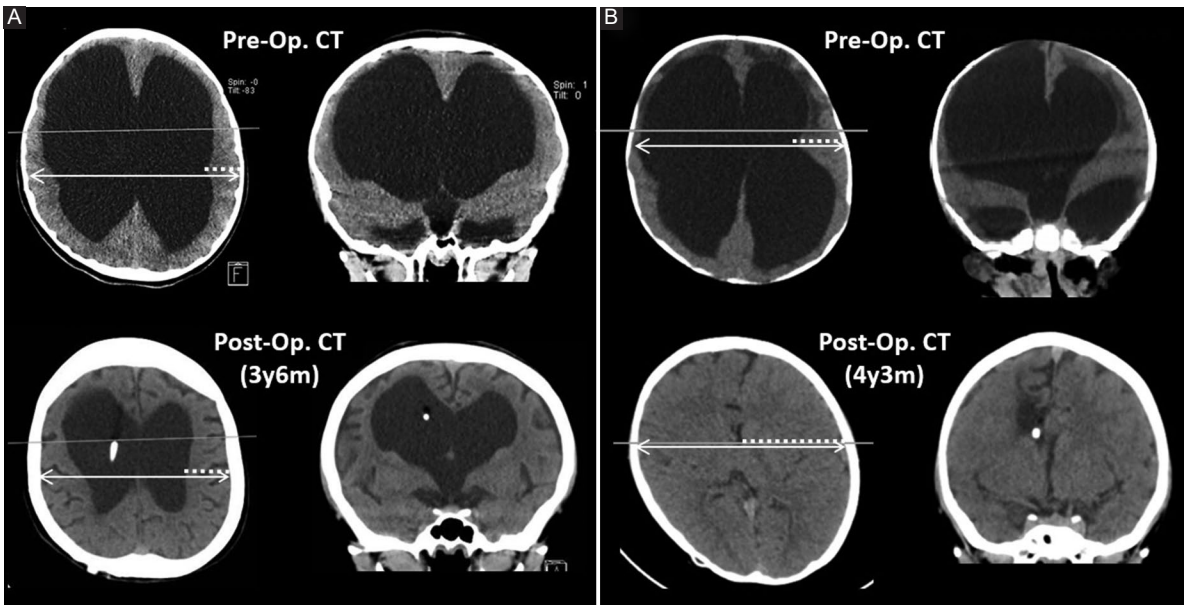

Figure 1. Computed tomography (CT) scans of two cases of extreme hydrocephalus treated with ventriculoperitoneal shunting. **A**: case 2, female, 10 years 9 months of age at the time of diagnosis (upper images) and 3 years 6 months after shunt placement (lower images). **B**: case 4, male, 6 months of age at the time of diagnosis (upper images) and 4 years 3 months after shunting. The horizontal continuous lines represent the level of CT sections; the dashed white lines on the axial images indicate the region where cerebral parenchymal thickness was measured, and the double-head arrow lines show how the intracranial diameter was measured at the same level.

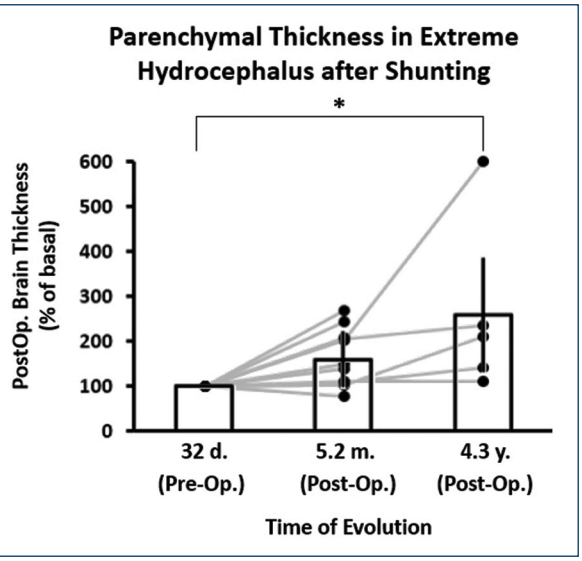

Figure 2. Temporal course graph of cerebral parenchymal thickness of shunted patients. Data are adjusted and normalized to the preoperative thickness (left column) of each case. Central and right columns with error bars represent post-operative mean values ± standard deviation, dots represent individual patients, *p < 0.05. mean value ± standard deviation.

Considerable variability was found in the development of cerebral parenchymal thickness and since 75% (n = 9) of the cases studied were congenital hydrocephalus, we analyzed whether there was a relationship between the time of evolution (neonatal age) and the change in parenchymal thickness at 5 months in these congenital cases. We found that the change in parenchymal thickness did not show a proportional relationship with the age of surgical treatment (Fig. 3A, $R^2 = 0.03$). However, when plotted against the pre-surgical parenchymal thickness, we observed that a greater pre-shunting parenchymal thickness was associated with a greater tendency to have increased cerebral parenchymal thickness at 5 months post-surgery (Fig. 3B, $R^2 = 0.70$).

All cases were successfully managed for hydrocephalus; however, shunt system revision was performed in three cases. Two revisions were due to shunt system dysfunction, and other one was due to CSF leakage into the subgaleal space at the trephination site. Another case experienced CSF infection, requiring externalization of the system, antibiotic treatment, and replacement with a new shunt.

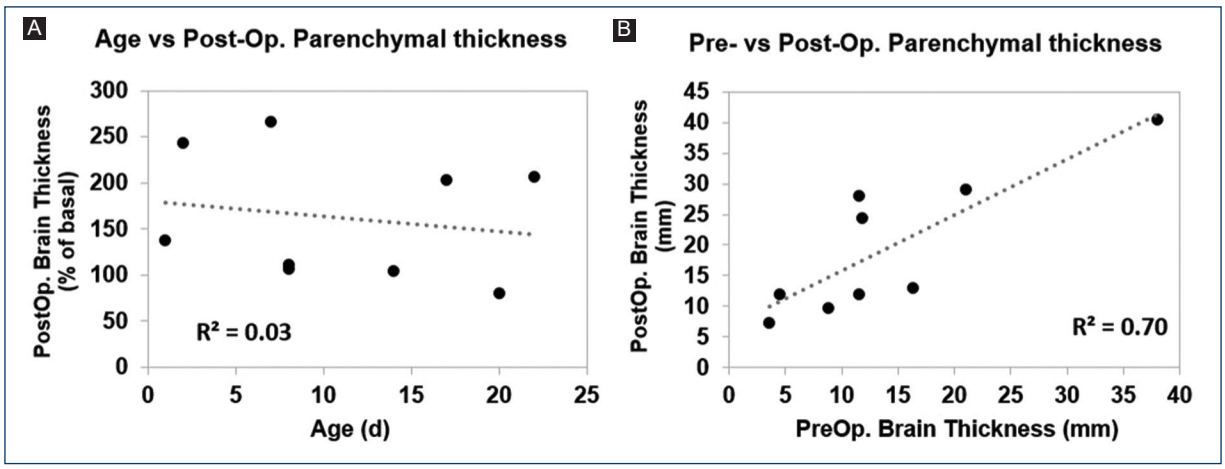

Figure 3. Correlations of postoperative cerebral parenchymal thickness in congenital extreme hydrocephalus. **A**: age vs. normalized parenchymal thickness at 5.2 months post-surgery. **B**: pre-operative parenchymal thickness versus post-operative thickness at 5.2 months. Note the R^2 value of 0.70 in the second graph.

Discussion

In the present study, we observed that even in extreme cases of hydrocephalus with severe compression of neuronal tissue, significant long-term improvement and recovery in cerebral parenchymal thickness can occur.

The first reports of extreme hydrocephalus (also known as maximum or massive hydrocephalus) were made in the 1960s[3,4]. In several cases, patients were not surgically treated as clinical findings suggested a poor prognosis, which was associated with intrauterine onset of hydrocephalus. Thus, cerebral tissue thickness was a decisive factor in determining whether a patient underwent surgical treatment or estimating their prognosis. In contrast, in our institution all the patients were shunted independently of the initial cerebral thickness. It has been shown that cortical mantle thickness did not show a deterministic correlation with the neurological status of patients[3,4]. Currently, it is known that extreme hydrocephalus *per se* is not a contraindication for intervention[5,7,8], but the presence of comorbidities (myelomeningocele and malnutrition) and delayed CSF diversion negatively influence the prognosis. In the present work, there are not patients with comorbidities, except malnutrition, and the delayed CSF shunt was only considered in the congenital cases. Interestingly, the data suggest that age is not directly or intrinsically important (Fig. 3A), but rather depends on the severity of hydrocephalus and the degree of parenchymal compression (Fig. 3B). An important consideration for diagnosis of these cases is whether there is extreme hydrocephalus or anencephaly. Sutton et al. (1980) observed that the latter cases show minimal occipital parenchyma and absence of EEG activity, which is useful for the diagnostics[7]. Although we did not conduct EEG studies on our patients, in hindsight, we observed that all treated patients were cases of PEH, as they all showed an increase in cerebral parenchyma. All cases in this report were treated with ventriculoperitoneal shunting; however, there are more than one alternative surgical treatments that can be effective for certain cases. Shitsama et al. (2014) reported stabilization of macrocephaly in 40% of cases of extreme hydrocephalus or anencephaly treated with endoscopic choroidal plexus coagulation[5].

Interestingly, the recovery in cerebral parenchymal thickness even in cases of massive hydrocephalus demonstrates the capacity for recovery and plasticity of the nervous system in certain cases. While neuron density and number are important for proper neurodevelopment, cases with massive CSF accumulation have been observed in which the brain can generate almost normal phenotype and behavior[9,10]. The cases reported serve as a reminder of the difficulty in managing these patients. Moreover, despite the challenges and possible complications of surgical treatment, like those observed in the patients in the present study, it is central to comprehensively treat these patients with a multidisciplinary management.

Finally, it is important to mention the limitations of this study: (a) it is an observational and retrospective study, (b) due to the nature and frequency of the condition, few cases were studied, and (c) in the 4-year follow-up,

some cases were lost because follow-up was not continued at our hospital. Given the above, it is necessary to have new data and case series in the future, preferably in controlled prospective studies.

Conclusions

In the present study, 25% of the patients with extreme hydrocephalus showed long-term recovery (> 200%) in cerebral parenchymal thickness. Timely diagnosis and immediate treatment are crucial in these cases.

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Conflicts of interest

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Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Orthokinetic splint as treatment of trigeminal neuralgia associated with temporomandibular dysfunction

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Abstract

Introduction: *Trigeminal neuralgia (TN) is a disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve, and triggered by innocuous stimuli. The worldwide prevalence of TN is estimated to be 0.3%. The prevalence of temporomandibular dysfunction (TMD) is assumed to be > 5% of the population. The study of the association of TN and TMD and their management with a repositioning splint is not enough, perhaps not studied yet.* **Objectives:** *The purpose of this study is to clinically observe the effectiveness of repositioning a splint in managing TN associated with TMD.* **Materials and methods:** *Thirty-three subjects fulfilled the selection criteria and were taken into consideration until a 4-month follow-up. The original sample enrolled 16 patients, but five declined the informed consent. Finally, 11 subjects were followed up until 4 months of clinical trial.* **Results:** *The use of splint had statistical differences and improved the visual analog scale scores and falling recurrent spasmodic attacks. In addition, the splint increases between 1.2 and 2.4 mm of the distance between the mandibular condyle and mandibular fossa.* **Conclusion:** *It can be concluded that the splint could be an option in managing TN associated with TMD.*

Keywords: *Trigeminal neuralgia. TMD. Splint.*

Introduction

The International Classification of Headache Disorders 3 of beta version defines Trigeminal Neuralgia (TN) as "a disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of trigeminal nerve and triggered by innocuous stimuli" also named as "tic douloureux"[1].

There is not enough statistical data on TN in Mexico. However, the worldwide prevalence of TN is estimated to be 0.3%[2]. TN is directly proportional to increasing age with an annual incidence of 17.5/100,000 in individuals aged from 60 to 69 years and 25.6/100, 000 in those older than 70 years[3]. The prevalence is 155 cases per million in the United States[4]. The approximate prevalence rate in the general population is expected to be between 0.1 and 0.3% and among the primary care settings that it is estimated at 12%/100,000 persons with a female-to-male ratio of 2:1[5].

TN can be treated by pharmacological, surgical, and neuromodulation methods like peripheral nerve stimulation[4-7]. Carbamazepine stands as the first-line therapy of TN. However, the failure of pharmacological treatment leads to surgical interventions, which are effective

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for pain relief at 80-90% with possible side-effects and recurrence rates in the span of 5-7 years[8,9]. Temporomandibular dysfunction (TMD) is a group of musculoskeletal and neuromuscular conditions that involve the temporomandibular joint (TMJ), the masticatory muscles, and all associated tissues and structures[10].

The prevalence of TMD is assumed to be greater than 5% of the population[11]. The ratio of female-to-male prevalence is generally found to be 2:1[12]. The etiology of TMD is unknown but is expected to be both multifactorial and biopsychosocial consisting of initiating, predisposing, and perpetuating factors such as macro-trauma or micro-trauma attributed to failed healing due to psychosocial profile of patient, failed treatment, or genotype[13,14]. One factor could be the partially edentulous and edentulous prosthetic or toothed for long period would promote a shift in the vertical and transverse mandibular positions; as a result, the position of the condyles in the mandibular fossae may also change[15]. Change of the rest position due to the reduction of vertical dimension of occlusion is also considered to be one of the predisposing factors[15].

Different management and treatment options exist for TMD. In 2014, Mansur Dogan mentioned the effective outcome of bio-oxidative ozone therapy in reducing the visual analog scale (VAS) scores, at an 87.8%, associated with TMD[16]. However, splint therapy is more frequent and may be defined as "the art and science" of establishing neuromuscular harmony in the masticatory system and creating a mechanical advantage for parafunctional forces with removable appliances[17]. Bite plane splint, Hydrostatic splint, Mandibular Orthopedic Repositioning Appliance, Pivot Splint, Soft Splint, Stabilization Splint, and Repositioning Splint are different kinds of available devices[18]. All of them are included in the category of occlusal splint.

The frequency of association of TN and TMD is unknown and the publication about that combination is not enough. In 2014, Speciali and Dach mentioned that TMD and headache share the same nociceptive system of trigeminus, and the first and second branches of trigeminus are affected in TMD[19]. This permits the transfer of nociceptive information toward the caudal nucleus of trigeminus which shares a specific central pathway, leading to a pain modulation[19]. Both conditions lead to craniofacial allodynia during painful exacerbations, a symptom associated with peripheral and central sensitization[19]. The Pain Clinic and Palliative Care of General Hospital of Mexico "Dr. Eduardo Liceaga" attends approximately 150 patients with TN at year. Non-published personal observation allows us to estimate this association around 10% in the department. The treatment of subjects with this association is challenging.

The aim of this study is to evaluate in a sample of patients the effect of the repositioning splint in the management of TN associated with TMD.

Materials and methods

The target population consisted of patients diagnosed with TN associated with TMD in the Pain Clinic and Palliative Care of General Hospital of Mexico "Dr. Eduardo Liceaga" who authorized under informed consent to participate in this study and met the following selection criteria. Patients were male or female, were aged over 18 years, diagnosed with TN in any branch associated with TMD, who could read and write, who were on pharmacological treatment with carbamazepine at least once for 6 months in the painful period, with or without the history nerve block with phenol or radiofrequency, and who were partially edentulous and edentulous prosthetic or toothed. The patients excluded were who presented hypersensitivity to polymers with a history of head injury, other brain diseases, those who suffered collagenopathies with a history of maxillary or mandibular surgery, neuralgia of herpetic origin, or uncontrolled psychiatric disorder. Patients who withdrew their informed consent and patients who did not complete at least one follow-up were eliminated.

To evaluate changes in pain intensity, VAS was applied, introduced by Scout Huskinson in 1976. It is a line of 10 cm without millimetric registration where one end represents no pain with a numeric value of "0" and the other end represents the maximum possible pain with a numeric value "10." The patient crosses a vertical line where he considers that the pain is best registered[20]. The score of VAS was performed by means of the technique proposed by Downie in 1978[20], which involves the transfer of original VAS record to a sheet of acetate that has a line of same length as previous scale but of millimeter division so that the data recorded by the patient could be converted to millimeters and quantified.

Pain was evaluated in six trigger points (trigger point was considered as the one that produced "Tic Douloureux"); the emergence of the supraorbital nerve (V1), the emergence of infraorbital nerve (V2), the emergence of the mental nerve (V3), temporalis muscle, external TMJ, and masseter muscle. The "Tic Douloureux" was produced by exerting a pressure of 3.0 kg/cm^2,

using a digital algometer (Wagner Inc.). This constant was obtained after quantifying subjective threshold of pain in 20 healthy subjects, not paired by age or sex and family members of patients.

All study subjects were evaluated by means of a digital panoramic radiography for Tatis analysis with no turns or tilts, 1:1 relation, where somatometric references portion, orbit, and menton were observed in maximum intercuspation[21,22]. These data were analyzed by the Orthoeditor and Orthokinetor Plus software 2[23].

The objective was to adequately analyze the position of the condyle in relation to the glenoid cavity, to develop the repositioning splint with acrylic (polymethyl methacrylate) according to the technique proposed by Dr. Tatis[24,25]. The splint maintained a space in the glenoid cavity between 4 and 6 mm[24,25]. Patients were indicated the employment and removal of the repositioning splint and its use for 24 h except during aliments.

Each subject underwent seven evaluations of pain by digital algometer at every trigger point according to the following plan: Baseline in the first interview (BL); immediately before placement of stabilizing splint (BS); and immediately after placing stabilizing splint (AS), 1 month (1M), 2 months (2M), 3 months (3M), and 4 months (4M) after placement of the repositioning splint.

Side effects were recorded on a list that included: nausea, dry mouth, sialorrea, and mucous membranes.

This pilot study was submitted to the Committee of Ethics and Research of General Hospital of Mexico "Dr. Eduardo Liceaga" and was approved with the registration number DI/13/203/04/079. The rights of research subjects according to the Declaration of Helsinki were respected and complied. The study was completed on December 9, 2015.

Results

In this study, the total target population was 150 subjects for 2015 year and 31 subjects fulfilled the selection criteria; the study was taken into consideration until a 4-month follow-up. The original sample enrolled 16 patients but five declined the consent informed. Finally, 11 subjects were followed up until 4 months of clinical trial (Fig. 1).

Subjects were categorized by their age, sex, weight in kilograms, height in centimeters, anesthetic block, and comorbidities, side of TN, and the branch involved. The mean age group of this study was 57.36 years SD ± 12.89, with a median of 63 years. TN had a female preponderance in accord to the subjects studied in this trial. In this study, we observed that although both the trigeminal branches V2 and V3 of the left side were involved, the right-side V2 branch was more commonly affected, leading to the highest number of anesthetic blocks (3 times) to manage the pain. Average of carbamazepine doses administrated was of 238.63mg SD ± 175.84 (Table 1).

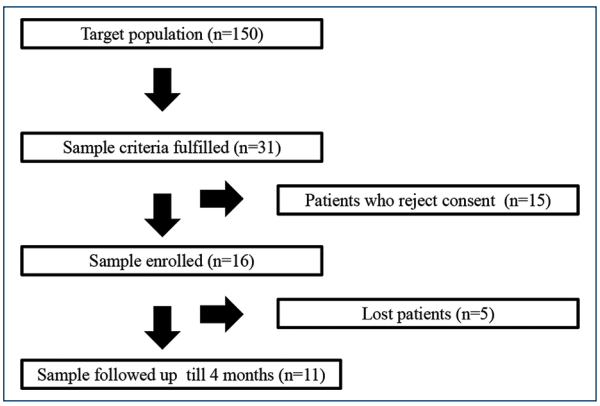

Figure 1. This diagram shows the distribution of patients from the target population until 4 months of follow-up. Eleven patients were followed-up for during this clinical trial.

The mean VAS score at BL (2 weeks before splint application) was 6.32 SD ± 0.857 and 5.76 SD ± 0.538 in BS. There was a significant decrease in pain after the application of splint among the 11 enrolled subjects at 4-month follow-up in all the trigger points with a mean VAS score of 0.79 SD ± 0.249 at M3 and 0.69 SD ± 0.162 at M4 (Fig. 2). The changes of VAS score obtained by the Freidman test ($p = 0.0001$) demonstrated substantial evidence indicating the success of repositioning splint use in managing TN in this trial.

The effect of repositioning splint is shown by differences between distance before and after the treatment. Fig. 3 shows the rest in millimeters (delta) observed between condyles and the mandibular fossae. Distance increase at least 1.2 mm in anterior-posterior projection and at least 2.2 mm in lateral projection.

Discussion

The results of this study showed that this therapeutic procedure improved VAS scores more than 80%, compared to two previous measurements (BL and BS). There was a significant decrease of more than five points at 4-month follow-up according to VAS indicating an alleviation of pain. With these preliminary data, we believe that the splint may be an alternative

Table 1. Demographic table shows that the mean age of the patients was 57.36 (SD ± 12.89) years and the median age was 63 years

Id	Sex	Age (years)	Weight (Kg)	Height (cm)	A-B	Doses (CBZ)	Com	Side	Branch
1	0	36	98	163	0	600	0	R	V3
2	0	63	54	150	2	100	0	R	V2
3	1	68	73	174	3	0	1	R	V2
4	0	49	87	160	2	300	2	R	V2
5	0	65	56	154	0	0	2	L	V3
6	0	53	69	167	1	200	0	R	V2
7	0	69	68	155	0	200	0	R	V3
8	0	34	69	157	0	200	0	R	V3
9	0	59	68	156	0	300	2	R	V2, V3
10	0	71	87	146	0	400	3	L	V2, V3
11	0	64	65	158	0	325	0	R	V3
Median/frequency	10F/1M	57.36	72.18	158.18	7N/4Y	238.64	6N/5Y	9R/2L	6V2/7V3

Female patients have more predominance than male patients with a ratio of 10:1. The frequency of anesthetic blocks (A-B) given is indicated in the table. The maxillary trigeminal branch (V2) is lightly less affected than mandibular trigeminal branch (V3) and had a frequent history of anesthetic blocks. We can also note that the most common side affected was right-side. All the patients are on carbamazepine with the mean doses of 238.63 mg (SD ± 175.84) per day (CBZ/d). 0: female; 1: male; Com: comorbidity (number of associated illnesses); R: right; L: left; V1: ophthalmic branch; V2: maxillary branch; V3: mandibular branch. 0: none; 1: diabetes mellitus; 2: HAS; 3: DM and HAS. Patients 3 and 5 were treated with carbamazepine before splint but side effects of medication caused dropout of carbamazepine.

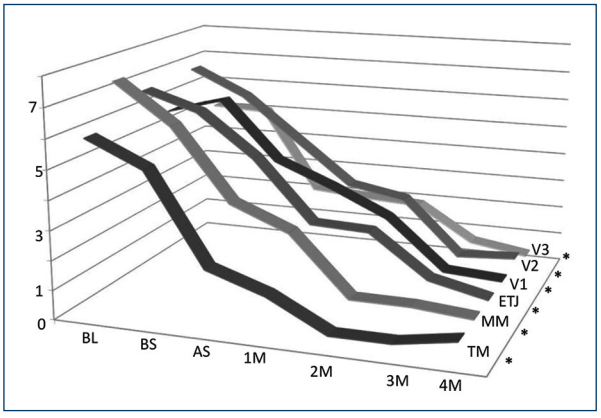

Figure 2. The graph shows the visual analog scale (VAS) score 2 times before the treatment (BL and BS). A follow-up after splint included immediately after splint (AS) and 1, 2, 3, and 4 months before splint (1M, 2M, 3M, and 4M). The mean of VAS was explored in the trigger points in each time. We can note that after the application of splint, there was a significant decline of VAS values at every trigger point TM, MM, ETJ, V1, V2, and V3 indicating a therapeutic success of splint with a mean VAS of 0.79 at 3rd month and 0.69 at 4th month. Base line: 2 weeks before splint; before splint: immediately before splint; After Splint: immediately after splint use; TM: temporal muscle; MM: masseter muscle; ETJ: external temporomandibular joint; V1 (ophthalmic branch); V2 (maxillary branch); V3 (mandibular branch); 1M: 1st month; 2M: 2nd month; 3M: 3rd month; and 4M: 4th month; p = 0.0001 is *(by Friedman test).

treatment for patients with TN associated with dysfunction of the TMJ.

We hypothesize than the repositioning splint could work by repositioning the mandibular joint. Hence, the splint could restore vertical, anterior-posterior, and medial-lateral position achieving the decompression of auriculotemporal nerve. The auriculotemporal nerve is derived from the mandibular branch of the trigeminus,[26] and we think that it suffers compression during its trajectory in the glenoid cavity in patients who suffer from the TMD. The splint would restore sensory and/or motor function by decreasing the trigeminal pain that is triggered when the auriculotemporal nerve is compressed[27,28].

This clinical trial has some limitations that include the small group of patients and just by a 4-month follow-up. Mainly, it was not a randomized and blinded clinical trial. It is a very heterogeneous group with anesthetic blocking and non-blocking, different doses of carbamazepine, different branches, and different age. Consequently, this is a pilot study, and its results are preliminary and could serve to design a new project. The splint has been associated with improving the myofascial pain (Table 2). However, the role of splint in the association of TN and TMD is not yet explained. The frequency of association between TN and TMD is a

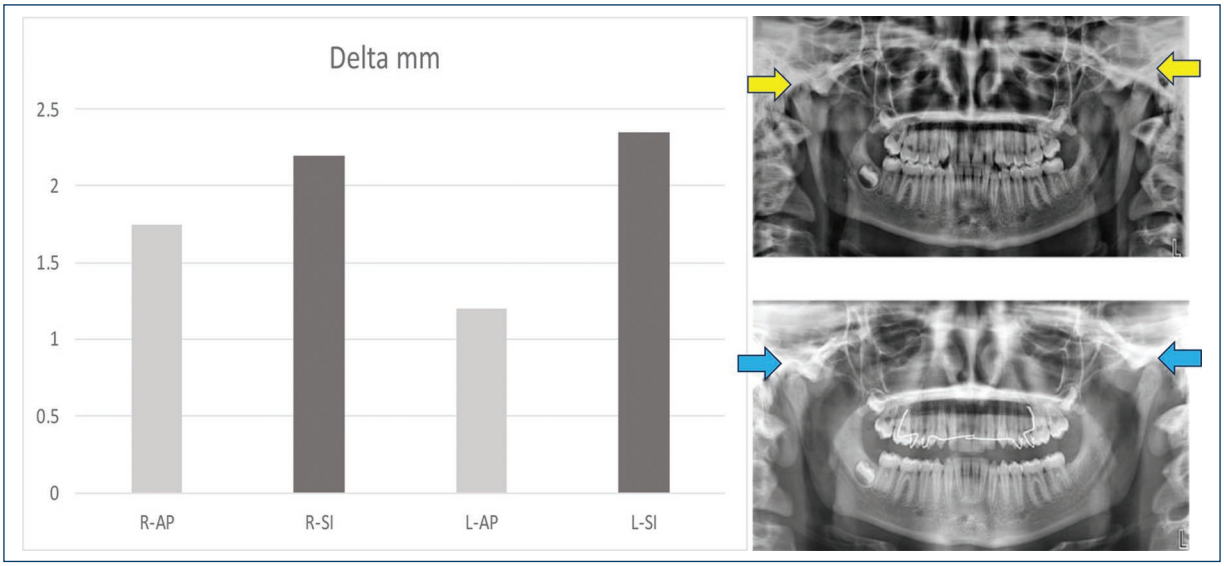

Figure 3. On the left, the graph represents the distance achieved between the mandibular condyle and mandibular fossa on either side (Left and Right) after the colocation of the repositioning splint. Delta (differences between before and after splint); R-AP: Right Anteroposterior; R-SI: Right Superoinferior; L-AP: Left-Anteroposterior; and L-SI: Left Superoinferior. On the right superior image, it shows the absence of space in condyle and mandibular fossa (yellow arrows). On the right inferior image, the space into this joint has been recovered (blue arrows).

Table 2. This table shows the mean of VAS score in different times of study

Pain trigger	BL	BS	AS	1M	2M	3M	4M	p-value
TM	5.98	5.11	2.08	1.43	0.39	0.39	0.73	0.0001
MM	7.45	6.09	3.69	2.9	0.91	0.9	0.73	0.0001
ETJ	6.77	6.17	4.73	2.65	2.57	1.15	0.7	0.0001
V1	5.69	6.2	4.19	3.4	2.5	0.82	0.7	0.0001
V2	6.88	5.99	4.5	3.01	2.65	0.77	0.9	0.0001
V3	5.15	5.05	2.19	2.027	1.92	0.71	0.4	0.0001
mean	6.32	5.77	3.56	2.57	1.82	0.79	0.69	0.0001

BL: 2 weeks before the splint application; BS: immediately before splint use; AS: immediately after splint use; 1M: 1st Month; 2M: 2nd Month; 3M: 3rd month; 4M: 4th Month; p: value of significance by Friedman test.

relatively common medical phenomenon at the Pain Clinic of Hospital General de México "Dr. Eduardo Liceaga."

Moreover, the study of the effect of splint in reducing the pain in this association does not exit. Probably, this is the first study attending the association between TN and TMD and its management.

Conclusion

Repositioning splint could serve as an option in the management of TN associated with TMD noting minimum side effects.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in

accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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ORIGINAL ARTICLE

Short-term prognostic factors in Guillain-Barré syndrome: cohort study at the Hospital General de México

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Abstract

Introduction: *Guillain-Barré syndrome (GBS) is the most frequent cause of acute flaccid paralysis. However, few studies have investigated short-term prognostic factors.* **Objectives:** *The objectives of the study were to describe the clinical characteristics of a sample of GBS patients treated at the General Hospital of Mexico and to identify the prognostic factors at discharge.* **Methods:** *A descriptive and analytical cohort study, including patients with GBS, was conducted from April 2020 to May 2022. Demographic information, comorbidities, clinical variants, neurophysiological alterations, modified Erasmus GBS Outcome Score (mEGOS) and Erasmus GBS Respiratory Insufficiency Score scales, etc., were collected. Functional recovery at discharge was measured with Hughes scales and Medical Research Council (MRC). A case-control analysis was performed among patients with good and poor functional recovery on discharge based on the Hughes scale.* **Results:** *Total sample was 69 patients: 74% men and 26% women, mean age: 43.7 ± 16.3 years; 38 (55%) patients presented classic variant, 22 pure motor variant (31%). Evolution time: 6.8 ± 6.7 days. Most common Hughes score at admission was 4 points (n = 54, 78%). 87% (n = 60) received plasmapheresis. 23 (33.3%) presented an axonal pattern and 46 (66.6%) demyelinating. On discharge, 31 patients had Hughes 3 or less (ambulatory) and 27 Hughes 4 or greater (non-ambulatory). When performing factor analysis, it was found that mEGOS, MRC, total lymphocytes, and creatine phosphokinase (CPK) were associated with the prognosis at discharge.* **Conclusions:** *The most frequent clinical variant was the classic (sensitive-motor) with demyelinating alteration; the factors related to better recovery at discharge were mEGOS, MRC on admission, total lymphocyte count, and serum CPK levels.*

Keywords: *Guillain Barré syndrome. Outcome. Modified Erasmus GBS outcome score. Mexico. Disability.*

Introduction

Guillain-Barré syndrome (GBS) is a symmetric, ascending, immune-mediated polyradiculoneuropathy, generally preceded by an infectious process that can occur at any age[1-3]. At present, GBS is the most common cause of acute flaccid paralysis in the world[3,4]. Its incidence and severity increase with age, generally associated with axonal damage, greater involvement of cranial nerves, and worse functional recovery[3-5]. It is estimated that the United States, Mexico, and Central America are countries with a high prevalence of GBS. In this sense, although there are no exact epidemiological reports, it is estimated that in Mexico, the prevalence is about 3.9/100 000 inhabitants (95% confidence interval: 3.1–4.9)[5-8]. Recent studies suggest an increase in the global prevalence of GBS, especially due to the SARS-CoV-2 pandemic and the mass vaccination used to combat it[9].

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The main electro-clinical variants are acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN), and Miller Fisher syndrome[1,2]. Recent evidence supports GBS as a spectrum disorder, that is to say, with geographical regional variations and significant clinical heterogeneity[3,10]. Its clinical spectrum varies from mild to severe symptoms, with ascending and rapidly progressive weakness. At the most severe end of the spectrum, up to 30% of patients develop paralysis of all four extremities and respiratory failure, requiring mechanical ventilation (MV).[1] Cranial nerve involvement is a predictor of MV, and patients with AIDP have a higher risk of MV than those with the AMAN/AMSAN variants[11,12].

GBS represents a neurological emergency since, despite appropriate treatment, up to 20% of patients will be severely disabled, and approximately 5% will have a fatal outcome[3,9,13]. Regardless of recent advances in the knowledge and care of GBS, it is reported that case fatality in Mexico reaches approximately 12%[5]. In 2019, México reported an incidence of 0.71 cases/100,000 people/year. The most common electrophysiological variant in México was AMAN, and its incidence has a seasonal distribution with a peak of axonal variants during the summer, while the AIDP variant was more frequent in winter, possibly associated with a higher incidence of respiratory infections[5].

Approximately 40-70% of patients with GBS have a previous infection, the nature of which can influence the clinical phenotype, prognosis, and the electrophysiological subtype. *Campylobacter jejuni* and *Cytomegalovirus* are the most commonly isolated pathogens; the former explains the pathogenesis of AMAN, and the latter mainly for AIDP, which may also explain the seasonal distribution[3,4].

Multiple studies have identified several adverse prognostic factors in GBS. The most commonly reported are advanced age (> 70 years), orotracheal intubation, the need for MV, systemic infection, and the neutrophil-lymphocyte index, among others (Table 1)[1,4,11,14-16].

The previous studies on prognostic factors in GBS have investigated these factors at different times during the evolution of the disease, from 1 year to several months after the acute stage[4,8]. Few studies report prognostic factors in the short term (at the time of hospital discharge). It is clear that these factors are also highly dependent on the type of population studied and the country[3,8]. Identifying these short-term prognostic factors in GBS is of great importance for the clinical physician since it will allow timely interventions to obtain better functional results in these patients. For all of the above, the objective of the present investigation was to describe the clinical features of a cohort of patients with GBS treated at the General Hospital of Mexico (GHM) and to analyze the factors related to a better functional prognosis at hospital discharge.

Table 1. Main reported factors of poor functional prognosis in GBS

Variable	OR	CI 95%
Older age (over 70-years-old)	10.3	1.3-77
Orotracheal intubation	2.087	1.057-4.119
Mechanical ventilation	4.323	1.882-9.931
Axonal subtype	9.2	1.3-63.9
CMAP distal < 0.4	8.67	2.33-32.27
Neutrophil-lymphocyte index in < 60 years	1.36	1.05-1.76
> 9-day delay in initiating immunotherapy treatment	4.34	1.28-14.66

GBS: Guillain-Barré syndrome; CMAP: muscular component of the action potential with distal stimulation; OR: odds ratio; CI: confidence interval.

Methods

A prospective, observational, descriptive, and analytical cohort study was carried out; all patients with a confirmed diagnosis of GBS who were admitted to the neurology service of GHM during the period from April 2020 to May 2022 were included in the study. Patients who met with the National Institute of Neurological Disorders and Stroke criteria for GBS at any Brighton level of certainty were included.[17] Patients with incomplete information in the clinical record and those not hospitalized were excluded from the study. Demographic information, comorbidities, clinical variant, neurophysiological study, days of hospitalization, blood count, Erasmus Guillain-Barré Syndrome Outcome Score (mEGOS), and Erasmus GBS Respiratory Insufficiency Score (EGRIS) scales were collected. The degree of functional recovery at discharge was measured with the Hughes and Medical Research Council (MRC) scales for muscle strength. A case (Hughes 3 or less = ambulatory) and control (Hughes greater than 3 = non-ambulatory) type analysis was performed for the analysis of prognostic factors. In the statistical analysis, descriptive statistics were first used, and to compare the groups with good vs. poor functional recovery, the

Table 2. Clinical and sociodemographic features in total sample of GBS patients

Variable	Total sample (n = 69)	No.	%
Sex	Female Male	18 51	26.1 73.9
Age	Average: 43.7 years (SD: 16.3)		
Civil status	With couple Without couple	41 28	59.4 40.6
Residency	Mexico city Estado de México Other states	34 23 12	49.3 33.3 17.4
Comorbidities (number)	Average: 2 (SD: 1.06)		
History of diarrhea	Yes No	25 44	36.2 63.8
History of upper tract respiratory infection	Yes No	13 56	18.8 81.2
Clinical variant	Classic Pure motor Miller Fisher syndrome Faringo-cervicobraquial	39 22 7 1	56.5 31.9 10.5 1.4
Acute treatment	Plasmapheresis (number of sessions) Immunoglobulin Without immunotherapy	61 (3-5) 4 4	88.4 5.8 5.8
Evolution time at the beginning of treatment (days)	Average: 2.57 (SD: 2.07) (Median: 2)		
mEGOS score	7.12 (SD: 2.9)		
EGRIS score	4.23 (SD: 1.76)		
Axonal/Demyelinating variant	Axonal Demyelinating	23 46	33.3 66.7

SD: standard deviation; GBS: Guillain-Barré syndrome; EGRIS: Erasmus GBS respiratory insufficiency score; mEGOS: modified erasmus GBS outcome score.

following tests were used: Fisher's exact test, Chi-square, Mann Whitney U, or Student's T test, depending on the type of variable.

Results

The total sample was 69 patients: 74% men and 26% women. Average age ± standard deviation (SD) was of 43.7 ± 16.3 years. 49 % of the patients were originally from Mexico City and 33% from Estado de México. Twenty-five patients (36 %) had a history of diarrhea. Regarding clinical variants, 55% patients presented the classic variant (sensory-motor), 31% pure motor variant and 10% presented Miller-Fisher variant (ataxia, ophthalmoplegia, and areflexia) and only one patient presented a pharyngo-cervicobrachial variant (Table 2). The mean evolution time from the onset of symptoms to time of hospital admission was 6.8 ± 6.7 days.

The average ± SD Hughes scale score at admission was 3.85 ± 0.60, and the most frequent Hughes scale category at admission was 4 points (78%), followed by 3 points (13%). Sixty-one patients (88%) received plasmapheresis, 4 (5.7%) received immunoglobulin as acute treatment, and 4 (5.7%) patients do not receive immunotherapy. In clinical neurophysiology studies, 66% (n = 46) showed a demyelinating pattern, and 33.3% presented an axonal pattern (n = 23). The average number of total days of hospitalization was 18.72 ± 9.4. Complications (for example, urinary tract infections, pulmonary infections, cardiac arrhythmias, and hyponatremia) were observed in 16 (23%) of patients; 23% of the cases required management in the Intensive Care Unit (ICU), with the average number of days spent in the ICU being 8.4 days ± 4.6. Two patients died during hospitalization (2.8%), and only two patients had a history of SARS-Cov2 infection (2.8%). The summary

of laboratory variables and the initial and final scores of the scales are presented in Tables 3 and 4. As expected from the treatment with immunotherapy, a significant improvement was observed in the two functional outcome variables between the evaluations of admission versus discharge: Hughes ($p < 0.0003$) and MRC ($p = 0.0004$) (Fig. 1).

At discharge, only 58 patients were evaluated on the Hughes scale. 31 patients had Hughes 3 or lower (ambulatory or good recovery), and 27 had Hughes 4 or higher (non-ambulatory or bad recovery). When factor analysis was carried out, it was observed that the mEGOS scale, the MRC for muscle strength, total lymphocytes, and elevated creatine phosphokinase (CPK) were associated with a better prognosis at discharge (Table 5).

Table 3. Laboratory characteristics in the total sample of patients with GBS

Variable	Average ± SD
Total leukocytes	10 194 ± 4551
Total neutrophils	6 215 ± 3931
Total lymphocytes	2 188 ± 3522
Neutrophil-to-lymphocyte ratio	6.66 ± 12.17
Lactate dehydrogenase (U/L)	197.97 ± 80.84
Creatine phosphokinase (U/L)	189.84 ± 247.68
CSF: Proteins (mg/dL)	126.56 ± 95.85
CSF: Leukocytes	2.95 ± 4.37
CSF: Lymphocytes	1.07 ± 1.30
CSF: Neutrophils	4.68 ± 10.47

GBS: Guillain-Barré syndrome; CSF: cerebrospinal fluid; SD: standard deviation.

Table 4. Initial and final scores in Hughes and MRC scales in patients with GBS

Variable	Category	No.	%
Hughes scale at admission Average: 3.85 ± 0.60 (n = 69)	0 1 2 3 4 5 6	0 1 1 9 54 4 0	0 1.4 1.4 13.1 78.3 5.8 0
Average MRC scale at admission (n = 69)	31.1 ± 14.6		
Hughes scale at discharge Average: 3.17 ± 1.15 (n = 58)	0 1 2 3 4 5 6	1 5 10 16 24 0 2	1.7 8.6 17.2 27.6 41.4 0 3.4
Average MRC scale at discharge (n = 58)	40.4 ± 14.55		

GBS: Guillain-Barré syndrome; MRC: Medical Research Council scale for muscle strength.

Discussion

To the best of our knowledge, no previous studies in Latin America describe prognostic factors at discharge from hospitalization of patients with GBS. The main focus of most studies is functional prognosis over longer periods, such as 3-6 months or a year. Unlike many other autoimmune disorders, GBS has been reported to be more common in men than in women. The male/female ratio in our study was higher (2.8:1) than reported in the international literature (1.5:1), with a 74% predominance of the male sex[18].

This predominance of the male sex in GBS is well established in the literature, but apparently, in children and adolescents, this predominance is not consistent. Although the explanation for this predominance of the male sex is not fully clear, it has been proposed that there are different immune responses in both sexes to different non-protein antigens[18].

In the present sample of patients, the average age was lower (43.7 years) than that reported in the International Guillain-Barré Syndrome Outcomes Study (IGOS) (51 years)[13,16]; however, it is similar to reported in other studies carried out in México (46.6 years)[1], this may be due to multiple factors, but it is possible that exposure to infectious agents at younger age in our country explains a lower average age in our population compared to populations of Europe or the United States[19].

According to the literature, up to 76% of patients with GBS have a history of an infectious disease, with C. jejuni diarrhea being the most commonly reported cause[16]. In our study, only 36% had a history of diarrhea before the onset of the clinical picture, without finding a significant association between this infection and more severe forms of presentation, which differs from what has been reported in various studies. However, in our study, it was impossible to determine stool culture or polymerase chain reaction (rt-PCR) to confirm *C. jejuni* infection, which may explain the underreporting of cases. On the other hand, it is noteworthy that only 2.8% of the cases had a documented

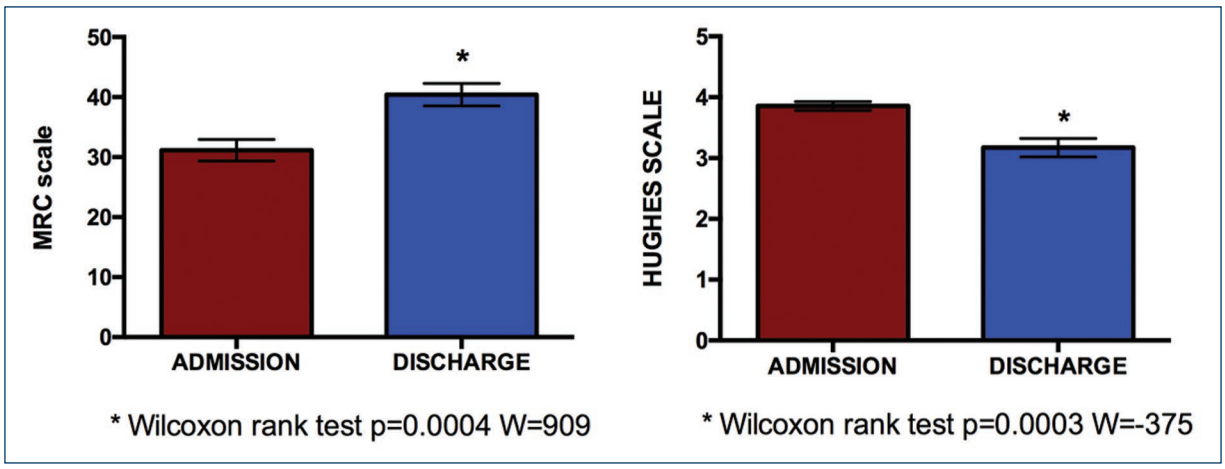

Figure 1. Effect of immunotherapy treatment. Baseline versus Endpoint MRC assessments for muscle strength and the Hughes scale. The bars represent the average ± the Standard Error of the Mean. MRC: Medical Research Council.

SARS-CoV-2 infection; this is despite the fact that patient sampling was carried out during the first two years of the pandemic; however, more patients may have presented SARS-CoV-2 infection asymptomatically or with minimal symptoms as has been previously reported[20].

The most common electrophysiological variant in our sample was AIDP (66%), being similar to what was reported in Europe and North America population[21] and in contrast with what was previously reported in another study carried out in our country, where the AMAN variant was the most reported subtype (45.4%)[1].

This difference observed in our study concerning the electrophysiological variant may be because the study by López-Hernandez et al. was carried out in a neurological medical center, while our study is more representative of a general hospital population.[1] Despite this, both studies agree well on the frequency of clinical variants: sensory-motor in the first place (50%), followed by a pure motor (31%)[1].

In the present study, we found a high percentage (82.3%) of non-ambulatory patients at the time of hospital admission (Hughes 4 or higher); this percentage is higher than that observed in the IGOS study, where 76% of the patients were non-ambulatory at the time of greater severity of the disease[22]. We consider that these findings may be due to sample bias, given that only hospitalized patients were included in this study, while those with less severity were not hospitalized.

In studies carried out in developing countries, mortality (17%) is usually higher than in developed countries (5%), which is probably due to a higher proportion of patients with axonal forms of GBS and less access and/or availability of mechanical respirators, intensive care facilities, and immunotherapy[23]. In our study, 91.9% of patients received immunotherapy, which was higher than expected, according to international reports. The need to require ventilatory support and stay in intensive care (23%) was greater, in contrast to reports from developed countries (19%), but lower (30.6%) than in other studies carried out in Mexico;[1] in addition to observing low mortality in our study (2.8%).

Regarding the factors associated with functional prognosis at hospital discharge, in the present investigation, we found that ambulatory patients at discharge (Hughes < 3) had a significantly higher MRC score at admission. Likewise, ambulatory patients had a significantly lower mEGOS score on admission. Both results are expected, given that these evaluations have previously been reported to be significantly associated with functional prognosis in GBS[24]. Similarly, significantly higher levels of total blood lymphocytes were observed in non-ambulatory patients at hospital discharge. In this sense, the previous studies have shown that the neutrophil-to-lymphocyte ratio (NLR) can represent a good inflammatory and prognostic marker in patients with several neurological diseases[25].

For example, one study investigated the relationship between the NLR measured on the day of admission and the subsequent motor deterioration in patients with GBS, finding an inverse and significant correlation between the NLR and the deterioration of motor function during the first 14 days in patients who did not receive immunotherapy[26]. In another study, the Hughes score had a positive

Table 5. Results of the comparative analysis between patients with good versus poor functional recovery at discharge (ambulatory vs. non-ambulatory patients)

Variable	Hughes at admission 3 or less (ambulatory) (n = 31)	Hughes at discharge more than 3 (non- ambulatory) (n = 27)	Statistic test p-value
Sex Female Male	 10 21	 8 19	Fisher (p = 1.000)
Age	43.26 ± 18.2	43.96 ± 15.8	T test (p = 0.8688)
Civil status With couple Whitout couple	 15 16	 21 6	Fisher (p = 0.0305)
Residency Mexico City Estado de México Other states	 12 10 9	 15 11 1	Xi Cuadrada (p = 0.0650)
Comorbidities	0.86 ± 1.2	1.29 ± 1.1	Mann Whitney (p = 0.0802)
History of diarrhea Yes No	 11 20	 10 17	Fisher (p = 1.000)
History of upper tract respiratory infection Yes No	 6 25	 6 21	Fisher (p = 0.896)
Clinical variant Classic Pure motor Miller Fisher Syndrome Faringocervico brachial	 18 7 6	 15 11 1	Fisher (p = 0.3823)
Hughes at admission Category 1 Category 2 Category 3 Category 4 Category 5	 1 1 4 24 1	 0 0 2 25 0	Xi cuadrada (p = 0.4890)
Acute treatment Plasmapheresis Immunoglobulin Without immunotherapy	 28 2 1	 25 1 1	Xi cuadrada (p = 0.8921)
Evolution time at the beginning of treatment (days)	2.41 ± 1.8	2.11 ± 1.3	Mann Whitney (p = 0.8952)
MRC at admission	36.03 ± 13.42	27.85 ± 14.07	T test (p = 0.0287)
Modified Erasmus GBS outcome score	6.16 ± 2.9	7.88 ± 2.8	Mann -Whitney (p = 0.0314)
Erasmus GBS respiratory insufficiency score	3.79 ± 1.6	4.29 ± 1.8	T test (p = 0.2885)
Neurophysiological variant Axonal Demyelinating	 8 23	 13 14	Fisher (p = 0.1032)
Total leukocytes	17,676 ± 29,648	9656 ± 3796	Mann Whitney (p = 0.5278)
Total neutrophils	5727 ± 3681	6069 ± 2760	Mann Whitney (p = 0.6789)

(Continues)

Table 5. Results of the comparative analysis between patients with good versus poor functional recovery at discharge (ambulatory vs. non-ambulatory patients) *(continued)*

Variable	Hughes at admission 3 or less (ambulatory) (n = 31)	Hughes at discharge more than 3 (non- ambulatory) (n = 27)	Statistic test p-value
Total lymphocytes	1405 ± 1078	2228 ± 1261	Mann Whitney (p = 0.0057)
Neutrophil-to-lymphocyte ratio	6.211 ± 8.2	6.425 ± 15.7	Mann Whitney (p = 0.2365)
Lactate dehydrogenase (U/L)	198.8 ± 99.4)	197.3 ± 62.4	T test (p = 0.9787)
Creatine phosphokinase (U/L)	185.3 ± 107.2	46.8 ± 20.29	Mann Whitney (p = 0.0462)
Days of evolution at the time of lumbar puncture	12.07 ± 8.0	9.46 ± 3.3	Mann Whtiney (p = 0.8766)
CSF: Proteins	157.6 ± 116	105.6 ± 81.16	Mann Whitney (p = 0.4173)
CSF: Leukocytes	3.0 ± 4.7	3.23 ± 4.33	Mann Whitney (p = 0.8251)
CSF: Lymphocytes	1.032 ± 1.3	1.037 ± 1.25	Mann Whitney (p = 0.9397)
CSF: Neutrophils	2.96 ± 4.24	7.73 ± 16.	Mann Whitney (p = 0.27770)
Medical complications	Si: 6, No: 25	Si: 6, No: 21	Fisher (p = 1.000)
Stay in ICU (days)	8.25 ± 5.7	8.16 ± 3.4	Mann Whitney (p = 0.6028)
Hospitalization days	19 ± 9.36	18.70 ± 10.53	Mann Whitney (p = 0.7313)

GBS: Guillain-Barré syndrome; MRC: Medical Research Council scale for muscle strength; CSF: cerebrospinal fluid; ICU: intensive care unit.

correlation with NLR, and the MRC had a negative correlation with NLR[25]. However, in our study, no association was observed between NLR and good recovery at discharge. However, it was observed with the total serum lymphocytes, which, in any case, suggests that the severity of GBS may be associated with a greater systemic inflammatory response[27]. Other serum biomarkers that have been associated with a worse prognosis how: low albumin, increased immunoglobulin, and increased levels of neurofilaments light chain[28]. Finally, it was observed that there were significantly higher levels of the serum CPK enzyme in patients with better functional recovery at discharge. This CPK elevation has already been reported in GBS in up to 16.7% of cases; however, its prognostic significance has yet to be fully understood, so it must be confirmed in subsequent studies[29].

The limitation of this study was that the number of patients was reduced, so it will be necessary to increase the number in future studies. The sample has a selection bias since only patients requiring hospitalization due to their severity were included in the study. Likewise, it would be important to have long-term functional and quality-of-life evaluations of patients to establish whether short- and long-term prognostic markers are the same or different. Finally, it will also be important in future studies to have more information on the different parameters of neurophysiology studies and the antiganglioside antibody profile of patients.

Conclusions

The most frequently observed clinical variant of GBS was the classic variety (sensory-motor), and the most common electrophysiological variant was the demyelinating variety. A significant effect of immunotherapy treatment on functional status at hospital discharge was

corroborated. MRC at admission, mEGOS scale, total serum lymphocyte count, and CPK levels were associated with functional prognosis at hospital discharge.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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REVIEW ARTICLE

Perioperative hypothermia: a systematic review

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Abstract

Temperature is a vital sign that is closely regulated by the hypothalamus. Perioperative hypothermia is a common event; as peripheral heat redistribution occurs, thermoregulation is altered by anesthesia and exposure to a cold environment (operating room). Hypothermia is defined as core body temperature below 36°C. The aim of this systematic review was to analyze the main risk factors and complications of perioperative hypothermia and, at the same time, find out which warming method is most useful in the perioperative period. Of the 20 articles that were analyzed, 17 of them indicate that the patients present hypothermia in the perioperative period, with a range of mean temperatures ranging from 32.8[9] to < 36.0°C; three of them mention that the mean temperature ranges ≥ 36.0°C. The mean complications associated with hypothermia are shivering and thermal discomfort. Perioperative temperature is still one of the least commonly monitored vital parameters during anesthesia and surgery. A combined approach through active and passive warming measures is the key to preventing its complications.

Keywords: *Hypothermia. Perioperative. Complications of hypothermia. Management of hypothermia.*

Introduction

Temperature is a vital sign that is closely regulated by the hypothalamus between the limits that go from 36°C to 37.5°C. In a conscious individual, thermoregulation is given by an afferent pathway, central regulation, and an efferent pathway. The efferent pathway gives us responses in the individual's behavior change (shelter) and an autonomic response. Behavior regulation is the strongest mechanism, and this requires the individual to be aware of the perception of body temperature[1,2]. The main mechanism of the hypothalamus to regulate the hypothermic effect is described in Fig. 1. Thermoregulation occurs through the muscles through involuntary tremors. At the same time, hypothalamus can produce peripherical vasoconstriction and finally, the hypophysis produces the peak of ACTH than increases metabolism through suprarenal epinephrin (Fig. 1).

Perioperative hypothermia is a common event, as peripheral heat redistribution occurs, thermoregulation altered by anesthesia, and exposure to a cold environment (operating room)[1].

Hypothermia is defined as core body temperature below 36°C. It can be classified as follows: mild (34°-36°C), moderate (34°-32°C), and severe (<32°C). The main forms of core temperature measurement are the pulmonary artery, esophageal, nasopharynx, and tympanic membrane, and peripheral temperature is axillary and forehead skin[1,3].

The hypothermia that occurs during generalized anesthesia follows different phases, and these are the different phases[2,4]:

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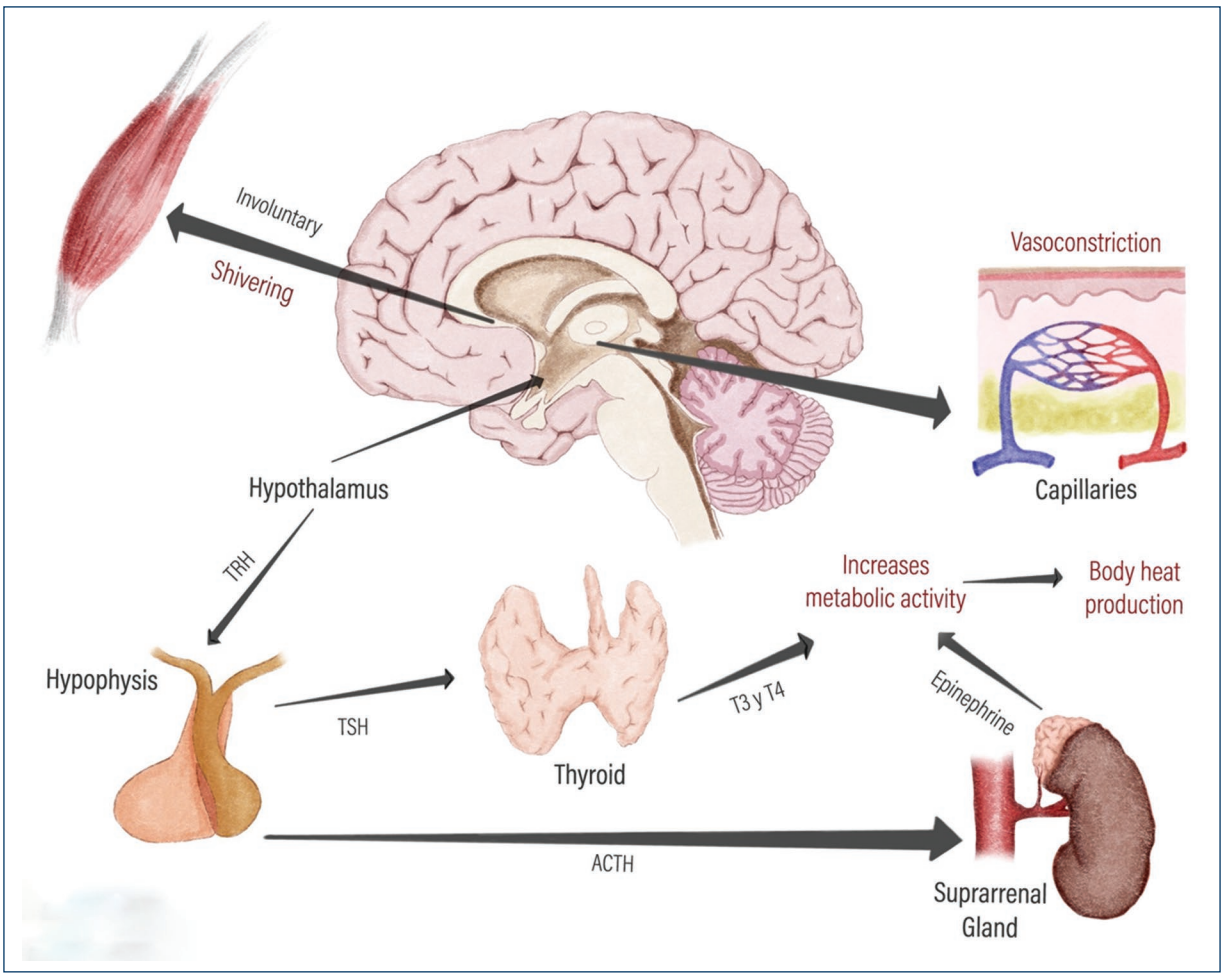

Figure 1. This image is showed several mechanisms of hypothalamus to counterbalance the hypothermia. There are two principal mechanisms; increase the metabolism (T3, T4, norepinephrine and shivering) and decreasing the body heat (vasoconstriction).
TRH = Thyrotrophin Release Hormone, TSH = Thyroid Stimulation Hormone, T3 = Triiodothyronine, T4 = Thyroxine.

- Phase I - *Redistribution*: gradual linear decrease that occurs within the 1st h. Circulatory redistribution (1-3°C)[2,4].
- Phase II - *Heat loss*: heat is transferred from the hottest periphery to the environment. Understood between 2-4 h. Metabolic overwhelmed[2,4].
- Phase III - *Plateau*: thermal homeostasis begins after 3-4 h once the core temperature is 33-35°C[2,4].

Perioperative hypothermia leads to several complications, among which are cardiac alterations, infection, coagulation alterations, tremors, delayed healing, and longer time in the recovery area[1,2,5].

Material and methods

A systematic review of the literature was carried out using the following methodology. The PubMed, Google Scholar, and Cochrane Library databases were searched for the open terms *perioperative hypothermia, accidental hypothermia, post-operative hypothermia*, and the MeSH term (perioperative hypothermia AND anesthesia). Articles were searched for a period from 1980 to the present. Articles such as systematic reviews, meta-analyses, and clinical trials were investigated. The following inclusion criteria are spanish and English language, which included anesthetic procedures in humans, which refers to temperature figures in the perioperative period, which included the anesthetic technique, and which included perioperative complications. Duplicate articles or articles that, although mentioned, did not meet the inclusion criteria were excluded from the study. The articles excluded were those that discussed hypothermia in cardiac surgeries, surgeries in which hypothermia was induced, and studies that were not found in their complete online

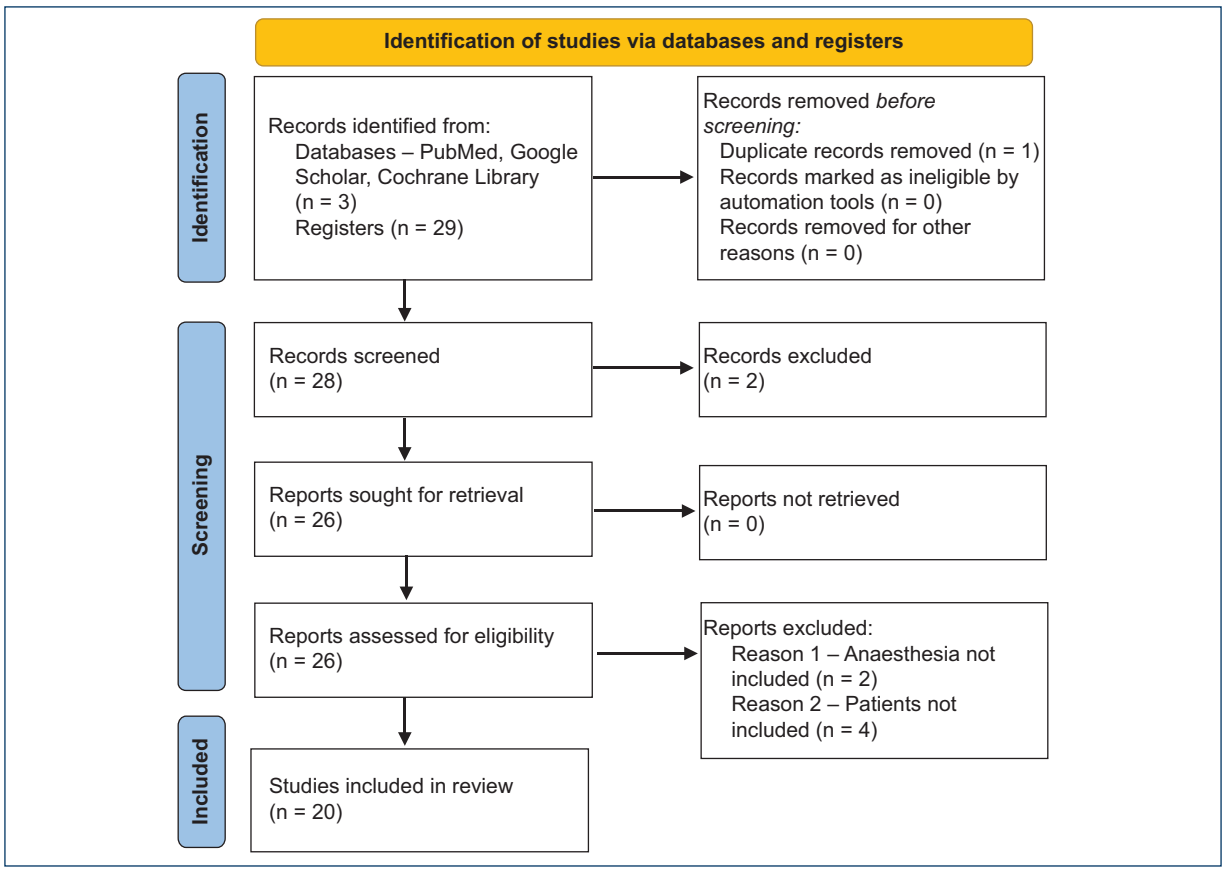

Figure 2. Flow chart for selection of studies using PRISMA flow diagram.

version. All articles were reviewed, and duplicates were removed (Fig. 2).

Results

Of the 20 articles that were analyzed, 17 of them indicate that the patients present hypothermia in the perioperative period, with a range of mean temperatures ranging from 32.8 to < 36.0°C; three of them mention that the mean temperature ranges ≥ 36.0°C[6-8].

The main complications associated with hypothermia are shivering and thermal discomfort. Cardiovascular alterations are also mentioned in three of the articles[9-11], and in four of them, various alterations are mentioned, such as increased infections, coagulopathies, and an increase in mortality[11-13]. Five articles do not report adverse events[6,8,14-18].

Four types of management for perioperative hypothermia have been reported: amino acid infusion[19], fluid prewarming[6], forced-air pump warming[6,7,20-22], swaddling[20-22], and increase in operating room temperature[9]. Of these types of management, the one that showed the best result and significance with respect to it was active heating with forced-air pumps (Table 1)[23-25].

Discussion

Perioperative hypothermia can be triggered by different risk factors, which can be divided into patient-related, anesthesia-related, surgery-related, environmental, and others[26] (Table 2).

Perioperative hypothermia is a problem that is often not given due importance, since, by not managing it, patients both intraoperatively and postoperatively leave with low body temperatures, and it has been seen that with hypothermia complications ranging from patient discomfort to serious ones that could compromise the patient's life, such as cardiovascular complications.

Core body temperature versus peripheral body temperature

Core body temperature (head, deep thorax abdominal) is normally around 37°C. The peripheral is typically 2°-4°C cooler than the central[3,4]. This gradient is maintained by thermoregulation given by vasoconstriction. Thermoregulation is the mechanism by which the

Table 1. This table shows the references of twenty authors. Number of patients in the sample, the mean of hypothermia, complications, management, and bias

Year	Title	Patients (n)	Anethetic technique	Mean Temperature ($\bar{X}$/Stardar deviation)	Complications	Observations	Biases
1981	Postoperative Hypothermia in Adults: Relationship of Age, Anesthesia, and Shivering to Rewarming[23]	198	Regional anesthesia: Subarachnoid block or with T 10 level or superior. General anesthesia	PACU arrival temperature: young 35.7 ± 0.06; elderly: 35.4 ± 0.11, general anesthesia: 35.5 ± 0.06; regional: 35.6 ± 0.14 PACU discharge temperature: young: 36.4 ± 0.04; elderly; 36.1 ± 0.9; general anesthesia: 36.4 ± 0.04; regional: 36.2 ± 0.12	Shivering	A tendency to hypothermia was show in older patients, compared to younger adults. Temperature difference admitted to the PACU (young vs adults - p = < 0.05), duration of hypothermia (young vs adults and general vs regional anesthesia - p = < 0.05), temperature increase in the 1st h (general vs regional anesthesia - p = < 0.05) and recovery time (general vs regional anesthesia - p = < 0.05); χ^2	It is a study performed in the eighties. In general anesthesia, the gases used ar currently out of use, which transposing it to the present could vary the results.
1995	Postoperative hemodynamic and thermoregulatory consequences of intraoperative core hypothermia[10]	74	General anesthesia, neuromuscular block	Normpthermic group: 37 ± 0.3; Hypothermic group: 34.4 ± 0.4	Shivering, thermal discomfort, peripheral vasoconstriction	It is a study that evaluates the effects of hypothermia on heart rate and blood pressure (without changes). Difference in core body temperature at the end of surgery (p = < 0.01).	It is only focused on one type of electivbe surgery, which is colon surgery. The anesthetics currently used no longer in use. The sample number of hypothermic patients was lower.
1996	Preoperative infusion of amino acids prevents postoperative hypothermia[19]	24	General anesthesia	Group A: 37.1ºC, Group B: 36.4ºC, Group C: 35.9ºC	Shivering	Group A: Adm. 1h before anesthesia, Group B: 2h before anesthesia, Group C: Adm. Saline solution. Amino acid infusion counteracts the hypothermic effect of anesthesia through preoperative heat buildup and delayed metabolic simulation. Tº 1h before group A (p = 0.001), 1 and 2 h before group B (p = 0.001) and decrease in Tº group C post-anesthesia (p = 0.05). Increased post-anesthesia O2 uptake, group A (p = 0.001)	It was performed on females patients who underwent hysterectomy for menorrhagia. A very small number of patients.

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Table 1. This table shows the references of twenty authors. Number of patients in the sample, the mean of hypothermia, complications, management, and bias *(continued)*

Year	Title	Patients (n)	Anethetic technique	Mean Temperature ($\bar{X}$/Stardar deviation)	Complications	Observations	Biases
1997	Mild Intraoperative Hypothermia Prolongs Postanesthesic Recovery[27]	150	General anesthesia	Intraoperative final temperature: Hypothermic group: 34.8 ± 0.6, Normothermic group: 36.7 ± 0.6	Shivering	2º of hypothermia, delays discharge fron the PACU by approximately 40 minutes when normothermia is not used as a criteria (36.0ºC) and when normothermia is used as a discharge criteria, it is delayed by approximately 90 min; core body temperature difference at the end of surgery (p = < 0.001); X^2 = 2, §	The anesthetics used in the trial ar currently out of use and one of the discharge criteria (Kroulik score) is still out of use.
2000	Age-Related Thermoregulatory Differences in a Warm Operating Room Enviroment (Approximately 26ºC)[9]	40	General anesthesia	PUCA arrival: Young (36.7ºC ± 0.1); Elderly (36.4ºC ± 0.1); after prewarming only 4 patients showed < 36.0ºC (3 elderly, 1 young) and 1 patient < 35.5ºC (elderly)	Shivering (40% young and 10% elderly) and peripheral vasoconstriction	It concludes that increasing the operating room temperature to 26ºC decreases the incidence of low hypothermia in both groups (young and adults). Postoperative shivering (p = 0.06); X^2	The sample size is small and only surgical speciality and one type of anesthesia.
2010	Incidence of Postoperative Hypothermia and the Relationship to Clinical Variables[17]	287	General anesthesia, regional anesthesia, combined anesthesia and MAC sedation.	Tº $\bar{X}$ postoperative: 36.8ºC, only 4% showed Tº < 36.0ºC	Not mentioned	It only seeks to see the percentage of incidence of hypothermia in the PACU (4% of the sample size)	As a limitation of the study is that the way in which body temperature was measured is not montined, and it does not have statistical tables.
2013	Postoperative hypothermia and patient outcomes after elective non-cardiac surgery[12]	50689	No mentioned	Highest temperature recorded: 36.9ºC ± 0.003; Lowest temperature: 35.5ºC ± 0.02	Increase in mortality	Age (p = 0.001), male sex (p = 0.001), APACHE III corrected (p = 0.001), transitory and persistent hypothermia vs. normothermia (p = 0.001), type of hospital (p = 0.001), surgical speciality (p = 0.001) and controlled ventilation (p = 0.001); **,***	The type of anesthesia required by each patient is not mentioned. Only the highest and lowest temperatures recorded in the postoperative period in a period of 24 h were obtained. Only patients in the ICU are taken into account in the analysis.
2013	Manejo de la temperatura en el preoperatorio y frecuencia de hipotermia inadvertida en un hospital general[15]	167	General anesthesia, neuraxial anesthesia, combined anesthesia and sedation.	$\bar{X}$ temperature of 35.6ºC ± 0.23	Not mentioned	Significant data: Age 65 years (p = 0.012), BMI (p = 0.018), female sex (0.029), difference in body temperatures (p = <0.01), ASA grade (p = <0.02) **	Complications associated with postoperative hypothermia are not mentioned. The form of measurement of body temperature was peripheral (skin of the forehead).

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Table 1. This table shows the references of twenty authors. Number of patients in the sample, the mean of hypothermia, complications, management, and bias *(continued)*

Year	Title	Patients (n)	Anethetic technique	Mean Temperature ($\bar{X}$/Stardar deviation)	Complications	Observations	Biases
2014	Efficacy of a novel prewarming system in the prevention of preoperative hypothermia. A prospective, randomized, multicenter study[20]	90	No mentioned	Whit active prewarmimg: 36.6°C ± 0.4 Passive prewarming: 35.9°C ± 0.3 Without prewarming: 35.9°C ± 0.6	Shivering	Differences in body temperature between the three groups, primarily between the active warming group versus the control group (p = < 0.05)	The type of anesthesia required by each patients is not mentioned.
2014	Survery on Posoperative Hypotermia Incidence in Operating Theatres of Kocaeli University[25]	564	General anesthesia, neuraxial anesthesia and peripheral nerve block.	PUCA arrival $\bar{X}$ 34.3 ± 0.5	Shivering and delayed postoperative recovery	Significant data: age (41.4 ± 20.5 p = 0.001), type of anesthesia (p = 0.001), fluid balance (0.001), surgery time (p = 0.001), recovery period (p = 0.001) and shivering (0.002)	Is taken as hypothermia temperature < 35°C
2018	Incidence and Risk Factor of Posoperative Hypotermia After Orthopaedic Surgery[8]	6950	General anesthesia and regional anesthesia.	Preoperative $\bar{X}$ 36.6°C ± 0.24; Postoperative. $\bar{X}$ 36.4°C ± 0.51	Not mentioned	Significant data: age (p = 0.004), male sex (p = 0.006), body mass index (p = 0.000), intraoperative hypothermia (p = 0.000), preoperative hypothermia (p = 0.007), reconstructive surgery (p = 0.001), hip and pelvis surgey (p = <0.000), **	The article is based only on orthopedic surgeries.
2018	Risk factors posoperative hypotermia in thepost-anesthetic care unit: a prospective pronostic pilot study[18]	70	General anesthesia, regional anesthesia and combined anesthesia.	OR: arrival 36.3°C ± 0.5 and discharge 35.6°C ± 0.55; UCPA: arrival 35.6°C ± 0.57 and discharge 36.0°C ± 0.59	Not mentioned	It was show that more than a half of the admitted patients presented hypothermia. Significant data: age (< 60 years and > 60 years; p = <0.001), ASDA grade (p = 0.006), arterial hipertension (p = <0.001), type of anesthesia (p = 0.004), warming in the OR (p = 0.008), fluids warming in the OR (p = 0.001); + , X^2	The sample size is small and complications are not mentioned. Surgeries are performed primarily in patients < 60 years with a high predominance in the speciality of Gynecology.

(Continues)

Table 1. This table shows the references of twenty authors. Number of patients in the sample, the mean of hypothermia, complications, management, and bias *(continued)*

Year	Title	Patients (n)	Anethetic technique	Mean Temperature ($\bar{X}$/Stardar deviation)	Complications	Observations	Biases
2018	Effect of preoperative warming on intraoperative hypothermia: a randomized-controlled trial[6]	200	General anesthesia	Preoperative: Control group (36.8ºC) - Prewarming group (36.9ºC); Intraoperative: Control group (36.0ºC) - Prewarming group (36.3ºC); Postoperative: Control group (36.0ºC) - Prewarming group (36.4ºC)	Not mentioned	Intraopetaive hypothermia 60 minutes ($p \leq 0.001$), Postoperative ($p \leq 0.001$). Risk factors surgery 2.5 h ($p = 0.002$), protective factor use of crystalloids pre-warmed to 37°C ($p = 0.014$); §, X^2	The temperature was measured peripherally, leading to biases related to a core boby temperature measurement.
2019	Effect of the ASPAN Guideline on Perioperative Hypothermia Among Patiens with Upper Extremity Surgery Under General Anesthesia: A Randomized Controlled Trial[21]	54	General anesthesia	Control group (blankets): preoperative: 36.68 ± 0.22; posoperative 35.81 ± 0.51. Experimental group (active warming): preoperative: 36.77 ± 0.30; posoperative: 36.92 ± 0.57	Shivering, thermal discomfort.	It was show: differences in body temperture ($p = < 0.001$), shivering ($p = 0.012$), thermal discomfort ($p = < 0.001$), thermal comfort ($p = < 0.001$); X^2	It is limited by the number of patients and only one type of anesthesia was used.
2019	Inadvertent Perioperative Hypothermia Risks and Postoperative Complications: A Retrospective Study[13]	298	General anesthesia and spinal block	First measurement $\bar{X}$ = 35.3 °C ± 0.8, and lowest temperature recorded was < 32.8ºC	Low hemoglobin and hematocrit levels, bloood transfusion, sepsis, pneumonia and increase in mortality	Hypotermic patients (n = 7; 100%) showed hemoglobin and hematocrit levels ($p = 0.0019$ --> Required blood transfusion. Age < 70 years ($\bar{X}$ ± 72.9 years - $p = 0.02$), type surgery ($p = 0.004$), +	General anesthesia was the most used type (98.7%), which could influence the results. Also it is not mentioned how the temperature was measured.
2020	The Effect of Active Warming on Postoperative Hypothermia on Body Temperature and Thermal Comfort: A Randomized Controlled Trial[22]	64	General anesthesia	Temperature one day before: 36.7 ± 0.69. Euthermia (37 l c) active warming $\bar{X}$ = 330 minutes, passive warming $\bar{X}$ = 555 minutes.	Shivering and thermal discomfort.	Active warming time vs passive warming ($p = 0.01$), shivering duration ($p = 0.05$), perception of thermal comfort ($p = 0.05$); +	The perception of thermal comfort is subjective, so this can bias a results. Just focus on warm up. The temperature measurement was made one day before and only takes into account the warming time in minutes.

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Table 1. This table shows the references of twenty authors. Number of patients in the sample, the mean of hypothermia, complications, management, and bias *(continued)*

Year	Title	Patients (n)	Anethetic technique	Mean Temperature ($\bar{X}$/Stardar deviation)	Complications	Observations	Biases
2021	Efficacy of active forced air warming during induction of anesthesia to prevent inadvertent perioperative hypothermia in intraoperative warming patients[6]	130	General anesthesia	Preoperative warming group : $\bar{X}$ 36.94ºC ± 0.66; Control group. : $\bar{X}$ 36.58ºC ± 0.70 (p = 0.004)	Shivering and thermal discomfort.	A decrease in hypothermia was observed in patients who received peri-induction warming, compared to the control group. Duration of perioperative warming (20.2 ± 8.7 min - p = <0.0001), duration of the period without warming (p = <0.001), severity of hypothermia (p = <0.001), intraoperative hypothermia (p = <0.001); *, **	It is limited since only focuses on warming the patient during the intraoperative period, in surgeries lasting more than 120 minutes.
2021	Incidence of postoperative hypothermia and risk factors in adults undergoing orthopedic surgery under brachial plexus block: A retrospective cohort study[16]	660	Brachial plexus block	Tympanic temperaturte < 36ºC at PUCA. Arrival Whith $\bar{X}$ of 35.7ºC	Not mentioned	Type of surgery (shoulder arthroscopy - p = <0.001), surgery time (p = 0.002), fluid administration (p = 0.035), midazolam + dexmetomidine (p = 0.001), fentanyl (p = 0.022), patient alcoholic (p = 0.029) and baseline body temperature (p = 0.002); *	Only one type of anesthesia mentioned, specifically the brachial plexus block in orthopedic surgeries.
2021	Postoperative hypothermia following non-cardiac high-risk surgery: A prospective study of temporal petterns and risk factors[11]	738	General anesthesia, neuraxial anesthesia and combined anesthesia	Core body temperature < 36ºC in 64% and < 36ºC in 19%	Primarly: infectio and coagulopathy. Others: cardiovascular, renal, and gastrointestinal	Age (< 50 years, > 70 years - p = <0.001), surgery time (p = <0.001), adbominal surgery (p = < 0.001), Comorbiidities (coronary insufficiency, SAH - p = < 0.001); *,**	The study was performed in the ICU, which could vary the temperature measurement method. And it was patients who had major non-cardiac surgery. Over 18 years. Temperature measurement with different devices (axillary, tympanic and esophageal).
2021	Analysis of the Risk Factors for the Onset of Postoperative Hypothermia in the Post anesthesia Care Unit[14]	2880	General anesthesia, epidural anesthesia, local anesthesia and total intravenous anesthesia	Hypothetic group: 35.79 ± 0.46 C Non hypothermic group: 36.75 ± 0.44 C	Not mentioned	Contributing factors: patient age (p = 0.01), type of anethesia (p = 0.027), ASA grade (p = 0.038), surgery time (p = 0.01), intraoperative fluid volume (p = 0.01), epidural anesthesia (p = 0.033), preoperative hypothermia (p = 0.003).	In the present study, the complications that occur in a patient with hypothermia are not explored.

ASA: American Society of Anesthesiologists; PACU: Postanesthetic Care Unit; ICU: Intensive Care Unit; SAH: Systemic Arterial Hypertension; BMI: Body Mass Index; OR: Operating Room; * Multivariate regression; ** Univariate regression; *** Linear regression; + Fisher's exact test; ǂ T-Student; § Wilcoxon test; $\chi 2$ Chi-square; $\bar{X}$ Mean; ϕ Mann-Whitney U test; Θ ANOVA.

Table 2. Risk factors for perioperative hypothermia

Risk factors source	Risk factors
Related to the patient	Female gender, of legal age, low BMI, ASA score between II and IV, diabetes mellitus, risk of cardiac complications, SBP < 140 mmHg.
Related to anesthesia	Combined or regional anesthesia, prolonged duration of anesthesia, level of spinal block.
Related to surgery	Pre-operative hypothermia, prolonged pre-operative fasting, major or intermediate surgery, size of surgical incision, long duration of surgery.
Environmental	Operating room temperature < 21°C, minimal patient coverage during surgery
Others	Infusion of cold IV fluids, use of cold irrigation solutions, blood transfusion, blood loss.

BMI: body mass index; ASA: American Society of Anesthesiologists; SBP: systolic blood pressure; IV: intravenous[28].

Table 3. Types of warming[28]

Active warming	Passive warming
Forced air or convective warm air transfer, heated intravenous fluids, heated fluid irrigation, warming and humidifying air (anesthesia).	Place warm blankets, remove any wet clothing, cover the person with dry clothing, and protect them from the cold wind (air conditioning), infusion of amino acids (1 h or 2 h before surgery).

hypothalamus regulates body temperature at a stable level. Thermoregulation is the basis of multiple signals coming from each nearby tissue[27]. Processing of thermal information occurs in three phases: afferent input, central regulation, and efferent responses[4].

Thermoregulation and complications

The human body has different methods to maintain core temperature. This requires sufficient intravascular volume and cardiovascular function, as the body must be able to transport rising internal heat to its surface for release. That is why older people are at increased risk of thermoregulation disorders due to a generally decreased intravascular volume and decreased cardiac function[4].

The main complications that occur in patients with hypothermia are hypothermic cardiac arrest, cardiac arrhythmias, coagulopathies, tremors, increased blood loss and increased need for blood transfusion, delayed healing, altered pharmacodynamics, and prolonged hospital stay[28].

Medulla oblongata reactivity decreases when body temperature falls below 34°C. Colder blood affects the sinoatrial node, atrioventricular node, and bundle of His and Purkinje fibers, leading to slow heart rate (bradycardia). This bradyarrhythmia can lead to a blockage.

The respiratory system is inhibited, leading to an increase in lung dead space, which causes the pooling of blood in the lungs. The oxygen dissociation curve shifts to the left and the affinity of hemoglobin for oxygen increases[5,28].

Cerebral circulation decreases by 6-10% for every 1°C that decreases in body temperature. Therefore, they lead to a deterioration of consciousness and rational thought when the temperature falls below 35°C[25].

Enzymatic coagulation reactions are affected by hypothermia since a correct pH and temperature are required for their proper functioning. A small drop in body temperature causes platelet dysfunction and clot formation. Bleeding time is longer while the lower the body temperature decreases[2,5,28]. The function of the coagulation system is reduced by 10% for every 1°C drop in body temperature[28].

Cardiac arrhythmia (sinus bradycardia, atrioventricular block, ventricular arrhythmia, and prolonged PR interval) is commonly seen on ECG in hypothermic patients. Included in these abnormalities in the ECG are the *Osborn wave*, also known as the *camel-hump sign*, (J wave or elevation of J point)[28]. Which is the elevation of the J point. This elevation is associated with hypoventilation and respiratory acidosis. Once the rise in body temperature begins, the J wave disappears[2,28].

Preventive measures

There are preventive measures for the appearance of hypothermia, which, for an easier understanding, we will divide into two. First, the passive warming measures and second, the active warming measures (Table 3).

Suggestions

To prevent perioperative hypothermia, it is necessary to make use of the tools and measures that are available. Those that have shown a better impact on the patient's body temperature, both pre-operative, intraoperative, and post-operative, are the previously mentioned active warming measures. The most relevant are

the following: use of forced air machines, thermal blankets, and heated intravenous fluids.

In a 2015 systematic review, it was shown that warmed intravenous fluids showed higher temperatures from the moment of anesthetic induction, with a mean at 60 min of 0.51°C higher (95% confidence interval [CI], 0.33-0.69) and at term and admission to the post-anesthesia care unit, with a mean of 0.63°C higher (95% CI, 0.28-0.98) than the control group[29].

In a 1996 clinical trial, it was found that the infusion of amino acids in the pre-operative period (1 or 2 h before the surgery) stimulates an increase in energy expenditure, thus preventing hypothermia induced by anesthesia to some degree[19].

Conclusions

Perioperative temperature is still one of the least commonly monitored vital parameters during anesthesia and surgery. With the results obtained, the main complications observed are: in cardiovascular impairment, shivering, thermal discomfort, coagulopathies, increased surgical site infections, and increased mortality. Temperature management in the pre-, intra-, and post-operative period is crucial to diminish the risks of perioperative hypothermia. A combined approach through active and passive warming measures is the key to preventing its complications.

Limitations

The limitations of our study include the type of secondary research, the small sample sizes, and the lack of information with respect to the fact that some studies did not mention the type of anesthesia used, types of surgery used, the lack of statistical analysis, and also lack of methodology in measuring body temperature.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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REVIEW ARTICLE

Aggressiveness and violence – An issue

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Abstract

Frequently, aggressiveness and violence are used as synonymous. However, these are two complex and different phenomena that scientists and philosophers have studied. In this paper, we make a difference between aggressiveness and violence. Aggressiveness must be considered utilitarian behavior that harms or destroys objects or subjects. Aggressiveness is a primitive way to conduct, and here, we discuss anatomic and functional encephalic systems. This involuntary and instinctive behavior is triggered when the animal is required to hunt a press, defend its territory when young, or compete for a mate for reproductive purposes. The aggressiveness will be violence when it pursues a social, political, economic, or criminal goal. A violent or aggressive act is not distinguished by the outcome but by intentionality. Indeed, a violent action could have the same material consequences as an aggressive act with a different goal. Aggression-violence is a biological phenomenon and the result of culture, societal life, political relations, and current moral conditions. We often tend to simplify the phenomena, and we have discussed aggressiveness-violence, but there are also other phenomena, such as empathy and mirror behavior. Empathy, compassion, and affection should be studied alongside the aggressive-violent process.

Keywords: *Aggressiveness. Violence. Psychosurgery. Stereotaxis. Biological evolution.*

Introduction

Frequently, aggressiveness and violence are used as synonymous. However, these are two complex and different phenomena that scientists and philosophers have studied widely. The evolutionary premise is to survive as invidious, as a group, and as a species and maintain our lineage. From an evolutionary point of view, the life of a human being was in danger because he was a link in the food chain. This circumstance has changed, and nowadays, the main predator of man is another man. In addition, today, the deterioration of the environment and depletion of natural resources is one of the main risks for our species.

Aggressiveness could be considered utilitarian behavior that harms or destroys objects or subjects. Aggressiveness is a primitive conduct. This involuntary and instinctive behavior is triggered when the animal is required to hunt a press, defend its territory when young, or compete for a mate for reproductive purposes. Nevertheless, aggressiveness and violence can be considered parallel conduct. The aggressiveness will be violence when it pursues a social, political, economic, or criminal goal. Indeed, a violent or aggressive act is not distinguished by the outcome but by intentionality. A violent action could have the same material consequences as an aggressive act with a different goal.

Today, the anatomic substrate of aggressiveness behavior is the limbic system[1,2]. The limbic system has consistent and congruent evidence about anatomical connections and physiological functions related to emotions[2]. This system is a transition between the primitive brain and the telencephalon. In 1937, Papez published a particular neural loop involved in emotional

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behavior; Papez's circuit was considered a loop between moderator centers of mood[1,3]. Later, in the middle of the 20th century, Mac Lean proposed a more prominent and more extensive neuronal circuitry related to excited and aggressive behavior named the limbic system[1,4]. Evidence has been accumulated about the areas involved in psychiatric disorders. In 1986, Yudofsky proposed the term neuroaggressive disorder as the presence of organic damage to brain structures involved in developing or containing aggressive behavior[5].

Aggressive behavior has been studied for many centuries. In 2017[6], Wrangham published the point of view of Jean-Jacques Rousseau and Peter Kropotkin; they state that the behavior of human beings is initially peaceful and becomes violent due to the influence of a hierarchical society. In that same paper, in the opposite sense, it is analyzed the thoughts of Thomas Hobbes and Thomas Henry Huxley. They establish that the behavior of the human being is initially aggressive and is modulated and limited by the influence of civilization. According to prior declarations, aggressiveness-violence could be understood as equivalent phenomena originated or regulated by natural conditions and social rules.

Two fundamental types of aggressive behavior are proposed: reactive and proactive[6,7]. Reactive aggression includes several conditions, such as being innate; it always involves vegetative responses of a sympathetic autonomic type (tachycardia, arterial hypertension, pupillary dilation, and others that depend on adrenaline secretion), and it depends on brain structures grouped in the limbic system that we will analyze. Reactive aggressiveness includes an emotion such as fear or anger; it could be considered primitive and directed to different "objectives," such as defense against a predator, the fight during the mating period, or the defense of the territory. This type of aggressiveness in its acme can attack without measuring the consequences or who is attacked; its goal is mainly to survive, and it manifests as an impulse, so it is uncontrolled.

On the other hand, proactive aggression is learned; it almost does not involve vegetative responses, it depends more on the frontal lobe than on the limbic system, it does not understand emotion for what is considered cold, it could be considered evolved, it always has a specific "directed target" for what his goal is a reward that can be of different kinds, not only to survive but to obtain satisfaction or power. Ultimately, it is instrumental, planned, and always controlled.

Biological behavior

Biologically, invertebrate animals (*arthropods*, *mollusks*, *nematodes*, echinoderms, cnidarians, and *Porifera*) can exhibit aggressive behavior if we define this as destructive behavior. However, in these groups of animals, no structure in their nervous system gives an emotional tone to this action. Consequently, this behavior is more a reaction than aggressive behavior. In mammals, the nervous system is transformed into a dorsal cord, the spinal cord protected within the vertebral column. Encephalization occurs as the nervous system evolves, which means that the anterior portion expands and predominates, forming the brain inside the skull[8,9]. The limbic system is a set of anatomical structures shaped like a ring around the diencephalon. The limbic system includes the "limbic cortices" (amygdala, hippocampus, cingulate cortex, and orbitofrontal cortex) (Fig. 1).

Specifically, the cerebral cortex has specific zones related to generating and controlling emotions. They are the amygdala complex, hippocampal cortex, cingulate gyrus, and orbitofrontal cortex. In this sense, in 1952, Mac Lean proposed a strong connection between the frontal and temporal cortex, and he included interaction with the hypothalamus, septal cortex, and rhinencephalon[1,10]. Mac Lean postulated the concept of the triune brain, which is integrated into three parts:

- The reptilian brain (ventral striatum and basal ganglia)
- The visceral brain (limbic system)
- The evolutionary neocortical brain (predominately cortex of frontal lobes).

This idea has been kept for many years. There has been an increment of anatomical structures in mood control, particularly in the vegetative response and aggressive behavior. The amygdala and the hypothalamus are the most critical neural nuclei for causing aggressive conduct, reproductive behavior, and anxiety or fear. The hypothalamus can trigger the visceral and autonomic functions of the subject (sympathetic and parasympathetic systems). The stimulus that triggers these responses produces a memory trace through the hippocampal formation of the temporal lobe. In this way, an aggressive or fearful response can be integrated. Hence, the edge between the reptilian brain, limbic system, and neocortex could be more precise. Parallel loops could be a better model of study.

On the other hand, despite controversial opinions on brain surgical treatment of psychiatric illness, neurosurgery has been used as a medical proposition to reduce aggressive conduct in these patients. These surgeries were hardly questioned in the last century, causing ethical

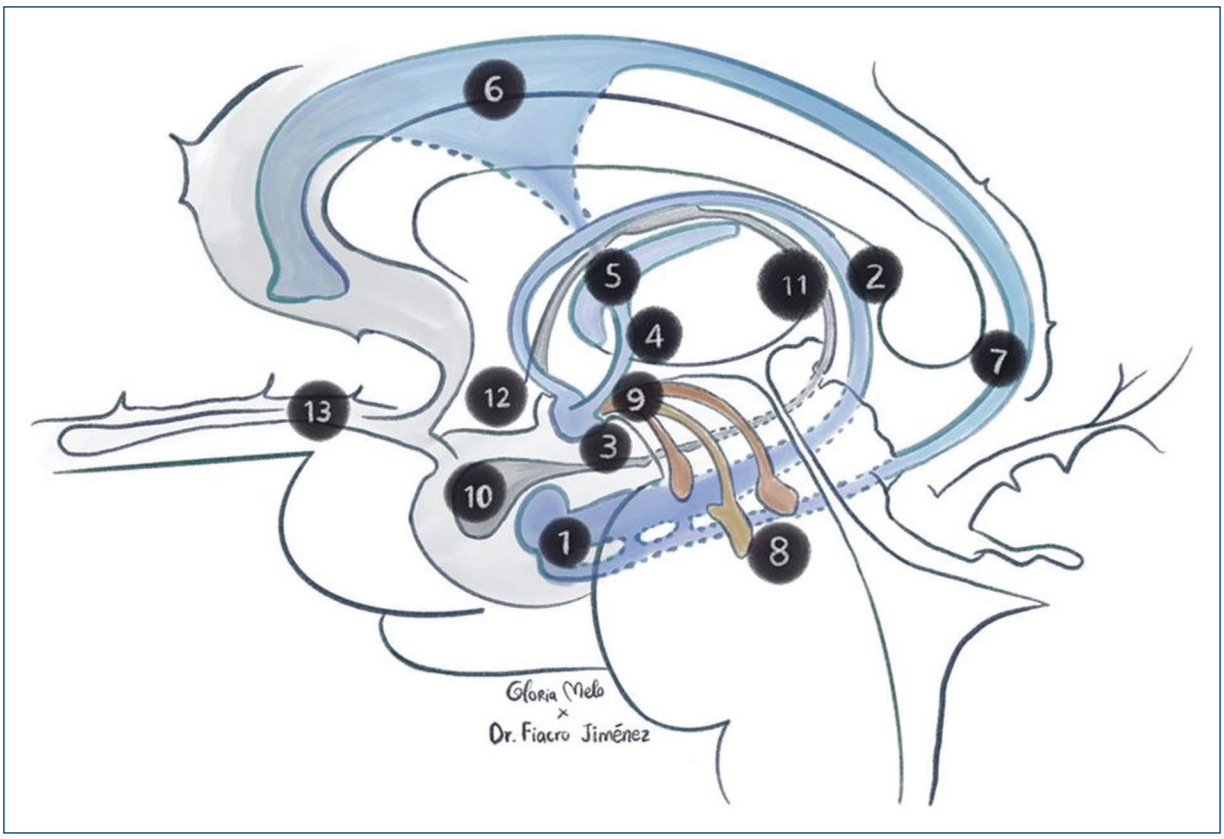

Figure 1. Diagram of the limbic and paralimbic system. (1) Hippocampus, (2) fornix, (3) mamillary body, (4) mammillothalamic bundle, (5) anterior nucleus of the thalamus, (6) cingulate cortex, (7) hippocampal connections, (8) medial forebrain bundle, (9) medial forebrain tract, (10) amygdaloid nucleus, (11) stria terminalis, (12) septal area-ventral striatum, and (13) rhinencephalon and orbitofrontal cortex.

issues, side effects, and unsteady outcomes. However, some well-established neurosurgical procedures have decreased aggressive behavior safely. Several authors have reported that ablative surgery or deep brain stimulation could reduce neuroaggressive disorder (Fig. 2)[11-24].

Personality: for two decades, we have performed a bilateral surgical procedure to control neuroaggressive states involving an anterior capsulotomy and a bilateral supragenual cingulotomy[22]. The results have shown a sustained reduction between 60 and 80% of the aggressive behavior of the patients. Recently, in other communication, we have been able to observe that the combined lesion of the lateral hypothalamus and the lateral and central nuclei of the amygdala on the "dominant" side can reduce aggressive behavior very efficiently compared to other more extensive procedures such as the one previously mentioned[25,26]. The left hemisphere is "dominant" for language, and the control of the right hemibody performs fine movements such as writing. We could conceptualize aggressive behavior as "a tool" under the control of the left fronto-parieto-temporal cortex. This proposal could explain the co-existence of reactive and proactive aggression. Both behaviors occur in humans, but proactive aggressiveness would seem to be the substrate for violence.

Seven hundred thousand years of evolution of primates allowed the frontal and parietal lobes of the brain to act on the limbic system and their parallel loops[27]. However, from an evolutive point of view, there is only a 1.23% difference between the genome of *Homo sapiens* and the two phylogenetically closest species, such as Pan paniscus (Bonobo) and Pan troglodytes (chimpanzee)[28]. Despite this, the phenotypic and cultural difference is enormous. Genetic or epigenetic aspects of primates could partially explain the control of reactive and proactive aggressiveness[27].

Developing the cerebral cortex is essential in understanding the behavior of vertebrates in general and humans (allocortex and isocortex)[28-30]. However, social environment and cultural development can make isocortex or allocortex

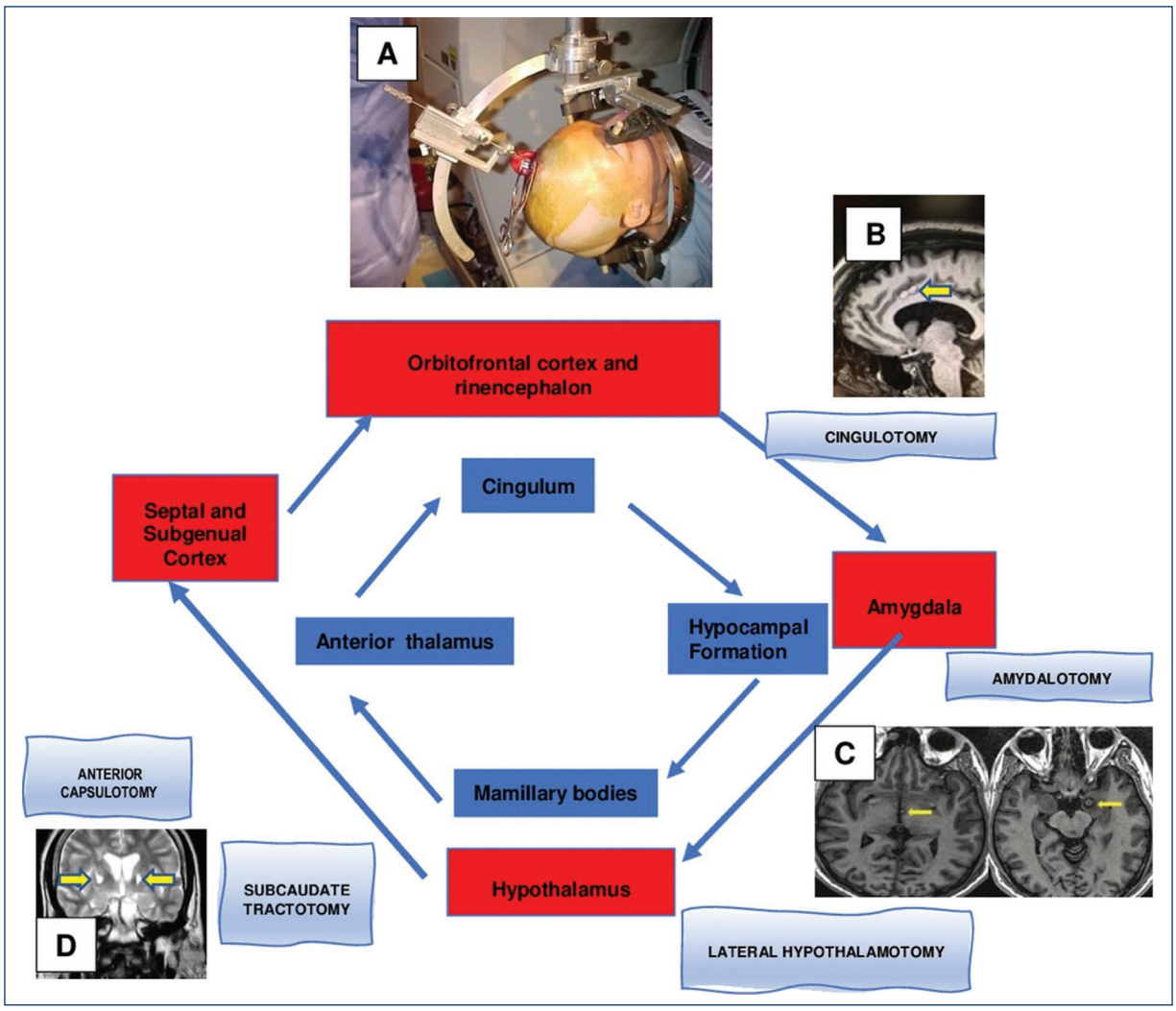

Figure 2. This figure shows the two primary circuits that make up the limbic system. In the center (in blue boxes), you can see the four main structures that Papez described at the beginning of the 20th century. Outside, a paralimbic circuit (in red boxes) constitutes a fundamental part of the control of emotions, and Mac Lean later described that. **A:** stereotactic surgery to control aggression. This procedure has demonstrated its efficacy and safety for over 50 years. **B-D:** different magnetic resonance images with the lesions resulting from surgery for aggressiveness, respectively cingulotomy, amygdalotomy, hypothalamotomy, and anterior capsulotomy.

circuits prevail to specific stimuli, such as aggression-violence in conflict resolution[30-32]. The growth in the volume of the human brain depended fundamentally on the parietal, frontal, temporal, and occipital neocortex and particularly on areas known as associations that are responsible for interrelating the specific functions of the primary sensory and motor cortices (Fig. 3).

Social behavior

In 2005, Baños established that aggressiveness is a biological-adaptive behavior and that violence is a cultural behavior, understanding culture as part of the environment that human beings have created[33]. He adds that violence is an intentional, premeditated, and conscious process of the individual and society.

The manufacture of weapons would be an example of how society establishes a culture of violence. Neolithic stone tools later became weapons for hunting, defense, and attack. Aggressive-adaptive behavior evolves as a behavior to exert discretionary force to harm and control.

Prehistoric society already set inter and intra-group violence. In the first circumstance, it would be due to the competition of the sources of resources, and in the second, it establishes a hierarchy and a social order.

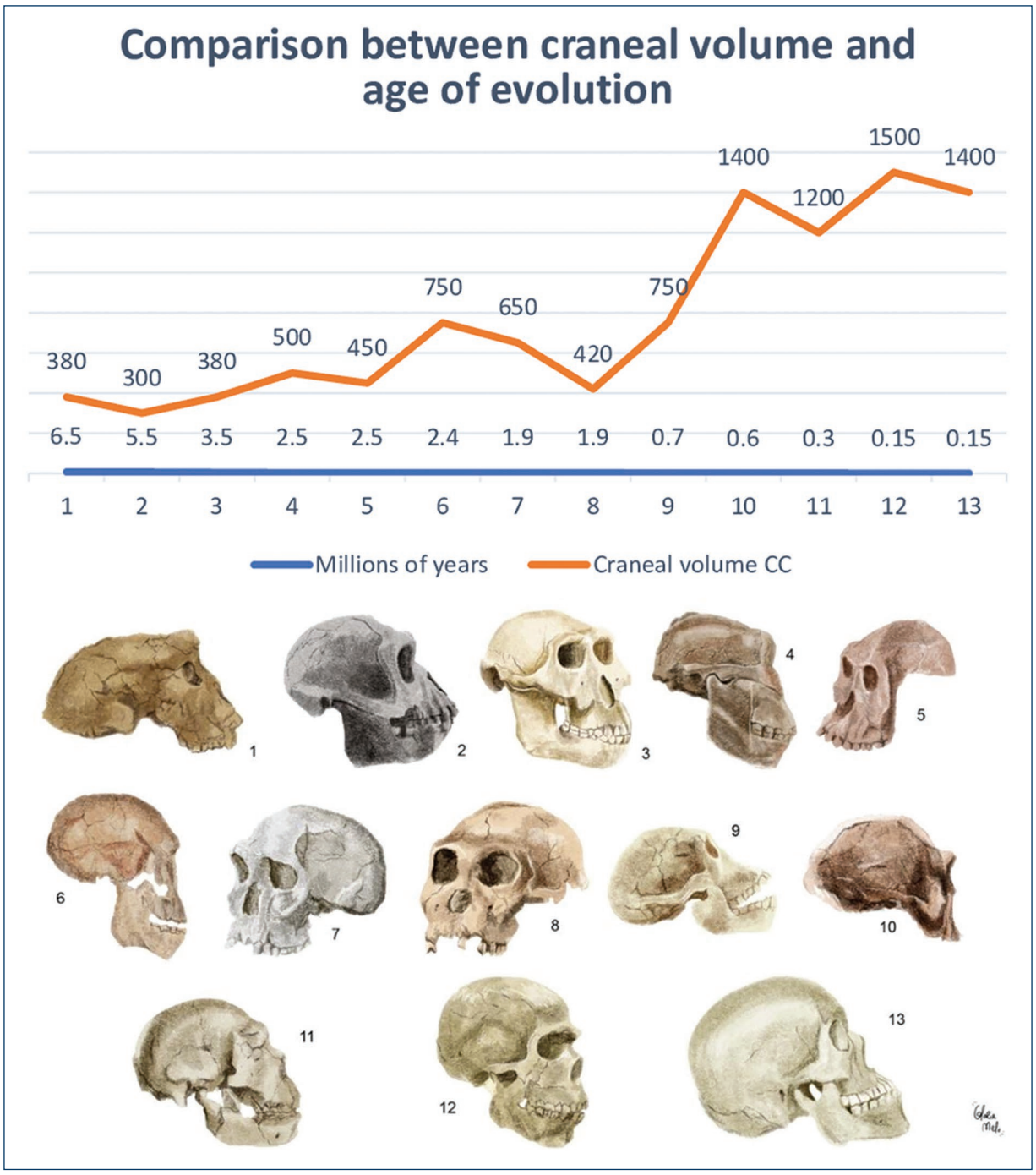

Figure 3. Comparison of brain volume from 6.5 million years of evolution to 150 thousand years in different skulls of 13 species of primitive human ancestors. (1) *Sahelanthropus tchadensis*, (2) *Ardipithecus*, (3) *Australopithecus afarensis,* (4) *Paranthropus*, (5) *Australopithecus garhi*, (6) *Homo rudolfensis*, (7) *Homo habilis*, (8) *Australopithecus sediba*, (9) *Homo georgicus*, (10) *Homo ergaster*, (11) *Homo heidelbergensis*, (12) *Homo neanderthal*, and (13) *Homo sapiens*.

A culture of violence is established. Fight with other clans for hunting sites, to defend their young, or to expand their territory. From one point of view, it could even be thought that the primitive family established patriarchal and chieftainship control of the clan. Violence is institutionalized and individuals act culturally following it. Baños notes, "Institutions are the way by which culture has to be reproduced since they are built

as a mechanism that shapes identities." He adds: "Violence, like any cultural pattern, is reproduced through institutions. Therefore, each culture will have a characteristic type of violence"[33]. He says that there is no linearity between aggressiveness and violence, but they are coherent. Although human behavior depends partly on social and economic conditions, human biology also plays a very important role. Their interrelationship is very complex and on many levels. Baños points out that violence is linked to a process of intentionality, premeditation, and conscience, and it is the culture and institutions of a society that allows or does not allow violent expressions.

Cultural behavior

Cultural violence is a special construct. Johan Galtung defined it in 1990 as "those aspects of culture, of the symbolic sphere of our existence (exemplified by religion and ideology, language and art, empirical science and formal science) that can be used to justify or legitimize direct or structural violence"[34]. He also mentions that the culture of violence makes structural and direct violence be seen as correct in the same way that the use of power is legitimized in politics. It even points out different types of violence for the four basic needs of a social group: the need to survive, the need for well-being, the need for identity, and the need for freedom. The sum of the five satisfactions produces conditions of peace[34].

Cavanaugh, in 2012, means that violence has usually been studied as a social and psychological phenomenon. However, it is a multifactorial problem, and consequently, it must be studied from different points of view: biological, anthropological, psychological, social, economic, and political[35].

Willem Schinkel proposes[36] that violence is hardly understood and poorly recognized in our society, immersed in several study perspectives, and points out a series of antinomies that would allow a better understanding of it, particularly the last one:

- Violence breaks the social order–violence is constitutive of the social order.
- Violence is a social problem–violence is a standard solution to social problems.
- Violence is only destructive of forms of socialization–violence is a positive form of socialization, leading people to come together.
- Violence is a coping mechanism–violence is a primary form and source of contingency.
- Violence breaks norms-violence strengthens norms.
- Violence is a visible phenomenon–violence is a hidden process.
- State violence is reactive toward illegitimate violence–state violence is already active in distinguishing between legitimacy and illegitimacy.
- Violence is an important social process in terms of an external referent–violence is a social process characterized exclusively by self-reference.
- Violence is a repellent–violence is an attractant.
- Violence is a means to an end–violence is an end.

Earlier, in 2004, Schinkel wrote an essay on what he refers to as the will to violence, where he discusses the possibility that violence has no other cause or sociological motivation than itself[37]. He describes it as self-referenced violence and that sociological science has tried to study or explain within a deterministic current and its causes without including the will to be violent.

Another explanation of violence comes from political science. Valentino, in 2014, established that since 1900, 100 million people have been murdered for political purposes, mostly civilians, and considers this circumstance as an action directed, instrumented, and orchestrated by the actors of power to achieve military and political objectives rather than the result of irrational and random violence from old ethnic feuds[38].

Discussion

Violence as a cultural outcome could be a part of the human condition. Aggressiveness behavior is a natural tool that is processed, optimized, and converted into violence. Violence as social behavior should be originated in the isocortex as proactive aggression. Too many situations in our complex society can elicit violence, but limbic and paralimbic systems uphold the physiologic substrate of aggressiveness.

In addition, Stevenson analyzed an evolutionary point of view raised by Charles Darwin, where violence could be understood as a consequent instrument[39]:

- There is a variation of the individual traits of a species, which makes each subject different in their biological conditions.
- The parents' traits are inherited by the children which allows the selection of the best phenotypic traits for changing environmental conditions by competition.
- Populations tend to have a geometric growth rate. Consequently, competition between individuals

becomes more acute if a species predominates for its best phenotypic traits.
– The environment's resources will eventually not support this growth, so insufficient satisfiers increase the struggle between subjects.

Here is the basis of competition for survival. The environment's limited resources will be controlled and used by the individuals with the best attributes. Natural selection allows different individuals to compete for resources, and those who best adapt and use their physical, mental, or social strengths will obtain power over the satisfiers.

In his essay on Anthropology of the Brain, Roger Bartra proposes the existence of social networks that enhance brain neural networks[40]. Bartra explains that the mutations that gave rise to brain volume and structure could not have been sufficient for the degree of human brain development. The language and the existence of specific social structures made it possible to non-specific cortical neural networks of the human primate.

Porcelli et al. have raised. That evolution has exerted a social pressure that has specialized areas of the cerebral cortex for processing stimuli and regulating neurotransmitter systems to the point of forming social networks that are now called the "social brain"[41]. Not only the cerebral cortex is involved in this interrelationship with culture and codes of social conduct, but extensive neural networks have also already been explored as myelinated structures in very diverse socialization processes[42]. The growing evidence on the direct relationship between brain function and structure with the social and cultural system is clear and has given rise to a growing area of social and neural sciences.

Thus, Porcelli's social brain (or the exobrain proposed by Bartra) requires its counterpart in the family structure or the clan to establish the basic codes of conduct. Linguistic or body communication establishes the primary habits that will be reinforced or modified at school, peer groups, or work.

The multiplicity of approaches tends to bias the perspective. Aggression-violence is a biological phenomenon resulting from culture, societal life, political relations, and current moral conditions (Fig. 4). We often tend to simplify the phenomena and we have discussed aggressiveness-violence, but there are also other phenomena, such as empathy and mirror behavior. Empathy, compassion, and affection should be studied alongside the aggressive-violent process.

Finally, violence for pleasure is a very serious and challenging issue that has been analyzed as a poorly understood behavior. Another circumstance about violent behavior due to "evil" is indolence as a way of ignoring an extremely violent system or is it a proactive action toward the possibility of exercising our power to obtain pleasure? Gil–Verona et al.[43] have analyzed the consequences of a lack of attachment to the mother that a primate can suffer, turning the individual into an irritable, aggressive, and stressed subject. The consequence is predictable if this subject continues developing in a society with a violent culture.

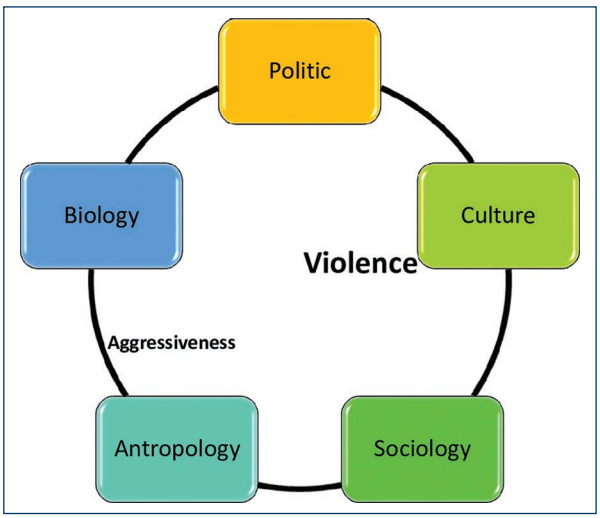

Figure 4. The participation of different aspects of the environment, the organization, and the biology of the human being that intervenes in aggressive and violent behavior.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

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CLINICAL CASES

Cerebral venous thrombosis in obstetrics: literature review and clinical case reports

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Abstract

The first case of cerebral venous thrombosis, described in the past century, was identified in obstetric patients in 1825. The clinical manifestations represent a real diagnostic challenge due to the few recorded cases, the wide variety of possible clinical symptoms, and the diversity of medical conditions that cause it. In the past century, the etiology was mainly associated with septic processes; however, due to the widespread use of antibiotics, this cause has been considerably reduced. In the context of the puerperium, several conditions make this group of patients more vulnerable, such as dehydration, hypercoagulable state, iron deficiency, puerperal sepsis, and preeclampsia, the latter is particularly known for an endothelial lesion with different degrees of associated severity, according to the clinical phenotype present. This review aims to highlight the most relevant aspects of cerebral thrombosis in the context of a puerperal patient. It will also present clinical cases reports treated successfully in this health unit.

Keywords: *Cerebral. Venous thrombosis. Preeclampsia.*

Introduction

Like the regional systemic circulation, approximately 80% of the brain's blood circulation is in the venous bed, while about 20% is in the arterial circulation. Cerebral venous thrombosis (CVT) accounts for approximately five to ten out of every thousand cases of cerebral vascular disease. The approximate incidence worldwide is three and a half cases per million inhabitants, predominantly found in young people and women, unlike arterial cerebral vascular disease. It is also worth mentioning that cerebral venous disease has significant clinical variability due to the anatomical variants in this system, with constantly changing and sometimes imprecise drainage patterns. Because the venous system at this level lacks valves, it has a substantial capacity for compensation when thrombosis occurs. Regardless of the anatomical variants present, multiple anastomoses between superficial cerebral veins facilitate collateral circulation in thrombosis of this system. These characteristics make this complication have a considerable clinical heterogeneity, dependent on the location, degree of an extension, and functionality of the regional collateral circulation. One of the characteristics of the clinical presentation that is almost invariable is the difference between the involvement of the deep venous system, which generally leads to a worse evolution, with the involvement of the superficial

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system, which is associated with mild and self-limited forms of development. Since it is a disease with a very low incidence, it is hard to perform epidemiological studies and randomized clinical trials (RCT) with high statistical value to clarify better diagnostic, preventive, and therapeutic options. In the present document, we review the bibliography concerning this topic, highlighting its epidemiology, pathological anatomy, diagnostics, and therapeutical options.

Epidemiology

Deep vein thrombosis incidence is estimated to be approximately three cases per million inhabitants. Note that case series in pediatric patients have been described with an incidence up to 10 times higher[1]. This clinical condition is much more frequent in females between the ages of 20-35, inherent to the related obstetric conditions and the hormonal characteristics particular to that sex. It is estimated that it accounts worldwide for five out of every 1000 cases of cerebral vascular events[2].

The ISCVT study "International Study on CVT and Dural Sinus Thrombosis," carried out between May 1998 and May 2001, included 624 adult patients with venous thrombosis. The type of study was prospective observational, multinational (21 countries), and multicenter (89 centers), making it one of the most important concerning this topic. It is worth mentioning that 58% of the cases reported in Mexico were associated with pregnancy or puerperium, as opposed to approximately 8% of the cases reported in other countries[3]. James et al. evaluated more than 9 million pregnant and puerperal patients and found significant results: a total of 2850 cases at a rate of 34.2/100,000 deliveries, a total of 117 deaths correspond to 1.4 deaths per 100,000 deliveries, 22% of the survivors were discharged to another facility, with increasing age, this risk rose with a cutoff point of 35 years or older. The group of patients of African descent had a higher risk with an odds ratio (OR) of 1.5 (95% confidence interval: 0.2-1.9). Medical conditions that were strongly associated with stroke overall included migraine (OR 16.9), thrombophilia (OR 16.0), systemic lupus erythematosus (OR 15.2), previous heart disease (OR 13.2), sickle cell disease (OR 9.1), hypertension (OR 6.1), and thrombocytopenia (OR 6.0). Some obstetric complications were also found to be associated with significantly increased risk, such as postpartum hemorrhage (OR 1.8), preeclampsia (OR 4.4), transfusion (OR 10.3), and puerperal infection (OR 25.0), in all the above, venous thrombosis accounted for 2% of cases[4].

One of the most significant cohort publications in the journal Continuum Neurology was conducted by Fadar et al. It was a retrospective study, which used validated codes to identify all new cases of CVT found (n = 5.567) in the New York and Florida State Inpatient Databases between 2006 and 2016. The standardized annual incidence for CVT by age and sex was 13.9-20.2 cases per 1 million inhabitants (females 20.3-26.9, males 6.8-16.8); by age/sex (age range; females 18-44 years, varying from 24.0% to 32.6%; males 18 to 44 years ranging from 5.3 to 12.8); according to race (Blacks: 18.6-27.2; Caucasians: 14.3-18.5; Asians: 5.1-13.8). The incidence in women aged 18-44 remained unchanged over time[5].

Etiology

It consists of a series of clinical conditions associated with hypercoagulable states, which, in turn, are linked with systemic venous thrombosis and, eventually, with CVT; some of these conditions include adenocarcinoma, polycythemia vera, thrombocytopenia, leukemia, sickle cell anemia, pregnancy, and the puerperal period. Other causes include direct head trauma, venous sinus procedures, bacterial meningitis, and invasive neuromonitoring.

Other predisposing conditions such as antiphospholipid syndrome, factor V Leiden mutation, protein C and S deficiency, prothrombin mutation, and hyperhomocysteinemia should be ruled out. In most cases, thrombophilias represent 22% of cases, antiphospholipid syndrome 6%, associated with the gestational and puerperal period in 10-58% of cases. With current doses of combined contraceptives, the risk of thrombosis has considerably decreased as an independent factor. It has related to a complication of oncology therapies, such as tamoxifen, cisplatin, and l-asparaginase. Reviews have also been found where CVT incidence increased within erythropoietin users[6].

Cerebral venous anatomy

The cerebral venous system drains through a superficial and deep system, draining into the principal sinuses: superior and inferior sagittal, lateral sinuses, cavernous sinus, and straight sinus. Finally, they drain through the internal jugular vein. The superficial venous system drains mainly in the superior sagittal sinus and lateral sinuses due to the large number of anastomoses; occlusion cases at this level are hard to diagnose. The deep system drains venous blood from the deep

white matter of the hemispheres and basal ganglia through the vein of Galen. This system also has multiple anastomoses, which hinders diagnosing small caliber vessel occlusion. However, in the case of thrombosis, it allows venous drainage to have alternative routes. The posterosuperior venous system is formed by the superior and inferior sagittal sinus, lateral sinuses (transverse and sigmoid portions), straight sinus, and occipital sinus. The anteroinferior venous system is made up of the superior and inferior petrosal sinuses and the cavernous sinus. It is crucial to mention that the venous sinuses play a significant role in the reabsorption of cerebrospinal fluid through the arachnoid villi. The superior sagittal system drains venous blood from most of the cerebral cortex and corresponds to the sickle border of the brain. The lateral sinuses drain from the press of the Herophilus to the jugular bulb, with its transverse and sigmoid portion attached to the mastoid process. This portion is susceptible to thrombosis in patients with mastoiditis and otitis media. Drainage from the lateral sinus also comes from the cerebellum, brain stem, and posterior part of the cerebral hemispheres. The cavernous sinuses are located at the cranial base, superolateral to the sphenoidal venous sinuses. There are significant anatomical relationships at this level through its lateral walls run the common ocular motor nerves (III), trochlear (IV), and the ophthalmic and maxillary branches of the trigeminal (V). Medially, the external ocular motor nerve (VI) and the internal carotid artery are accompanied by its sympathetic plexus. The cavernous venous sinuses drain to the internal jugular veins through the petrosal sinuses[1,6].

Physiopathology

CVT is caused by an imbalance between prothrombotic substances and thrombotic processes, leading to the initiation and propagation of the coagulation cascade in the venous sinuses or cerebral veins. Venous blood is forced to remain in the system of small vessels and capillaries provoking an increase in venous and capillary pressure. The specific anatomy of the cerebral venous system and its extensive anastomoses often provides sufficient collateral circulation to compensate for such pressure changes. When this collateral circulation system becomes insufficient, it disrupts the blood-brain barrier and decreases cerebral perfusion pressure, resulting in cerebral edema, ischemia, and often intracerebral hemorrhage. It has been shown that cerebral perfusion is possible in the early stages of venous thrombosis through collateral circulation, as demonstrated in experimental models by laser and Doppler flowmetry. In most cases, parenchymal injury occurs when the thrombus extends to cortical veins; however, in animal models, it has been found that sinus occlusion may be sufficient to cause venous infarcts. Parenchymal lesions occur in approximately 60% of cases, with vasogenic components and cytotoxic edema. As mentioned above, the dural sinuses play a significant role in the absorption of cerebrospinal fluid, mediated by arachnoid villi, known as Pacchionian granulations, found in the walls of the venous sinuses. Dysfunction of these granulations may cause a decrease in cerebrospinal fluid absorption, resulting in intracranial hypertension[7].

Clinical presentation

Symptoms associated with CVT can range from asymptomatic events to life-threatening clinical pictures, depending on the degree of involvement and the venous territory involved. The superior sagittal sinus is the most affected in approximately six out of ten cases, with symptoms ranging from headache due to increased intracranial pressure (ICP) to focal neurological deficits, such as hemiparesis, hemianopsia, and even seizures. Thrombosis of the transverse sinus affected four out of ten cases; if it presents occlusion of the vein of Labbé, it may be related to hemorrhage and is characterized by cephalea, aphasia, and less frequent seizures. Involvement of the sigmoid venous sinus is rare and may cause mastoid pain and, less frequently, cranial nerve neuropathy. Thrombosis of deep veins such as the internal cerebral veins, basal veins of Rosenthal, the vein of Galen, and the sinus rectus can affect up to 18%, causing edema of the thalamus, causing altered alertness, and occasionally paralysis. Isolated intracranial hypertension (typically due to chronically evolving sagittal sinus thrombosis) manifests with papilledema, headache, and visual disturbances. Cavernous sinus thrombosis is the rarest; however, it is easier to diagnose due to its clinical presentation (ocular pain, chemosis, ocular ptosis, and oculomotor nerve palsy associated with previous sinus infection).

Cephalea is present in nine out of ten symptomatic CVT cases. It is a very nonspecific symptom; however, in any patient with disabling intensity, new onset, persistent, worsening with valsalva maneuver, lack of improvement with regular analgesia, and with risk factors for thrombosis or clinical evidence of papilledema, a

complete protocol for a vascular headache should be performed, including contrasted imaging methods.

In the peripartum period, symptoms are non-specific and atypical, with no specific recommendations concerning gestation and puerperium[8]. Post-anesthetic puncture headaches can be confused with cases of CVT, so they should not be underestimated and should be adequately assessed, especially in patients with thrombotic risk factors[9]. After applying an epidural patch due to rupture of the dura mater in post-operative cesarean section patients who present intense and progressive cephalea, imaging studies should be performed quickly to rule out CVT[10].

The "STANDARD GOLD" diagnostic test is a digital subtraction angiography with a sensitivity of 95% and a specificity of 91%. This test demonstrates the absence of flow in the involved venous territory. D-dimer measurements can be performed; however, the evidence level and recommendation strength reported in most guidelines are weak[11].

Treatment

In an acute event of cerebral venous thrombosis, heparin at therapeutic dose should be used, unless there are absolute contraindications. In case of cerebral hemorrhage, there should be an individual evaluation. Evidence: moderate. Recommendation: Strong.

The administration of low-molecular-weight heparins over unfractionated heparins is suggested.

This information does not apply to patients with contraindications for low-molecular-weight heparins (e.g., renal failure) or in situations where rapid reversal of anticoagulation is required. Evidence: Low. Recommendation: Weak.

In the case of thrombolysis as a therapeutic option, no studies with compelling evidence were found. Therefore, the patient's context should be individualized and approached in a multidisciplinary fashion to consider this option.

The use of acetazolamide as part of the treatment protocol is not recommended. Evidence: Low. Recommendation: Weak.

Low-molecular-weight heparin therapy is suggested as a first antithrombotic option in pregnant and postpartum patients. Evidence: Low. Recommendation: Weak[12].

Coumarins are a safe option. However, they should be used as a second line. Direct anticoagulants use is a safe option and an alternative to Warfarin use[13]. The duration of treatment per most of the consulted guidelines should be from 3 to 12 months; it may be shorter if the cause of thrombosis was provoked (traumatic, surgical, and non-surgical) and longer if it was spontaneous[14].

In the context of neurocritical patients, special care is established aimed at maintaining adequate cerebral homeostasis.

In the context of neurocritical patient, special care is established aimed at maintaining adequate brain homeostasis, acronyms such as "THE MANTLE" OR "GHOST-CAP" are used according to publications that arise certain particular neuroprotection goals to favor adequate evolution especially in clinical scenario of trauma; however, they are used in obstetric patients who require neurocritical care[15,16].

Taccone et al., suggest the following goals:

Glucose: target levels between 80 and 180 mg/dL may be reasonable.

Hemoglobin: is an important determinant of oxygen delivery (DO2). No well-designed RCT has addressed ideal transfusion thresholds in patients with acute brain injury, but a 7-9-g/dL threshold seems reasonable.

Oxygen: targeting a SpO2 between 94 and 97% seems reasonable.

Sodium: avoid sodium levels < 135 mEq/L, hypernatremia may occur as a result of ICP-directed therapies, and sodium levels up to 155 mEq/L may be tolerated in such conditions.

Temperature > 38.0°C should be avoided, particularly if associated with neurological deterioration or altered cerebral homeostasis.

Comfort, including control of pain, agitation, anxiety, and shivering, is an important goal, to avoid physical and psychological distress, excessive cerebral stimulation, increased ICP, and secondary tissue.

Arterial blood pressure is the main determinant of CBF. Maintaining a mean arterial pressure (MAP) ≥ 80 mmHg and a CPP ≥ 60 mmHg may be reasonable in unconscious patients; in awake patients, MAP targets can be titrated according to repeated neurological examination.

PaCO2 causes changes in CBF (a 4% change in CBF per mmHg change in PaCO2). If intracranial compliance is reduced, any increase in CBF may increase cerebral blood volume, and thereby ICP. On the other hand, excessive hyperventilation can result in cerebral ischemia, and PaCO2 < 35 mmHg should be avoided.

Godoy et al. suggest the following goals:

Temperature, to avoid hyperthermia is fundamental, goal 36-37°C (core). Hyperthermia can also yield to cerebral hypoxia due to increased metabolism. Therefore, it is desirable to maintain central temperature levels between 36 and 37°C.

Hemoglobin, to keep and maintain good quality and quantity of transporter, is essential. The optimal levels

of Hgb remain unknown; however, it seems reasonable to reach and maintain Hgb values between 7 and 9 g/dL.

Electrolytes and acid basic status: ''Physiological balance is the cornerstone.'' To ensure that Hgb dissociation curve remains within functional ranges (p50 = 26-28 mmHg), to reduce the risk of cerebral ischemia and intracranial hypertension pH: 7.35-7.45 36-37.5°C, and to minimize or treat cerebral edema, it is crucial to maintain a slight hyperosmolar state (serum Na+140-150 mEq/L) and to avoid hypotonic fluids.

Metabolism: ''If metabolism is accelerated, O2 demands increase.'' Brain metabolism is the main determinant of the rate of cerebral O2 consumption. Oxygen pressure of the brain parenchyma locally reflects the balance between the supply and consumption of O2 and should be maintained at values above 18 mmHg. The venous oxygen saturation obtained from the jugular bulb (SvjO2), globally represents the O2 that returns to the general circulation after being consumed by brain cells and should be maintained at values > 55%.

Arterial blood pressure: ''Arterial hypotension is apocalyptic for injured brain.'' Recommended blood pressure targets include systolic blood pressure > 100-110 mmHg; normal volemia, diuresis > 30 mL/h, preserved peripheral perfusion, and central venous pressure: 6-10 cmH2O.

Nutrition and glucose: ''Glucose, essential fuel for the damaged brain.'' Glycemia levels < 110 mg/dL may cause non-ischemic metabolic crises. In contrast, hyperglycemia > 180 mg/dL causes neurotoxic cascades (inflammation, micro thrombosis, and edema) and disturbs the homeostasis of the internal environment (hyperosmolarity and dehydration), compromising the immune status, among other alterations.

Target of oxygenation: ''Both extremes of systemic oxygenation are deleterious.'' Measures must be taken to achieve PaO2 80-120 mmHg, and SaO2 >95%.

Lung protective ventilation: ''Protecting the lungs protects the brain.'' According to available evidence lung protective ventilation with a controlled mode, tidal volumes between 6 and 8 mL/kg, minimum respiratory rates to ensure levels of PaCO2 between 35 and 45 mmHg, and FiO2 and PEEP necessary to achieve systemic oxygenation targets as we mentioned above, to prevent mechanical ventilation-induced lung injury (barotrauma, biotrauma, and volutrauma), plateau pressure should be kept < 2 cm H2O, driving pressure < 13 cm H2O, and mechanical power below 17 J/min. It is recommended not to use routinely hyperventilation and to maintain PaCO2 levels between 35 and 45 mmHg.

Edema and ICP control: ''Brain swollen, brain on the ledge.'' The recommended main targets to be achieved should be the following: (a) ICP< 22 mmHg; (b) CPP: 55-70 mmHg; (c) optic nerve sheath diameter (ONSD)<5.5 mm; d) pulsatility index (PI)<1.2; and e) cerebral CT scan without edema signs.

Tonny et al. suggest based on analysis of recent investigation: "Tissue hypoxia after brain injury is not confined to regions with structural abnormality and can occur in the absence of conventional macrovascular ischemia. This physiologic signature is consistent with microvascular ischemia and is a target for novel neuroprotective strategies" [17]. Godoy et al. suggest a different model on evaluation of brain injury: "For decades, one of the main targets in the management of severe acute brain injury (ABI) has been intracranial hypertension (IH) control. Meanwhile, progress in the understanding of intracranial content (brain, blood, and cerebrospinal fluid) dynamics and recent development in monitoring techniques suggests that targeting intracranial compliance (ICC) could be a more reliable approach rather than guiding actions by predetermined ICP values. Therefore, an intracranial compartmental syndrome (ICCS) can occur with deleterious brain effects, precipitating a reduction in brain perfusion, thereby inducing brain ischemia"[18].

Clinical cases

Case number 1

General characterization

Thirty years old, with no chronic personal or family history of degenerative. Three previous pregnancies with vaginal delivery, history of hospitalization due to urinary tract infection during the second trimester of pregnancy, negative control of culture posterior to treatment with nitrofurantoin. COVID vaccines one dose (Sputnik®), five prenatal medical care, with adequate fetal growth, received aspirin 81 mg from 14 weeks of gestation. Height 1.57 meters, weight 94 kg at the beginning of pregnancy, 108 kg at the end of pregnancy.

Summary of symptoms

During her 36th week of pregnancy without presenting any previous obstetric symptoms, she went (by herself) to the emergency room of this hospital, with a history of 6 h of evolution of pulsatile headache, tinnitus, scotomas, vertigo, facial hemiparesis, nausea, and vomiting on two occasions of gastric content, associated with an episode of loss of consciousness for 3 min

with fall of the same level and subsequent recovery of alertness with drowsiness, no other symptoms related.

Physical examination summary

Height 1.57 meters, weight 94 kg at the beginning of pregnancy, body mass index 38.1 Kg/m^2, body surface area 2.02 m^2.

Blood pressure on admission 200/140 mmHg, MAP 160 mmHg, heart rate 65 beats per minute (BPM), respiratory rate 21 cycles per minute (CPM), treated as severe pre-eclampsia with nifedipine 10 mg and modified Zuspan scheme (four grams in continuous infusion), 15 min after this treatment 151/121 mmHg, MAP 131 mmHg.

Neurological findings

Glasgow Coma Scale (GCS) 14 puntos: verbal response 4 points, motor response 6 points, eye opening 4 points, right pupillary diameter 3 mm, left pupillary diameter 2 mm, brainstem reflexes, no other cranial nerve alterations, unaltered motor sensitivity and response, preserved mental functions, grade III osteotendinous reflexes.

She underwent neurocritical care on the recommendation of the neurology service, with ICP monitoring inferred by optic nerve sheaths diameter measurement ICP 15-16 mmHg, remained under deep sedation after cesarean section for 48 h and subsequently emerged without data of delirium, without any manifestation of neurological deterioration. Tomographic: Areas compatible with subarachnoid hemorrhage of the right frontal region and on the free edge of the cerebellum tent on the right side, both not > 1 cm, rest of the study with cisterns of the base and subarachnoid space of the normal convexity, at the level of cerebral parenchyma basal ganglia with hypodense images in their entirety compatible with edema and subtotal deep venous circulation thrombosis (Fig. 1).

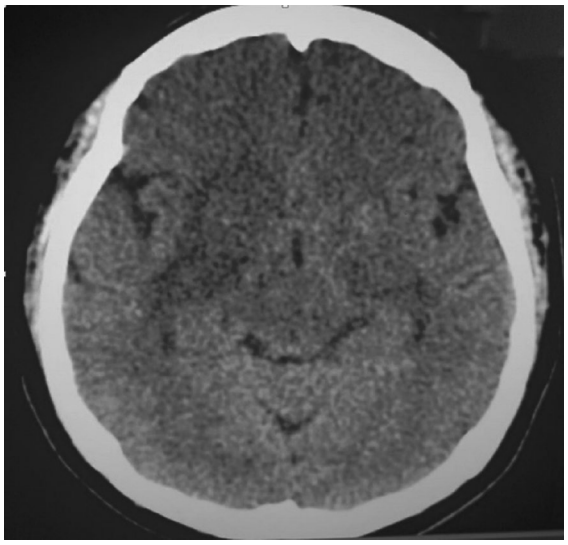

Figure 1. Cranial tomography on axial projection where hypodensity corresponding to the affected area is observed. *Source: Clinical record.*

Summary of clinical evolution

Treated in the emergency area with severe hypertension, MAP stabilized to a reduction of 20% during 1st h, then cesarean section was performed due to GCS neurological deterioration of 14 points at admission and 10 points before cesarean delivery, after the surgery she remained in neurocritical care, deep sedation was maintained with propofol at 4 mg/kg/h and midazolam 0.2 mg/kg/h, achieving RASS –5 for 48 h, mechanical ventilation with pressure-controlled mode for 80 h; subsequently, mechanical ventilation progressed without criteria for ventilatory failure, required antihypertensive treatment based on nifedipine 30 mg every 12 h, maintaining MAP between 90 and 100 mmHg, after withdrawal from ventilation required adjustment of antihypertensives required nifedipine 60 mg every 12 h and nebivolol 5 mg every 24 h. Maintained uresis, urea, creatinine, urea nitrogen in normal ranges, adjustment of antihypertensives required nifedipine 60 mg every 12 h, and nebivolol 5 mg every 24 h did not present relevant electrolyte alterations. On admission to hospitalization, her platelet levels were in normal ranges, later she presented moderate thrombocytopenia verified with platelet levels in citrate, at discharge from intensive care with platelet levels in ranges of moderate thrombocytopenia, treatment with intravenous dexamethasone 8 mg twice daily for 48 h (Table 1).

Treatment received

Received enoxaparin at a therapeutic dose for 7 days and then prophylactically for 3 months, without any complications from treatment, modified Zuspan scheme (four grams in continuous infusion) and then 1 g/h 24 h, in neurocritical care measures for 48 h, including temperature 36-37°C, hemoglobin > 8 g/dL, sodium levels 135-145 meq/L, systolic arterial blood pressure > 110 mmHg, PO2 80-100 mmHg, lung protective ventilation, ICP control optic nerve < 5.5 mm, IP ACM 0.6-1.2, intracerebral pressure < 22 mmHg, and no hypertonic saline solution was necessary.

Table 1. Blood test results.

Day	1	2	3	4	5	6	7	8
Ph (Acidity Index)	7.49	7.38	7.39	7.41	7.39	7.39	7.44	7.42
HCO^{3}- (mmoL/L)	19	21	21	22	22	23	21	20.9
PCO^{2} (mmHg)	27	35	35.2	36	36	29	29	30
PO^{2} (mmHg)	125	92	89	79	78	81	78	71
Base excess (mmoL/L)	8	2	2	1	1.2	1.5	0.5	0.5
Lactate (mmoL/L)	1.9	0.9	1	1	0.9	0.5	0.6	0.8
INR	1	1.33	1.16	1.18	1.2	1.19	1.23	1.25
PT (seconds)	14	15.2	11.6	20.7	20.4	17.8	18.2	17.3
PTT (seconds)	34	60	30	25	32.5	32.3	35.8	49.3
Hematocrit (%)	37	31.5	31	32	31	29	31	28
Platelets ($x10^{3}/mm^{3}$)	159	75	78	81	102	105	110	151
White blood cells ($x10^{3}/mm^{3}$)	12	15.1	5	5.4	8.9	11.5	9.4	8
Glucose (mg/dL)	87	125	92	94	87	85	88	79
Creatinine (mg/dL)	0.8	1.17	1.05	0.95	0.98	1	1	0.98
BUN (mg/dL)	11	16	21	23	24	28	21	18.1
Urea (mg/dL)	19	32	34	45	40	35	32	29
Total Bilirubin (mg/dL)	0.4	0.63	0.8	1	1	0.9	0.9	0.6
AST (UI/L)	29	31	42	60	45	44	40	39
ALT (UI/L)	19	28	32	39	31	32	36	29
LDH (UI/L)	345	450	430	428	390	345	330	290
Sodium (meq/L)	141	144	144	143	140	140	145	140
Potassium (meq/L)	4	4.1	4.4	4.2	4.1	4.1	3.95	3.96
Chlorine (meq/L)	108	110	109	108	104	103	108	106
Calcium (mg/dL)	7.3	8.1	8.2	8.2	8.4	8.4	8.9	8.8

HCO^{3}-: denotes Bicarbonate; PCO^{2} CO^{2}: partial pressure; PO^{2} O^{2}: partial pressure; INR: International Normalized Ratio; PT: prothrombin time; PTT: partial thromboplastin time; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.
Source: Clinical record.

Obstetric outcome

Cesarean delivery under general anesthesia with estimated bleeding of 450 mL, surgical sterilization, product of gestation with 37 weeks calculated by Capurro, 2900 g, male, with Apgar 7/9, without maternal or neonatal neurological impact. Withdrawal of antihypertensives was achieved at 7 days of puerperium, neurological evaluation without any alteration at discharge, and 1 month later when evaluated by neurology.

5 days of hospitalization in intensive care unit, 3 days in intermediate care room of obstetrics. The newborn was hospitalized for 4 days in intermediate care and subsequently discharged without complications.

Case number 2

General characterization

Twenty-four years old, with no chronic personal or family history of degenerative. Two previous pregnancies

with vaginal delivery, no history of hospitalization during pregnancy. COVID vaccines one dose (Sputnik), six prenatal care, with adequate fetal growth, no intake of aspirin 81 mg. Height 1.59 meters, weight 71 kg at the beginning of pregnancy, 81 kg at the end of pregnancy.

Summary of symptoms

Frontal and temporal headache of moderate to severe intensity of 12 h of evolution, associated with unique episode of convulsion, characterized by generalized tonic and clonic movements approximately 60 s of duration without relaxation of sphincters witnessed by her husband, subsequent recovery of alertness with drowsiness immediately.

Physical examination summary

Height 1.57 meters, weight 94 kg at the beginning of pregnancy, body mass index 28.1 Kg/m^2, and body surface area 1.7 m^2. Blood pressure on admission 143/96 mmHg, MAP 116 mmHg, heart rate 62 BPM, respiratory rate 21 CPM, treated with nifedipine 30 mg, subsequently maintained blood pressure in target ranges MAP 90-95 mmHg, without requiring additional antihypertensives during hospitalization.

Neurological findings

GCS 15 puntos: bilateral pupillary diameter 3 mm, brainstem reflexes and no cranial nerve alterations, unaltered motor sensitivity and response, preserved mental functions. Grade III osteotendinous reflexes. She was provided to neurocritical care on the recommendation of the neurology service, remained under deep sedation after cesarean section for 48 h, with ICP monitoring inferred by optic nerve sheaths diameter measurement ICP 12-14 mmHg, and subsequently emerged without data of delirium, without any manifestation of neurological deterioration. Tomography: Density changes compatible with thrombosis of the superior longitudinal sinus, without any other alteration at the intraparenchymal or ventricular level (Fig. 2).

Summary of clinical evolution

After being treated in the emergency area by history of seizure, diphenylhydantoin was administered initial dose 20 mg per kilogram, then 125 mg every 8 h for 7 days, cesarean section was performed due to initial diagnose of eclampsia. After cesarean delivery, she remained in neurocritical care, deep sedation was maintained with propofol at 3 mg/kg/h and midazolam 0.15 mg/kg/h, achieving RASS –5 for 48 h, mechanical ventilation with pressure-controlled mode with alveolar protection parameters for 60 h, subsequently, mechanical ventilation progressed without criteria for ventilatory failure, required antihypertensive treatment based on nifedipine 30 mg every 24 h, maintaining MAP between 90- and 95 mmHg. Uresis, urea, creatinine, and urea nitrogen in normal ranges did not present relevant electrolyte or metabolic alterations. On admission to hospitalization, her platelet levels were in normal ranges verified with platelet levels in citrate, at discharge from intensive care with platelet levels in normal ranges too (Table 2).

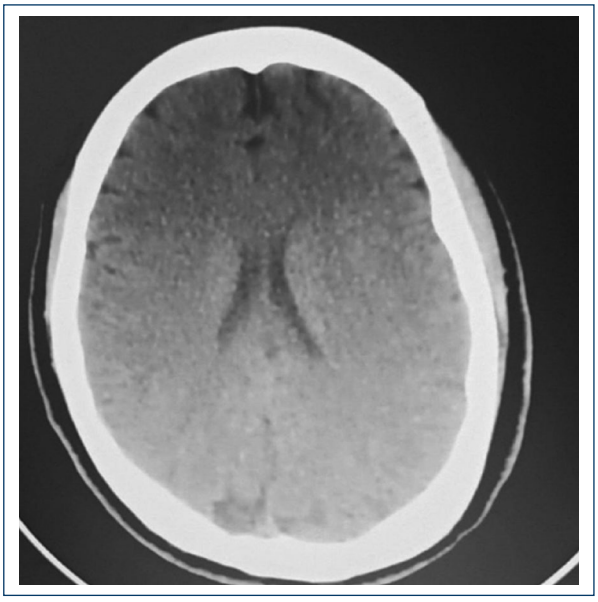

Figure 2. Cranial tomography on axial projection, hypodensity corresponding to the affected area is observed. *Source: Clinical record.*

Treatment received

Received enoxaparin at a therapeutic dose for 7 days and then prophylactically for 3 months, without any complications from treatment, diphenylhydantoin as anticonvulsant, modified Zuspan scheme (four grams in continuous infusion), and then 1 g/h 24 h, in neurocritical care measures for 48 h, including targets of temperature 36-37°C, hemoglobin > 8 g/dL, sodium levels 135-145 meq/L, systolic arterial blood pressure > 110 mmHg, PO2 80-100 mmHg, lung protective ventilation, ICP control optic nerve < 5.5 mm, IP ACM 0.6-1.2, intracerebral pressure < 22 mmHg, and no hypertonic saline solution was necessary.

Table 2. Blood test results.

Day	1	2	3	4	5	6	7	8
Ph (Acidity Index)	7.39	7.40	7.40	7.45	7.44	7.43	7.41	7.44
HCO^{3}- (mmoL/L)	19.1	17.9	17.9	21	21	19	19	20
PCO^{2} (mmHg)	31	28.6	28.6	27	26	26	27	25
PO^{2} (mmHg)	102	70	70	72	71	81	78	71
Base excess (mmoL/L)	-6	-7	-7	-4	-1	-1.5	-1	-0.5
Lactate (mmoL/L)	1.9	0.9	1	1	0.9	0.5	0.6	0.8
INR	0.82	0.94	0.91	1	1.1	1.08	1.05	1
PT (seconds)	10.4	11.8	11.5	12	12.5	12	12.5	12
PTT (seconds)	22.3	28.5	37.5	34	33	34	35	35
Hematocrit (%)	40	40.8	31.7	32	32	32	32.1	32.1
Platelets ($x10^{3}/mm^{3}$)	154	165	165	159	162	165	168	165
White blood cells ($x10^{3}/mm^{3}$)	9.0	15.4	8.5	8.9	7.9	7.9	8	8.1
Glucose (mg/dL)	81	103	84	88	85	92	90	79
Creatinine (mg/dL)	0.64	0.9	0.5	0.6	0.6	0.7	0.78	0.7
BUN (mg/dL)	11	13	9	11	11	10.5	11	12
Urea (mg/dL)	23.5	27.8	19.3	20	22	21	23	22
Total Bilirubin (mg/dL)	0.64	0.9	0.7	1	1.2	0.9	0.8	0.7
AST (UI/L)	118	166	60	65	59	61	60	58
ALT (UI/L)	117	181	99	98	81	88	85	90
LDH (UI/L)	356	424	264	270	220	250	255	245
Sodium (meq/L)	144	141	136	138	139	138	139	138
Potassium (meq/L)	4.39	4.18	4.3	4.2	4.1	4.2	4.1	4.1
Chlorine (meq/L)	113	113	107	106	105	105	104	104
Calcium (mg/dL)	8.4	8.2	8	8.1	8.2	8.3	8.5	8.2

HCO^{3}-: denotes Bicarbonate; PCO^{2} CO^{2}: partial pressure, PO^{2} O^{2}: partial pressure; INR: International Normalized Ratio; PT: prothrombin time; PTT: partial thromboplastin time; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.
Source: Clinical record.

Obstetric outcome

Delivery by cesarean section, with estimated bleeding of 1200 mL, surgical sterilization, product of gestation with 38 weeks calculated by Capurro 2190 g, masculine with Apgar 8/9, without neonatal neurological impact. Withdrawal of antihypertensives was achieved at 15 days of puerperium, neurological evaluation without any alteration at discharge and 28 days later when evaluated by neurology.

Four days of hospitalization in intensive care unit, 4 days in intermediate care room of obstetrics. The newborn was hospitalized for 2 days in intermediate care and subsequently discharged without complications.

Case number 3

General characterization

Nineteen years old, no chronic degenerative history, no previous symptoms, no prenatal medical care, unknown that she was pregnant, no history of hospitalization during pregnancy. No COVID vaccines, no prenatal care, unknown fetal growth, no intake of aspirin 81 mg. Height 1.47 meters, weight 55 kg at the end of pregnancy.

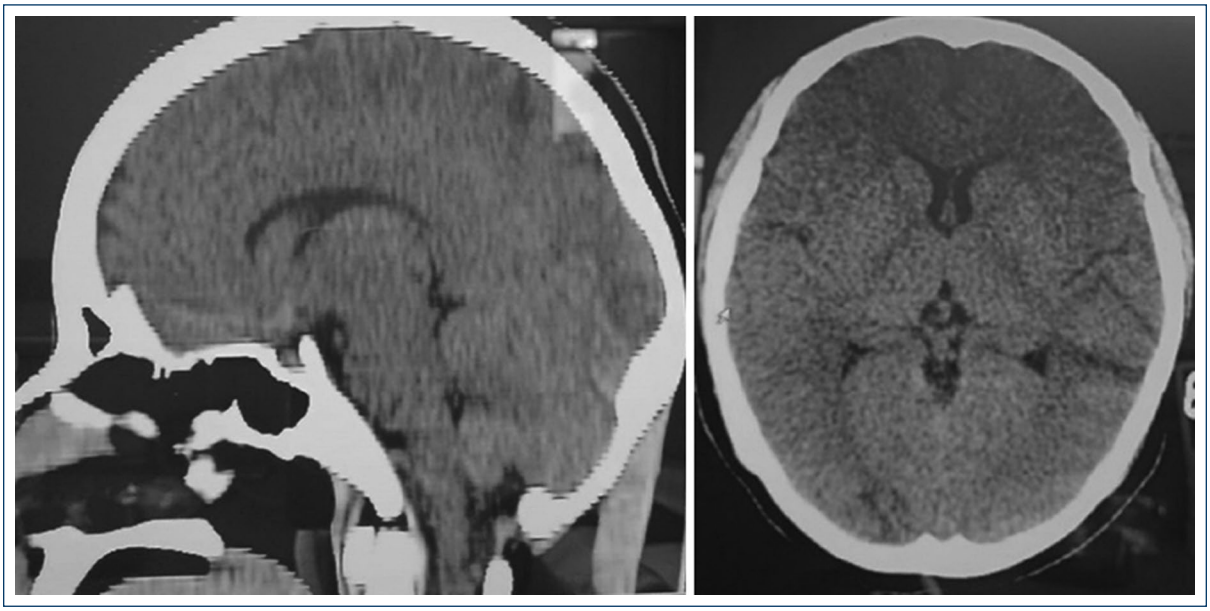

Figure 3. Cranial tomography on axial and sagittal projection hypodensity corresponding to the affected area is observed.
Source: Clinical record.

Summary of symptoms

Frontal and temporal headache of moderate-to-severe intensity of 24 h of evolution, associated with three episodes of convulsion, characterized by generalized, tonic and clonic movements, of approximately 2 min of duration without relaxation of sphincters witnessed by her brother, subsequent recovery of alertness with drowsiness immediately. Initially treated in a private health unit where pregnancy and possible eclampsia were diagnosed, nifedipine 30 mg and magnesium sulfate 4 g were administered and she was referred to this unit urgently.

Physical examination summary

Height 1.47 m, weight 50 kg at the beginning of pregnancy, body mass index 23.1 Kg/m^2, and body surface area 1.43 m^2.

Blood pressure on admission 171/120 mmHg, MAP 137 mmHg, heart rate 110 BPM, respiratory rate 21 CPM, treated with nifedipine 10 mg, 3 dosages, 1 h later 161/123 mmHg, MAP 135 mmHg, heart rate 110 BPM, then it was necessary to administer hydralazine 10 mg to reduce blood pressure to goals (reduction of blood pressure about 20% in the 1st h TAM about 100-110 mmHg), before cesarean delivery maintained blood pressure, but required nitroprusside infusion at doses of 0.5 mcg/kg/min for 12 h, then adjustment of antihypertensives with nebivolol 5 mg daily, nifedipine 30 mg twice a day. A month later no needed of antihypertensives.

Neurological findings

GCS 15 points: bilateral pupillary diameter 3 mm, brainstem reflexes and no cranial nerve alterations, unaltered motor sensitivity and response, and preserved mental functions. Grade III osteotendinous reflexes. She received neurocritical care on the recommendation of the neurology service, remained under deep sedation after cesarean section for 48 h, with ICP monitoring inferred by optic nerve sheaths diameter measurement ICP 10-12 mmHg, and subsequently emerged with delirium treated with haloperidol 5 mg every 6 h for 7 days without any other manifestation of neurological deterioration. Tomography: hypodensities in corticosubcortical areas in the biparietal region, as well as hypodense images of the superior longitudinal sinus, which makes the diagnosis of venous sinus thrombosis highly suggestive (Fig. 3).

Summary of clinical evolution

After stabilization in the shock room by history of seizure, then cesarean delivery was performed due to it. After surgery she remained in neurocritical care, deep sedation was maintained with propofol at 4 mg kg hour and midazolam 0.2 mg kg hour, achieving RASS –5 for

Table 3. Blood test results.

Day	1	2	3	4	5	6	7	8
Ph (Acidity Index)	7.36	7.41	7.39	7.44	7.45	7.39	7.48	7.48
HCO^{3}- (mmoL/L)	12	17.9	18.9	21.5	21.7	19.9	19.9	20.7
PCO^{2} (mmHg)	19	26	27	30	24	27.5	27.9	26.9
PO^{2} (mmHg)	102	95	90	82	80	79	70	74
Base excess (mmoL/L)	-9	-4	-7	-4	-1	-1.5	-1	-0.5
Lactate (mmoL/L)	2.1	0.9	1	1	1	0.4	0.3	0.3
INR	0.82	0.94	0.91	1	1.1	1.08	1.05	1
PT (seconds)	10.4	11.8	11.5	12	12.5	12	12.5	12
PTT (seconds)	22.3	28.5	37.5	34	33	34	35	35
Hematocrit (%)	40.4	40.8	31.7	32	32	32	32.1	32.1
Platelets ($x10^{3}/mm^{3}$)	69	70	92	90	110	120	118	125
White blood cells (x103/mm3)	13	16.4	13	12	12	8	8.5	9
Glucose (mg/dL)	97	95	90	98	99	97	99	78
Creatinine (mg/dL)	1.23	1	1	1	0.98	0.8	0.7	0.49
BUN (mg/dL)	19	21	22	21	18	12	11	12
Urea (mg/dL)	44	43	41	41	39	38	34	26
Total bilirubin (mg/dL)	0.84	1	0.8	0.7	0.8	0.7	0.4	0.21
AST (UI/L)	602	459	458	399	378	359	225	121
ALT (UI/L)	402	300	295	189	126	98	89	62
LDH (UI/L)	957	865	813	785	625	436	318	273
Sodium (meq/L)	138	141	144	144	143	144	142	143
Potassium (meq/L)	4.5	4.8	4.7	4.7	4.9	4	3.9	3.51
Chlorine (meq/L)	109	108	107	109	108	106	105	107
Calcium (mg/dL)	8.6	8.6	8.9	9	9.1	9.1	9	8.9

HCO^{3}-: denotes Bicarbonate; PCO^{2} CO^{2}: partial pressure; PO^{2} O^{2}: partial pressure; INR: International Normalized Ratio; PT: prothrombin time; PTT: partial thromboplastin time; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.
Source: Clinical record.

48 h, mechanical ventilation with pressure-controlled mode for 56 h; subsequently, mechanical ventilation progressed without criteria for ventilatory failure, required antihypertensive treatment based on sodium nitroprusside (dose of 0.1-0.5 gammas for 12 h), nifedipine 30 mg every 24 h, and nebivolol, maintaining MAP between 90- and 95 mmHg. Maintained uresis, urea, creatinine, and urea nitrogen in normal ranges did not present relevant metabolic nor electrolyte alterations. On admission to hospitalization, her platelet levels were in a normal ranges verified with platelet levels in citrate, at discharge from intensive care with platelet levels in normal ranges (Table 3).

Treatment received

Received enoxaparin at a therapeutic dose for 7 days and then prophylactically for 3 months, without any complications from treatment, modified Zuspan scheme (4 g in continuous infusion) and then 1 g/h 24 h, neurocritical care for 48 h, including targets of temperature 36-37°C, hemoglobin > 8 g/dL, sodium levels 135-145 meq/L, systolic arterial blood pressure > 110 mmHg,

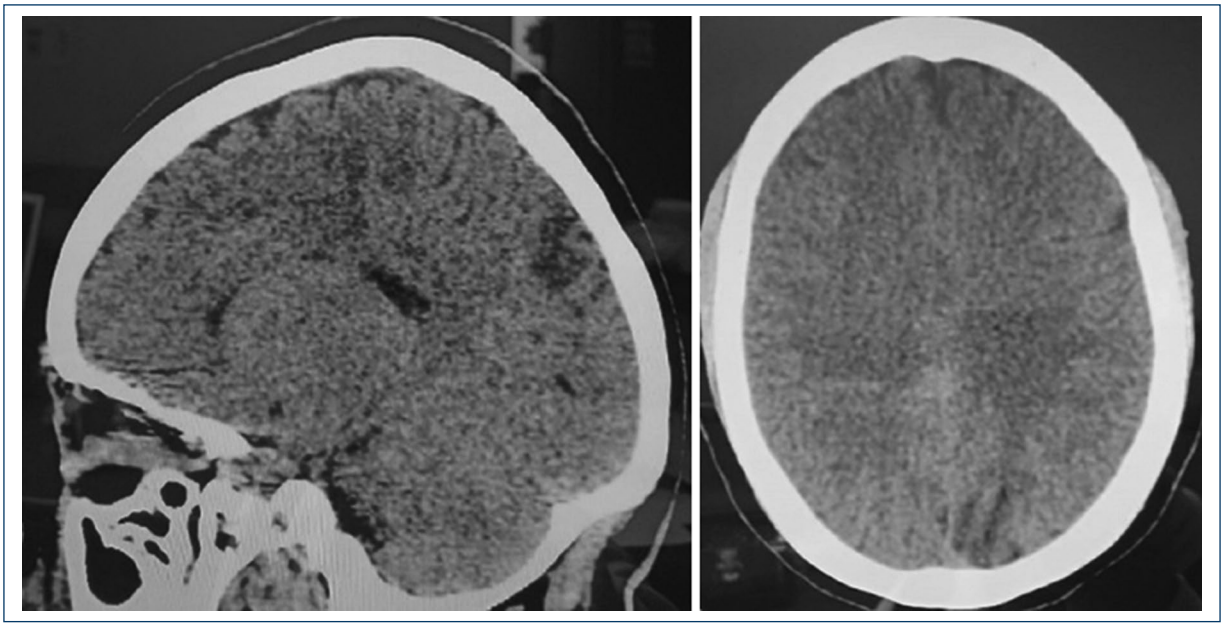

Figure 4. Cranial tomography on axial projection and sagittal hypodensity corresponding to the affected area is observed. *Source: Clinical record.*

PO2 80-100 mmHg, lung protective ventilation, optic nerve < 5.5 mm, IP ACM 0.6-1.2, intracerebral pressure < 22 mmHg, and no hypertonic saline solution was necessary, treated with haloperidol 5 mg every 6 h for 7 days for diagnose of delirium.

Obstetric outcome

Resolution of pregnancy by cesarean section, with estimated bleeding of 350 mL, surgical sterilization, product of gestation with 32 weeks calculated by Capurro, with Apgar 8/9, 1370 g, female, without maternal or neonatal neurological impact. Withdrawal of antihypertensives was achieved at 28 days of puerperium, neurological evaluation without any alteration at discharge and 28 days later when evaluated by neurology.

Five days of hospitalization in intensive care unit, 3 days in intermediate care room of obstetrics. The newborn was hospitalized for 15 days in intensive care neonatal unit by the diagnosis of neonatal sepsis, subsequently discharged without complications.

Case number 4

General characterization

Twenty-two years old, with no chronic personal or family history of degenerative. One previous pregnancy with vaginal delivery, no history of hospitalization during pregnancy. No COVID vaccines, eight prenatal care, with adequate fetal growth, no intake of aspirin 81 mg. Height 1.54 m, weight 60 kg at the beginning of pregnancy, 66 kg at the end of pregnancy.

Summary of symptoms

Frontal and temporal headache of moderate intensity of 36 h of evolution, associated with three episodes of seizures, characterized by generalized, tonic and clonic movements, of approximately 45-60 s duration without relaxation of sphincters witnessed by her mother, subsequent no total recovery of alertness with drowsiness, her parents took her to a first level hospital for initial care, in that health unit she presented a new episode of witnessed seizure with 1 min of generalized duration, tonic and clonic without relaxation of sphincters, 4 g of magnesium sulfate and 10 mg of diazepam were administered, she was referred to this care center by ambulance for care at the third hospital level.

Physical examination summary

Height 1.54 m, weight 60 kg at the beginning of pregnancy, body mass index 25.3 Kg/m^2, body surface area 1.6 m^2.

Blood pressure on admission 150/110 mmHg, MAP 126 mmHg, heart rate 110 BPM, respiratory rate 21

Table 4. Blood test results.

Day	1	2	3	4	5	6	7	8
Ph (Acidity Index)	7.32	7.35	7.41	7.42	7.43	7.44	7.45	7.47
HCO^{3}- (mmoL/L)	17	19	19	21	21	22	23	23.2
PCO^{2} (mmHg)	31	32	30	31	30	29	28	29
PO^{2} (mmHg)	102	95	90	95	79	79	74	69
Base excess (mmoL/L)	-10	-11	-9	-8.5	-7	-4.5	-3	-2.5
Lactate (mmoL/L)	1.9	0.9	1	1	1.1	1.1	1	0.9
INR	0.91	1	1.2	1	1.1	1.2	1.1	1
PT (seconds)	11.5	11.5	12	12	11.5	11.5	11.5	12.5
PTT (seconds)	22	23	23	22	23	23	22	22.9
Hematocrit (%)	42.3	40	39	40	39	38	36	35
Platelets ($x10^{3}/mm^{3}$)	107	110	110	118	125	151	154	230
White blood cells ($x10^{3}/mm^{3}$)	16.8	15	15	19	14	14.5	15	9.4
Glucose (mg/dL)	80	91	90	89	96	82	87	92
Creatinin (mg/dL)	0.67	0.7	0.69	0.66	0.9	0.7	0.65	0.51
BUN (mg/dL)	12	11	13	14	17	15	13	12
Urea (mg/dL)	25.7	29	28	31	31	29	24	25.7
Total Bilirrubin (mg/dL)	0.5	0.8	0.7	0.45	0.5	0.4	0.41	0.3
AST (UI/L)	85	80	78	76	74	53	41	35
ALT (UI/L)	49	44	41	43	42	41	39	44
LDH (UI/L)	423	325	335	495	329	291	300	290
Sodium (meq/L)	137	139	140	141	142	139	140	140
Potassium (meq/L)	3.79	3.9	3.8	3.9	4.1	4.1	4.2	4
Chlorine (meq/L)	110	109	109	108	108	107	108	110
Calcium (mg/dL)	8.4	8.6	8.5	8.7	8.6	8.5	8.8	8.8

HCO^{3}-: denotes Bicarbonate; PCO^{2} CO^{2}: partial pressure; PO^{2} O^{2}: partial pressure; INR: International Normalized Ratio; PT: prothrombin time; PTT: partial thromboplastin time; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.
Source: Clinical record.

CPM, treated with nifedipine 30 mg, levetiracetam 2 g initially then 1 g each 12 h, subsequently maintained blood pressure in target ranges MAP 100-105 mmHg, blood pressure on admission to Intensive Care Unit 134/81 mmHg, MAP 98 mmHg, heart rate 98 BPM requiring nifedipine (60 mg twice a day), and prazosina (2 mg each 6 horas) during hospitalization.

Neurological findings

GCS 12 points: bilateral pupillary diameter 2 mm, brainstem reflexes and no cranial nerve alterations, unaltered motor sensitivity and response, and altered mental functions. Grade III osteotendinous reflexes. She underwent neurocritical care on the recommendation of the neurology service, remained under deep sedation after cesarean section for 48 h, with ICP monitoring inferred by optic nerve sheaths diameter measurement ICP 10-12 mmHg, and subsequently emerged without data of delirium, without any manifestation of neurological deterioration. Tomography: Density changes compatible with thrombosis of the superior longitudinal sinus, without any other alteration at the intraparenchymal or ventricular level (Fig. 4).

Summary of clinical evolution

Treated in the shock room by history of symptoms suspected diagnose of eclampsia, on admission treated with magnesium sulfate and levetiracetam, then cesarean delivery was performed due to it. After cesarean procedure, she remained in neurocritical care, deep sedation was maintained with propofol at 4 mg/kg/h and midazolam 0.3 mg/kg/h, achieving RASS −5 for 48 h, mechanical ventilation with pressure-controlled mode for 56 h; subsequently, mechanical ventilation progressed without criteria for ventilatory failure, required antihypertensive treatment based on nifedipine 30 mg every 24 h, maintaining MAP between 90- and 95 mmHg. No alterations on uresis, urea, creatinine, and urea nitrogen in normal ranges did not present relevant electrolyte nor metabolic alterations. On admission to hospitalization, her platelet levels were in mild thrombocytopenia verified with platelet levels in citrate (Table 4), at discharge from intensive care with platelet levels in normal ranges too, received dexamethasone 8 mg each 12 h for 4 days.

Obstetric outcome

Completion of pregnancy by cesarean section, with estimated bleeding of 400 mL, product of gestation with 35 weeks calculated by Capurro, male, 1996 g, Apgar 8/9, without maternal or neonatal neurological impact. Withdrawal of antihypertensives was achieved at 21 days of puerperium, neurological evaluation without any alteration at discharge and 28 days later when evaluated by neurology.

Four days of hospitalization in intensive care unit, 4 days in intermediate care room of obstetrics. The newborn was hospitalized for 6 days in intermediate care and subsequently discharged without complications.

Discussion

CVT generally has a limited behavior since the veins of the cerebral system do not have valves and have an extensive system of venous anastomoses. The severity of clinical symptoms and neurological involvement depends on the area involved. In these clinical cases, the disease manifested with symptoms such as horizontal nystagmus, cephalea, and hyperreflexia. The affected venous territory was the left Trolard vein. The patient presented mild cerebral edema without intracranial hemorrhage. One of the most feared complications associated with cerebral edema is hemorrhage in the compromised venous system and the association with life-threatening endocranial hypertension. The most relevant obstetric risk factors are postpartum hemorrhage, preeclampsia, transfusion history, and puerperal infection, the latter being the most significant cause. The symptom reported in the clinical case was preeclampsia, which coincides with the literature reviewed. The treatment described in the different guidelines on venous thrombosis is mainly pharmacological and based on low-molecular-weight heparin, Warfarin, and direct-acting anticoagulants. There are descriptions of a series of cases in which thrombectomy was implemented. In this case, there was an adequate response when using enoxaparin at therapeutic doses, with clinical and imaging resolution of the event. CVT is still a significant diagnostic and therapeutic challenge, due to its high variability of clinical manifestations and its lack of a clear therapeutic consensus[1]. The most affected area in the reported cases was the longitudinal sinus with associated ischemic changes in the occipital region, similar to the cases reported in recent literature, approximately 6-7 of 10 cases[1-4]. The most frequent symptomatology was in relation to frontal and occipital headache of moderate to severe intensity in the four reported cases, similar to the previous case reports that have been reported in the international literature. It is worth mentioning that none of the patients presented data of intracranial hypertension and the highest value of ICP inferred was 16 mmHg; however, three of the cases presented seizures and in one of the cases anisocoria with mild cerebral edema by computed tomography, which suggests that obstetric patients may have less capacity for brain self-regulation. Pérez Lázaro et al. suggest “early, accurate diagnosis can reduce the rate and severity of complications,” Fortunately, in the reported cases, the associated symptoms were detected early[2]. A 28-day follow-up in patients of reported cases found no new evidence of thrombotic events or neurological symptoms, not similar to cases reported by Ferro et al., “patients had a moderate risk of further thrombotic events and seizures”[3].

The incidence, mortality, and disability from pregnancy-related-stroke are higher than previously reported as reported by James et al. where African-American women are at an increased risk, as are women aged 35 years and older[4], similar was found on male patients[5]. In our study, the cases were reported in young patients 30, 24, 22, and 19 years old and mestizo ethnics. In the cases reported, no one of patients developed intracranial hypertension as described by Ropper et al. “CVT is characterized by infarction with focal neurologic deficits and increased ICP,” the level of ICP on the reported cases

was between 10 and 16 mmHg, and only one case with associated cerebral edema[6]. Silvis et al. suggest variety of therapies for CVT, and each should be used in the appropriate setting, preferably guided by data from randomized trials and well-designed cohort studies[7]; however, obstetric patients are very particular due to physiologic conditions related to pregnancy and puerperium, in our experience, 7 days of therapeutic dosage of low molecular heparin is enough to avoid extension of damage related to cerebral thrombosis. The neurocritical care on minimizing injury is based on studies made in patients with traumatic brain injuries because there are no specific recommendations on obstetrics[8-12]. Therapeutic Goals created by Goddoy et al. and Taccone et al., such as the acronyms THE MANTLE and GHOST CAP were provided in the care of the patients reported in our case series.

No specific mechanism has been clearly described to explain how brain tissue damage occurs after CVT[13-18]. It is believed that tissue damage is related to the development of edema and venous congestion that compromises the supply of oxygen, so certain strategies for studying the lesion should be studied with adequate RCT.

Conclusion

CVT is a rarely suspected clinical entity during the puerperal period; however, the prothrombotic state per se of this condition predisposes to this type of thrombosis, as mentioned in this review, as well as at any other level. The clinical manifestations of CVT can be changeable, from a symptom as non-specific as cephalea to seizures and brain death. The appearance of new neurological symptoms in the puerperium should not be underestimated, particularly in patients with additional risk factors such as obesity, preeclampsia, or a history of other thrombotic episodes. Implementing the necessary diagnostic means to clarify the cause of a new-onset neurological clinical manifestation should not be delayed. First-line treatment, despite weak evidence and recommendations, should be initiated with low-molecular-weight heparins, which provided that there are no contraindications. In the obstetric patient, no benefits have been studied with other therapies such as direct anticoagulants or thrombectomy.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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CLINICAL CASES

Management of intracranial melanoma metastasis with radiosurgery: a case report and literature review

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Abstract

Malignant melanoma is a devastating disease with a 5-year survival rate of approximately 20%. At the time of diagnosis, approximately 4% of patients had metastatic disease and between 5% and 20% had brain metastases. Most patients with intracranial metastatic melanoma have been treated with holocranial radiotherapy. Stereotactic radiosurgery is non-inferior to holocranial radiotherapy and has the advantage of preserving cognitive functions. This manuscript aims to show a case report of multiple melanoma metastases treated with stereotactic radiosurgery.

Keywords: *Melanoma. Metastasis. Central nervous system. Radiosurgery.*

Introduction

Malignant melanoma is a devastating disease with a 5-year survival rate of approximately 20%. At the time of diagnosis, approximately 4% of patients course with metastatic disease, between 5% and 20% with brain metastases; the 5-year survival rate in these patients is usually less than 10%. In Colombia, for the year 2005, an approximate incidence of malignant melanoma was estimated at 13 cases per 10,000 habitants, this being the main cause of death due to dermatological diseases (40%), representing 1% of total deaths from cancer. Most patients with intracranial metastatic melanoma have been treated with holocranial radiotherapy. However, stereotactic radiosurgery is non-inferior to holocranial radiotherapy, with the advantage of preserving cognitive functions[1,2]. This manuscript is the case of a 68-year-old patient with multiple intracranial brain metastases and their combined management with surgery, radiosurgery, and immunotherapy.

Case report

A 68-year-old male with no significant history who presents with a 1 week of evolution characterized by holocranial headache, decreased strength of the left hemibody (3/5), and epileptic seizures of focal onset that are secondarily generalized is admitted through the emergency room to the central military hospital. Treatment is started with levetiracetam 1000 mg every 12 h. Computed axial tomography and cerebral magnetic resonance imaging studies were done, which showed 6 supra and infratentorial intracranial lesions of heterogeneous intensity with enhancement ring contrast (Fig. 1).

A stereotactic-guided resection of the right frontoparietal lesion was done. The pathology report documented melanoma metastasis with immunohistochemical markers HMB45-red, S 100 MELAN a, and Ki67 50%, with no BRAF mutation identified. Two months after the resection, he received a dose of immunotherapy with nivolumab without any adverse effects (Fig. 2).

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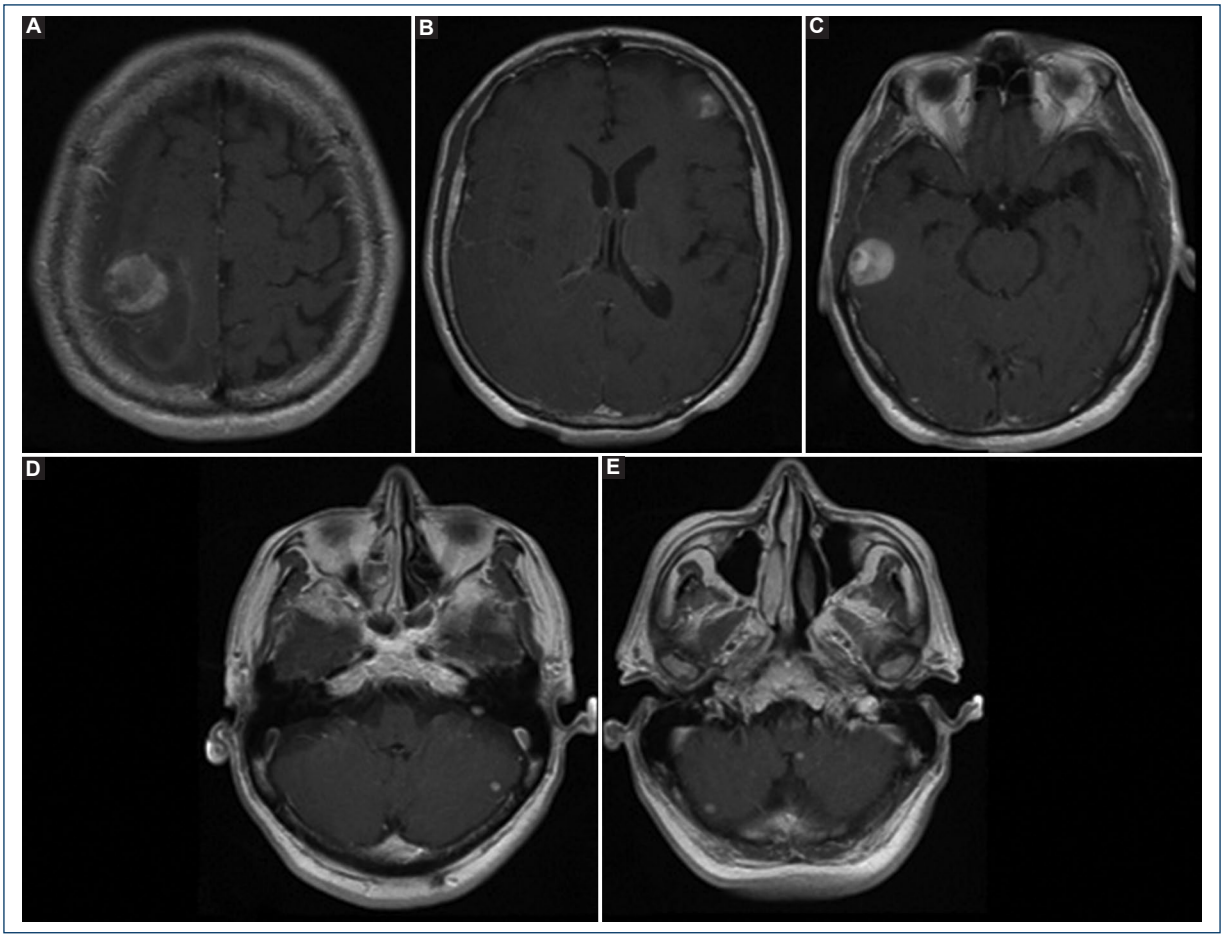

Figure 1. Pre-operative magnetic resonance imaging in the T1 sequence in the axial section **A:** right frontoparietal lesion of heterogeneous intensity with ring contrast enhancement. **B:** left frontal lesion. **C:** right temporal lesion. **D:** lesion in the left cerebellar hemisphere. **E:** lesion in the hemisphere right cerebellar and left cerebellar peduncle.

The patient is sent for an evaluation by dermatologists who perform a complete examination of the patient and continuous monitoring without finding the primary melanoma lesion.

Three months after the first intervention, the patient presented left hemiparesis again and seizures of focal onset that were secondarily generalized, so phenytoin 100 mg every 8 h was added to the treatment. Neuroimaging was performed again, identifying tumor recurrence of the right frontoparietal lesion and growth of the right temporal metastasis, which requires a second surgical procedure and subsequently fractionated radiosurgery with a linear accelerator treating 5 lesions at a dose of 18 GY using modulated volumetric arctherapy (Fig. 3).

In the 4-year follow-up, there is no evidence of disease progression, the epilepsy is controlled, and the size of the tumor lesions has remained stable. To date, the patient has completed 51 cycles of immunotherapy with nivolumab without complications (Figs. 4 and 5).

Discussion

Patients with solid tumors often present with metastases to the central nervous system; among the therapeutic options for the treatment of brain metastases are local strategies such as surgery, stereotactic radiosurgery, or holoencephalic radiotherapy to define what type of treatment is appropriate for each patient. It is necessary to individualize each case according to age, the number of intracranial metastases and extracranial metastatic involvement, the probability of survival, and the patient's functional status[3].

Malignant melanoma is a devastating disease; at the time of diagnosis, approximately 4% of patients present metastatic disease and between 5% and 20% present brain metastases with a 5-year survival rate of <10%. Recent developments in immunotherapy, stereotactic radiosurgery, and fractionated stereotactic radiotherapy have significantly improved the survival rate; the

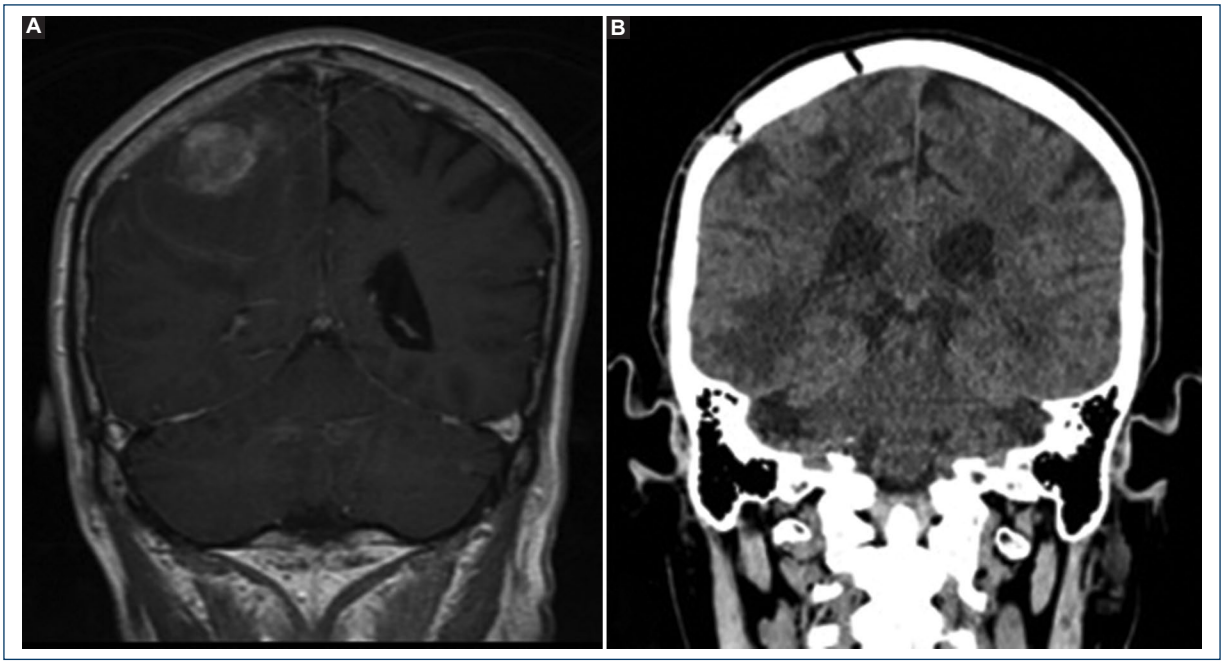

Figure 2. A: pre-operative magnetic resonance imaging in coronal section T1 sequence, right parietal lesion of heterogeneous intensity with ring contrast enhancement. **B:** simple computed axial tomography in coronal section, right parietal craniotomy, and total resection.

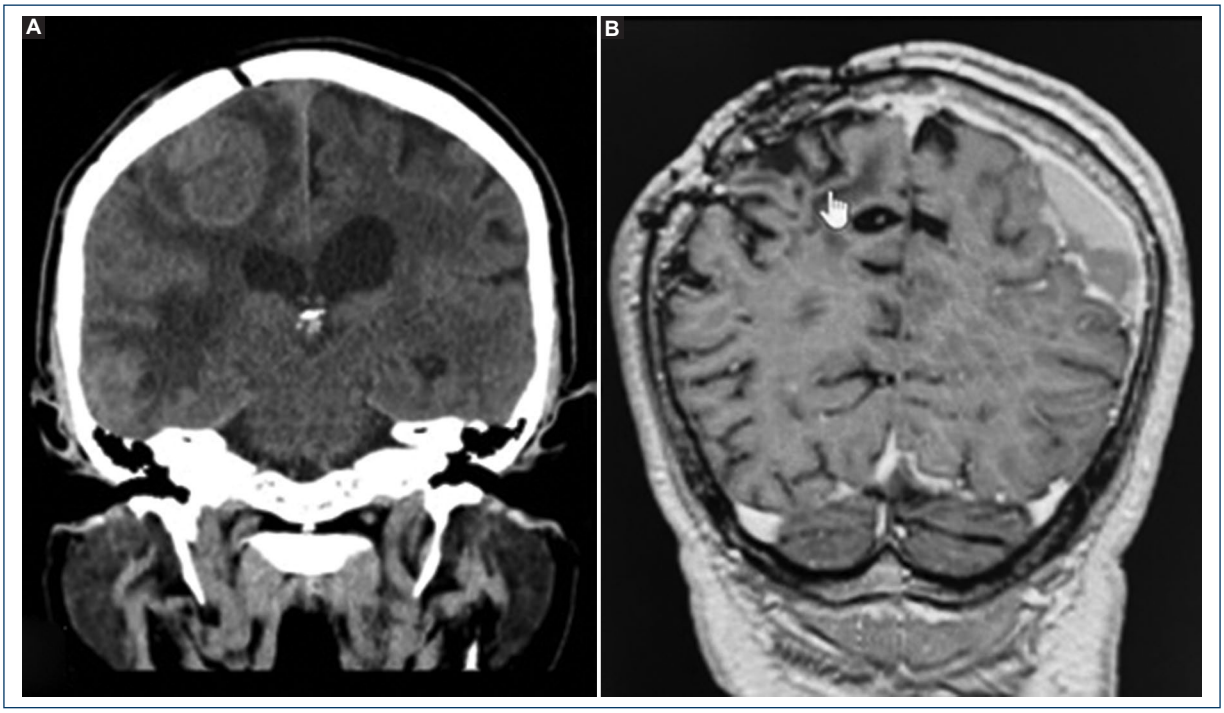

Figure 3. A: simple computed axial tomography in coronal section, tumor recurrence of right frontoparietal lesion, and perilesional vasogenic edema 3 months after intervention. **B:** post-operative magnetic nuclear resonance of the second intervention in the T1 sequence coronal section, total resection of the right frontoparietal lesion.

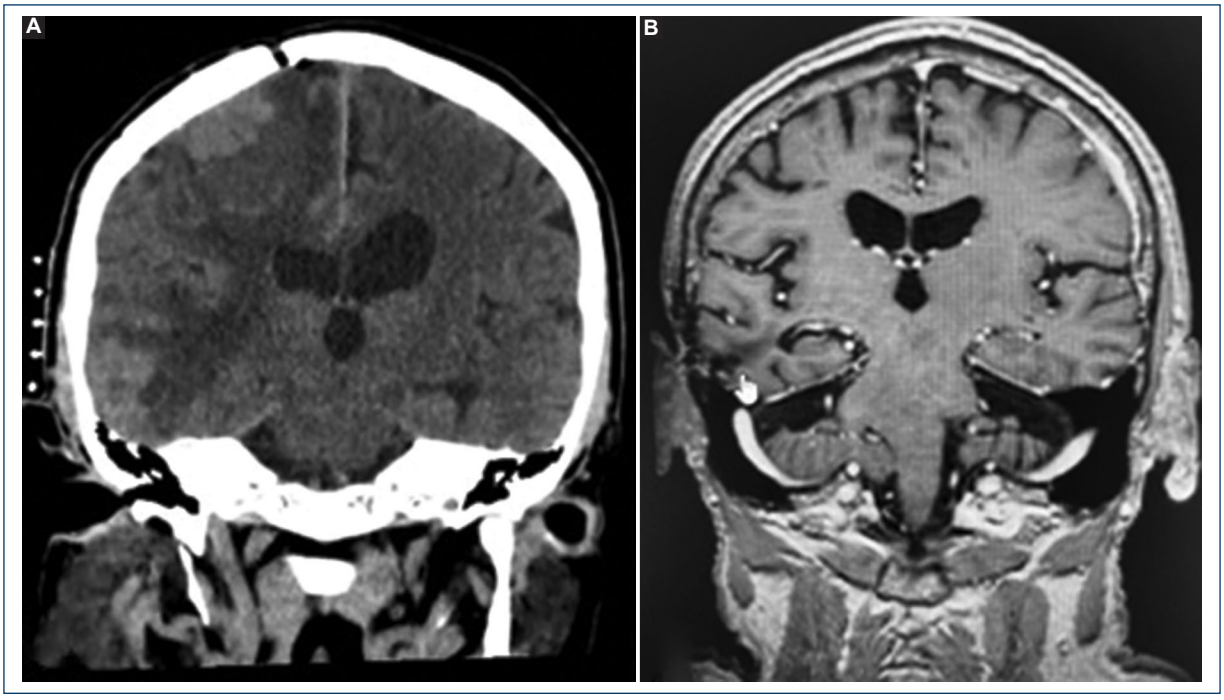

Figure 4. A: simple computed axial tomography in coronal section, right temporal lesion enlarged with perilesional edema. **B:** magnetic nuclear resonance in coronal section post-operative T1 sequence at the second surgical stage, total resection of the right temporal lesion.

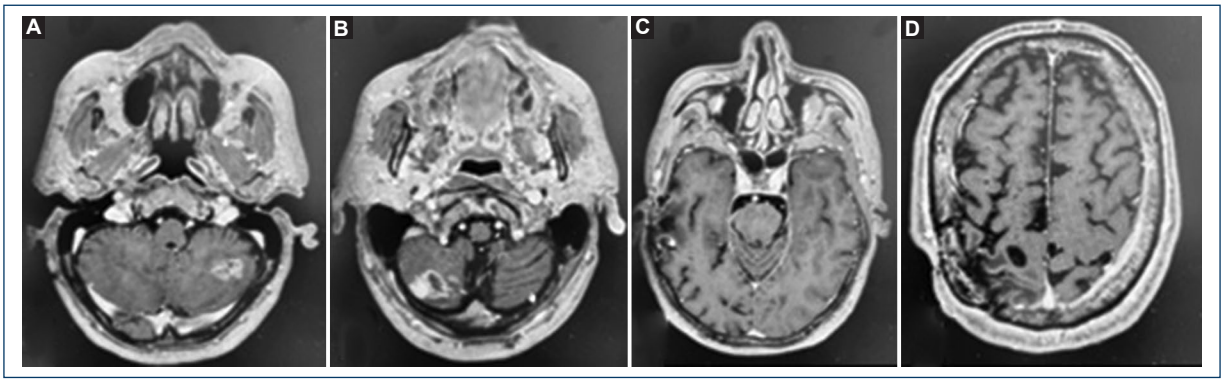

Figure 5. A: magnetic nuclear resonance in the axial section T1 sequence without evidence of the growth of the left cerebellar lesion at 4 years of follow-up. **B:** magnetic nuclear resonance in the axial section T1 sequence without evidence of growth of the right cerebellar lesion at 4 years of resection. **C:** magnetic nuclear resonance in the axial section T1 sequence, without evidence of tumor recurrence of the right temporal lesion at 4 years of follow-up. **D:** magnetic nuclear resonance in the axial section T1 sequence without evidence of the right frontoparietal lesion at 4 years of follow-up.

advantage of this type of therapy over holocranial radiotherapy is the preservation of cognitive functions. However, it has been shown that only 25% of patients have access to said combined therapy[4,5].

Brain metastases from malignant melanoma are classically considered radioresistant to conventional fractionated external radiation therapy and holocranial radiotherapy. However, during the last decade, stereotactic radiosurgery has become an effective treatment modality for selected patients (1-4 metastases that measure < 3-4 cm)[3].

Guidelines for the treatment of metastatic melanoma suggest combined therapy with stereotactic radiosurgery

and immunotherapy; this therapy significantly improves overall survival compared with radiosurgery alone or holocranial radiotherapy, with no difference in the rate of radionecrosis, even in patients with more than 4 intracranial metastases; in addition, immunotherapy has demonstrated a protective effect in terms of local control: Radiosurgery induces migration of T cells toward the tumor environment, and immunotherapy requires these cells to have a significant effect[5-7].

Conclusion

In the case presented, the adequate response and good tumor control achieved with multimodal management, including surgery, immunotherapy, and radiosurgery in a patient with multiple melanoma brain metastases are evident.

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CLINICAL CASES

Coexistence of neuromyelitis optica AQP4+, myasthenia gravis, and ulcerative colitis: a case report

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Abstract

Neuromyelitis optica (NMO), myasthenia gravis (MG), and ulcerative colitis (UC) are disorders in which various autoimmune pathophysiological mechanisms are involved, some of them being shared. According to the literature, these diseases are associated with other autoimmune disorders. However, there are no published cases about the coexistence of these three entities as a continuum of autoimmune manifestations. Here, we present the case of a patient who presented UC posteriorly, MG treated with thymectomy, and finally, met the criteria for NMO, treated with rituximab.

Keywords: *Neuromyelitis optica spectrum disorder. Myasthenia gravis. Ulcerative colitis. Thymectomy. Rituximab.*

Introduction

Neuromyelitis optica spectrum disorder (NMOSD), formerly known as Devic disease, is a rare demyelinating disease characterized mainly by optic neuritis and longitudinally extensive transverse myelitis, which has a clear association (about 90% of patients) with immunoglobulin (Ig) G type autoantibodies against the transmembrane channel aquaporin 4 (AQP4-IgG) of astrocytes[1]. Myasthenia gravis (MG) is a neuromuscular junction disorder clinically characterized by fatigue weakness, particularly of the eye muscles, eyelids, and limbs. There have been identified autoantibodies against the acetylcholine receptor (anti-AChR), autoantibodies against the muscle-specific tyrosine kinase receptor, or autoantibodies against the receptor of low-density lipoprotein-related protein 4[2]. MG may be associated with thymomas, a therapeutic target. Ulcerative colitis (UC), one of the two main types of inflammatory bowel disease (IBD), presents inflammation and ulcerations of the colonic mucosa starting in the rectum, with proximal extension, and manifested clinically with bloody diarrhea; its pathophysiology is multifactorial and mainly involves immunity due to neutrophils, T cells, and interleukins, without specific diagnostic antibodies, resulting in the need for biopsy[3].

Recognizing these diseases in an association is important for proper management and appropriate treatment since these may differ and even be contraindicated due to the coexistence of these disorders. In this case report, we present a patient who developed multiple autoimmune syndromes, defined as at least 3 autoimmune diseases, looking for a potential pathophysiological association with therapeutic implications to prevent long-term neurological and systemic disability.

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Case report

A 43-year-old hispanic man with no known medical history debuted in 2010 with a clinical presentation of 4 months of evolution characterized by hematochezia associated with high-intensity colicky abdominal pain and changes in intestinal habits, presenting mucous-bloody diarrhea, which became very frequent. In 2012, he underwent a colonoscopy where a biopsy was taken, demonstrating the presence of multiple ulcerative lesions consistent with UC. Treatment was started with mesalazine 500 mg every 24 h, with no relapses.

In 2017, he presented with neurological symptoms manifested by vertical binocular diplopia and left eyelid ptosis, so the diagnosis of MG with ocular muscle involvement was suspected, and a therapeutic trial with neostigmine was initiated, with a favorable response. One month later, he presented weakness in all four extremities, predominantly proximal, with exacerbation of weakness during physical exertion, preponderantly in the evening. Anti-AChR positivity was documented, and the repetitive stimulation test showed an electrodecrement > 10%. The patient was categorized in Group IIIb of the Osserman classification, and a quantitative myasthenia score of 24 points was calculated, for which treatment with steroids and oral immunosuppressants was initiated. Despite multiple relapses, a thymectomy and five sessions of therapeutic plasma exchange (PLEX) were performed, with clinical improvement in muscle strength and binocular vision.

In February 2023, the patient presented new neurological symptoms, characterized by paresthesias in the lower extremities, managing to identify a supraumbilical sensory level. Later, paraparesis was added, with difficulty climbing stairs progressing until ambulation was limited, requiring bilateral support and sphincter involvement. The neurological examination revealed a transverse myelopathy syndrome with a sensory level in the T6 dermatome and the anatomical lesion being located in the T8 segment. He was hospitalized for diagnostic and therapeutic treatment. A lumbar puncture was performed, showing inflammatory characteristics (leukocytes 3 cells/μL and microproteins 59 mg/dL), and viral serology (including herpes simplex viruses 1 and 2 [HSV-1, HSV-2], cytomegalovirus [CMV], Epstein–Barr virus [EBV], and human immunodeficiency virus) with negative results, amplifying with polymerase chain reaction (PCR) determination, also negative, for HSV 1, HSV 2, CMV, EBV, human herpesvirus type 7 and 8, varicella-zoster virus (VZV), enterovirus, *Toxoplasma gondii*, human parvovirus B19, hepatitis C virus, lymphocytic choriomeningitis virus, and rubella virus. AQP4-IgG was determined by indirect immunofluorescence technique in a cell-based study and reported positive. Magnetic resonance imaging of the spinal cord was performed with T2-weighted images with fat suppression showing a hyperintense lesion with irregular edges in the T7 and T8 segments, which reinforced after applying gadolinium-based contrast medium, being compatible with longitudinal transverse myelitis of the short segment (Fig. 1).

The diagnosis of NMOSD was established. The patient received three pulses of methylprednisolone with improvement in symptoms and subsequently received disease-modifying treatment with rituximab, with no relapses until January 2024.

Discussion

The association between NMOSD, MG, and UC has not been identified in the literature so far. However, it has been reported that a potential association between NMOSD and other autoimmune diseases in an isolated manner since 20-30% of patients with NMOSD may present immunological disorders isolated to one organ, such as thyroid disease, MG, thrombotic thrombocytopenic purpura, pernicious anemia, IBD, or systemic, such as systemic lupus erythematosus and Sjögren syndrome[4].

NMOSD and MG

In general, both diseases can be considered as autoimmune channelopathies whose pathophysiology is based on processes mediated by B cells, with the production of autoantibodies and mediation by Th-2 lymphocyted[5,6]. A prevalence of 2-3% of both diseases has been reported[7] and an association of 50 cases since 1995[5]. It has been postulated that, in addition to being expressed in astrocytes, AQP[4] can be found in the neuromuscular junction so that it could be a common target in case of autoimmunity and that it can even be expressed in the thymocytes of patients with MG and thymoma[8] or thymomas without MG[9]. Likewise, defects in autoimmune regulation or induction of tolerance and survival of autoreactive T cells have been documented. MG usually precedes NMOSD, with an early onset, appearing before age 50[10] with an unusually mild clinical course[11].

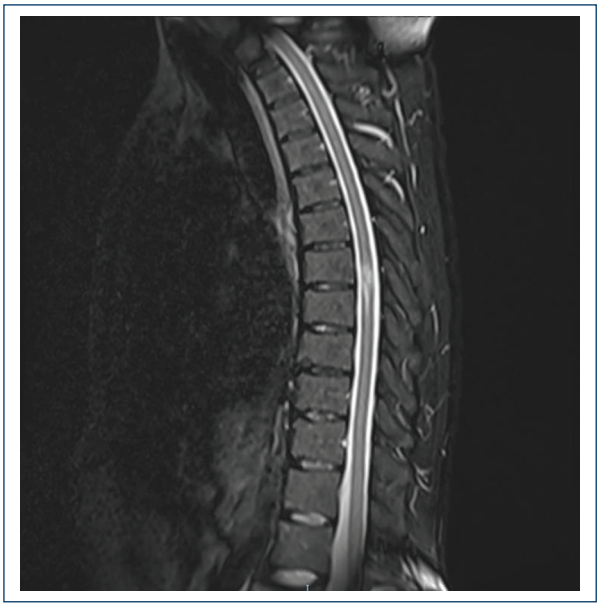

Figure 1. Magnetic resonance imaging in T2-weighted sagittal projection with fat suppression with evidence of central medullary hyperintensity of irregular borders in T7 and T8 segments compatible with short-segment longitudinal myelitis secondary to aquaporin 4+neuromyelitis optica spectrum disorder.

Thymectomy as part of the treatment of MG is one of the factors that promote the development of NMOSD since its symptoms appear after the surgical procedure[5], and this may be due to depletion of regulatory cells and self-tolerance, which is also considered a risk factor for the appearance of other autoimmune diseases[12]. The persistence of pathological peripheral T cells has been demonstrated many years after thymectomy[10]. However, in patients with thymomas, the organ predisposes to producing specific autoantibodies against targets in the central nervous system (CNS), such as AQP4 channels[8]. Hence, the coexistence of both disorders is viable before thymectomy, as has been reported in the literature[13,14]. Likewise, anti-AChR can occur in patients with NMOSD without developing neuromuscular symptoms[4]. Associations between MG and other CNS autoimmune disorders have been documented elsewhere[10].

NMOSD and UC

NMOSD and UC are rare by themselves, and the prevalence of their association is 2.6%[15]. Isolated optic neuritis can be an extraintestinal manifestation of UC and has even been described as a complication of therapy with monoclonal antibodies against tumor necrosis factor alfa (anti-TNFa)[16]. An association between UC and other demyelinating diseases of the CNS, such as multiple sclerosis or acute disseminated encephalomyelitis, has also been documented[17]. Aquaporins are ubiquitous, and their location in the colon is vital for the homeostasis of water and the pathophysiology of UC since the involvement of these channels during the inflammatory process explains the diarrhea in these patients. 15 Interestingly, it has been shown that the disruption of the gut mucosal barrier and dysbiosis could be involved in the appearance of NMOSD[18].

The Gram-negative bacillus *Enterocloster bolteae* (previously within the genus *Clostridium*) is implicated in the dysbiosis of IBD, although mainly involved in Crohn's disease[19]. It is noteworthy that *E. bolteae* has been identified in stool samples from patients with NMOSD, there being a correlation between this bacteria and the levels of inflammatory genes useful for the differentiation of plasma cells, B cell chemotaxis, among other functions[20].

The use of anti-TNFa for the treatment of IBD can unmask underlying aberrant autoimmune responses, with subsequent appearance of inflammatory events in the CNS, and its use is contraindicated in patients with an overt demyelinating disorder[17].

MG and UC

As described above, the pathophysiological basis of both disorders is immunological. Although inflammation is mediated mainly by cells and interleukins in UC, and there are autoantibodies, these are not as specific as in MG. However, it has been shown that they play a role in the onset and duration of the disease, inducing colon inflammation and cytotoxicity[21]. Thymectomy produces good outcomes in the treatment of both disorders[22,23], as stated by Sanghi and Bremner in the case of a woman with UC, MG, and other symptoms associated with a thymoma[24].

Treatment

The treatment of these coexisting conditions is complex. In the NMOSD-MG association, methylprednisolone has been used in acute attacks, PLEX, and intravenous IgG. In these cases, azathioprine is considered first-line therapy as a long-term immunosuppressive treatment combined with steroids in the first 6 months. Methotrexate and mycophenolate mofetil should be considered as second-line treatments[6].

In UC, tacrolimus, a calcineurin inhibitor, has been used as an immunosuppressive treatment[3]. This drug has been proposed for the treatment of NMOSD, initially by Tanaka et al. in 2015[25]. In a retrospective study with 25 patients with NMOSD with positivity for AQP4-IgG made in 2017, where tacrolimus was compared with azathioprine, a significant reduction in the relapse rate was demonstrated (72% vs. 48% p = 0.1 respectively), as well as in the Expanded Disability Status Scale (EDSS) (96% vs. 62%, p = 0.003, respectively). Tacrolimus was well tolerated. However, the study had limitations due to its small sample size, as well as its short follow-up period, which was 5 years[26]. The drug was evaluated again in 2019 in patients with NMOSD with and without positivity for AQP4-IgG (n = 42 vs. 8, respectively) in another retrospective study, using tacrolimus for at least 1 year, where a reduction in the relapse rate of 92% ($p < 0.001$) was documented for the seropositive group and 86% ($p < 0.05$) for the seronegative group. The EDSS also decreased significantly for both groups, although with a greater impact in seropositive patients[27]. These findings theoretically support the use of tacrolimus in the coexistence of NMOSD and UC; however, no randomized controlled trials could justify its use in clinical practice.

Treatment of the coexistence of MG and UC is similar to their isolated forms. It may require surgical treatment in severe cases of UC, and immunosuppressants, such as azathioprine, have been used in case report[22]. As mentioned in the previous section, thymectomy is useful in treating the association of MG and UC. Biological therapies targeting B cells are widely used to treat multiple autoimmune diseases, including the three presented in this paper. In a 2019 systematic review and meta-analysis, Kaegi et al. demonstrated the safety and efficacy of rituximab in treating CNS demyelinating disorders, MG, and IBD[28]. Rituximab was used in the patient presented in this case report. This drug was chosen based on its effectiveness in treating these three conditions in their isolated presentations.

Conclusions

No reported cases in the literature on the presence of these three diseases cojoined, although the coexistence of NMOSD, MG, and UC in isolation is not negligible. Different pathophysiological mechanisms have been proposed, including the hypothesis of intestinal dysbiosis. However, they remain unknown. These immunological associations can be a therapeutic challenge. Inflammatory mediation by B cells is vital for using anti-CD20 monoclonal antibodies for the long-term control of these autoimmune disorders. We considered that rituximab and other anti-CD20 could be an alternative for immunosuppressive treatment in isolated or grouped coexistence of these diseases. However, their justification through randomized controlled trials will be difficult due to the rarity of this finding. Therefore, it will be important to monitor this group of patients closely. The feasibility of the coexistence of three autoimmune disorders, two of them being neurological, clearly justifies long-term follow-up and surveillance to avoid relapses and accumulated disability.

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