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Aims and Scope

Journal of Neurocritical Care (JNC) aims to improve the quality of diagnoses and management of neurocritically ill patients by sharing practical knowledge and professional experience with our reader. Although JNC publishes papers on a variety of neurological disorders, it focuses on cerebrovascular diseases, epileptic seizures and status epilepticus, infectious and inflammatory diseases of the nervous system, neuromuscular diseases, and neurotrauma. We are also interested in research on neurological manifestations of general medical illnesses as well as general critical care of neurological diseases.

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Editorial Board

Journal of Neurocritical Care

Contents

Journal of Neurocritical Care

Vol. 14, No. 1, June 2021

REVIEW ARTICLE

ORIGINAL ARTICLE

CASE REPORT

IMAGES IN NEUROCRITICAL CARE

eISSN 2508-1349
J Neurocrit Care 2021;14(1):1-7
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Journal of Neurocritical Care

Role of continuous hypertonic saline in acute ischemic infarcts: a systematic literature review

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REVIEW ARTICLE

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Continuous hypertonic saline for hemispheric ischemic infarcts has been routinely used in neurocritical centers for the management of malignant cerebral edema. However, the data supporting its use are extremely limited. We present a systematic literature review that highlights five studies (one randomized control trial and four retrospective cohort) where the effects of continuous hypertonic saline were studied in patients with acute ischemic infarcts. Collectively, there is a lack of substantial evidence supporting its use. Also, this review emphasizes significant study flaws that make the conclusions largely nongeneralizable. Although the reported studies demonstrate improvement in control of intracranial pressure, there are no significant differences in neurological or functional outcomes or overall mortality.

Keywords: Brain edema; Saline solution, hypertonic; Ischemic strokes; Mortality; Critical care outcomes

INTRODUCTION

Malignant cerebral edema is a general term that describes pathologic swelling of the brain parenchyma and can be the result of influx of fluid into the extravascular space. In the setting of acute ischemic infarcts, cytotoxic edema results from cellular death and resultant intracellular influx of water. Although this is thought to be the mechanism of early cerebral edema in ischemic infarcts, later stages likely involve a loss of the integrity of the blood-brain barrier as well [1,2]. Cerebral edema is directly correlated with increased intracranial pressure (ICP) and has been determined to be an independent marker of poor outcomes in patients with stroke [3]. Malignant middle cerebral artery (MCA) syndrome refers to severe cerebral edema and subsequent neurologic decline that occurs as a result of a large MCA territory infarct.

There are several mechanisms by which hypertonic therapy has been postulated to decrease cerebral edema and subsequently ICP. Increasing osmolality in the intravascular space produces an osmotic gradient and draws fluid out of the extravascular spaces; by decreasing the viscosity in the intravascular space, there is a reflexive vasoconstriction that reduces cerebral blood flow. However, these mechanisms may only decrease ICP transiently [2]. Also,

the eventual loss of autoregulation that occurs in ischemic infarcts means loss of the blood brain barrier and resultant efflux of the hyperosmolar contents, which could theoretically increase cerebral edema [1].

The role of continuous hypertonic saline infusion for control of malignant cerebral edema is controversial. Despite its widespread use in clinical practice, the data supporting its use over intermittent boluses dosing are limited. Although continuous infusion of hypertonic saline has been effective in reducing cerebral edema in animals, limited data was found in humans [4-7]. In this systematic literature review, we present the current data on the use of continuous hypertonic saline. Our objectives were to determine the mortality and neurological outcomes when continuous hypertonic saline is used in the management of malignant cerebral edema secondary to acute ischemic infarcts and to determine the rates of systemic complications, hospital length of stay, and functional outcomes in patients in whom continuous hypertonic saline was used.

METHODOLOGY

A systematic literature review of the use of continuous hypertonic saline in the setting of malignant cerebral edema secondary to acute ischemic infarcts was performed in accordance with guidelines for the preferred reporting items for systematic review and meta-analysis (PRISMA) [8]. A search strategy using controlled vocabulary, in combination with keywords, pertaining to administration of hypertonic saline in acute ischemic infarcts was performed by a health science librarian via the following electronic databases: Medline via PubMed, Ovid, Embase via Embase.com, the Cochrane Library (Wiley interface, current issue), Web of Science/Knowledge via Clarivate Analytics, ClinicalTrials.gov, and Scopus. The search was limited to English language literature. The references of the searched literature were utilized to expand the search and include all grey literature.

Data Management was conducted through Rayyan online services [9]. Abstracts obtained under previously described platforms were reviewed independently by the following authors for relevance: AJSC, MM, and KS. The eligible studies were then independently reviewed in full to determine adherence to inclusion and exclusion criteria by these same authors. Nonduplicated studies were then reviewed by AJSC for appropriateness. AJSC and MM then utilized the Newcastle-Ottawa Assessment of Quality for evaluation of the quality of the included studies.

Inclusion criteria were the following: randomized controlled trials, prospective and retrospective cohort studies, and database studies in English language; Adult patients ≥ 18 years old with acute ischemic infarcts (including anterior and posterior circulation) in whom hypertonic saline was administered. Exclusion criteria were the following: reviews, meta-analysis, animal studies, studies involving pediatric patients (< 18 years of age), traumatic brain injury studies, and non-English language studies.

The initial intended primary outcome was mortality rate (overall and/or neurological death defined by death secondary to brain herniation, refractory elevated ICP, or direct involvement of vital neurologic structures) among patients that received hypertonic saline as means of reducing cerebral edema. Secondary outcomes were the following: (1) neurological outcomes (Glasgow Outcome Scale) among patients that received continuous hypertonic saline, (2) rates of adverse events (i.e., congestive heart failure, pulmonary edema, and acute kidney injury), (3) hospital and intensive care unit length of stay, and (4) functional outcomes (modified Rankin Scale).

RESULTS

Eight hundred ninety-nine records were initially identified. After initial screening, 154 abstracts were reviewed. After further application of exclusion criteria, 14 full-length articles were reviewed. However, of these studies, only five involved continuous administration of hypertonic saline and were thus included for data synthesis (Fig. 1, Table 1) [10-14]. The overall quality of the studies as determined by the Newcastle-Ottawa scale ranged from fair to good, and most were limited by follow-up length and comparability of the study groups (Table 2) [10-14].

In 1998, Qureshi et al. [10] conducted a single-center retrospective review of 27 patients with cerebral edema, six of whom

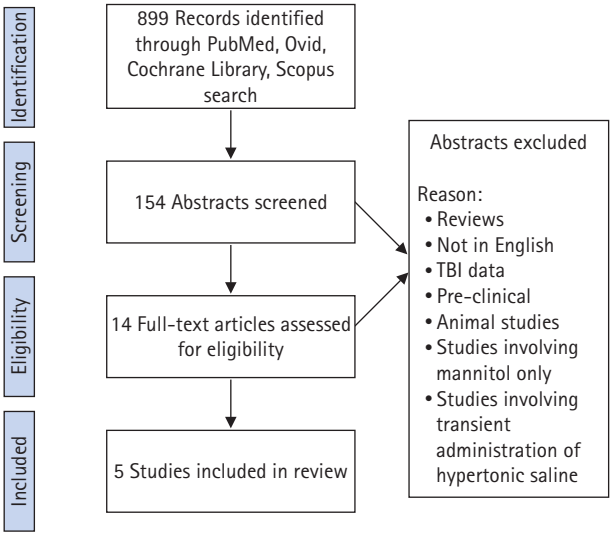

Fig. 1. Study flowchart. TBI, traumatic brain injury.

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Table 1. Studies that utilized continuous hypertonic saline in ischemic strokes

Study	Sample size	Study design	Intervention	Control/ comparative group	Neurologic outcome	Mortality	Adverse event	Length of ICU and hospital stay	Functional outcome	Level of evidence
Qureshi et al. (1998) [10]	27 Overall (6 ischemic strokes)	R	3% NaCl/infusion with goal Na 145–155 mEq/L	None	Trend towards to ICP reduction in intervention group; no ICP reduction or radiographic changes with serum Na^+; no changes in neurological outcomes	Not reported	Not reported	Not reported	Mean GCS score improved in treatment group in all etiologies except cerebral infarction, where it worsened	Level 4
Larive et al. (2004) [11]	19 Overall (2 ischemic strokes)	R	2% or 3% NaCl infusion with goal Na 145–155 mEq/L	Mannitol	Direct association between serum sodium concentrations and GCS score in first 8 days of hypertonic infusion	Not reported	No significant differences in rates of adverse events	Not reported	Not reported	Level 3
Harutjunyan et al. (2005) [13]	40 Overall (8 ischemic strokes)	RCT	7.2% NaCl/ HES 200/0.5 continuous infusion (n=17)	15% Mannitol continuous infusion (n=15)	Hypertonic saline with faster and greater reduction in ICPs for a longer duration; no significant differences in mortality among two groups	No significant difference in mortality	No significant difference in rates of adverse events	Not reported	Not reported	Level 2
Hauer et al. (2011) [12]	215 Overall (57 ischemic strokes)	R	3% NaCl infusion with goal Na 145–155 mEq/L (n=28)	Historical cohort not receiving 3% NaCl (n=29)	Fewer episodes of elevated ICP crises, no changes in neurological outcomes	In-hospital mortality decreased (17.0% vs. 29.6%, P=0.037)	No significant differences in rates of adverse events	Not reported	Not reported	Level 3
Erdman et al. (2017) [14]	337 Overall (113 ischemic strokes)	R	3% NaCl	None	Neurologic outcomes not reported	Increased mortality in AKI group (P≤0.001)	16% Developed AKI	Increased length of stay in AKI group (P=0.05)	No significant difference in functional outcomes defined by discharge status	Level 4

ICU, intensive care unit; R, retrospective; ICP, intracranial pressure; GCS, Glasgow Coma Scale; RCT, Randomized control trial; HES, hydroxyethyl starch; AKI, acute kidney injury.

Table 2. Newcastle-Ottawa Scale for quality assessment

Study	Selection				Comparability		Outcome			Total
	REC	SNEC	AE	DO	SC	AF	AO	FU	AFU	
Qureshi et al. (1998) [10]	○	×	○	○	○	×	○	×	×	5 (Fair)
Hauer et al. (2011) [12]	○	○	○	○	○	×	○	×	×	6 (Fair)
Larive et al. (2004) [11]	○	×	○	○	○	×	○	×	×	5 (Fair)
Erdman et al. (2017) [14]	○	×	○	○	×	×	○	×	×	4 (Fair)
Harutjunyan et al. (2005) [13]	○	○	○	○	○	○	○	×	×	7 (Good)

○, the study satisfied an item; ×, the study did not satisfy an item. Quality conversion: good quality (7–9), fair quality (4–6), poor quality (0–3).
REC, representativeness of the exposed cohort; SNEC, selection of the nonexposed cohort; AE, ascertainment of exposure; DO, demonstration that outcome of interest was not present at start of study; SC, study controls for hypertonic saline solution; AF, study controls for any additional factor; AO, assessment of outcome; FU, follow-up long enough for outcomes to occur; AFU, adequacy of follow-up cohorts.

had ischemic stroke. They investigated the effect of continuous hypertonic saline on ICP and lateral displacement in cerebral edema. Three percent hypertonic saline was infused with a target serum sodium concentration of 145–155 mmol/L, with therapy continuing until patients showed improvement, complications, or lack of response. A significant correlation was observed between ICP reduction and increasing serum sodium concentration in patients with head trauma and postoperative edema but not in patients with ischemic strokes. In addition, there was no reduction in radiographic cerebral edema within 72 hours of starting the infusion. The authors proposed that low mean baseline ICP and predominance of cytotoxic edema (as opposed to primarily vasogenic edema seen in head trauma) as possible contributing factors to lack of response seen in ischemic stroke patients. Limitations of this study include the lack of a control group and small sample size [10].

In 2004, Larive et al. [11] studied 19 consecutive patients who were treated with 2% or 3% hypertonic saline—two of them with ischemic strokes. The primary objective was to assess the efficiency and time required to achieve a target serum sodium concentration of 145–155 mEq/L. The secondary objective of the study was to assess the safety of hypertonic saline infusion measured by adverse effects including development of phlebitis, pneumonia, adult respiratory distress syndrome, bacteremia, sepsis, seizures, acute renal failure, arrhythmias, electrolyte disturbances, acid base disturbance, anemia, and coagulopathy. Adverse effects from the hypertonic saline cohort were compared to a mannitol cohort; however, no statistical significance between the adverse effects of the two groups was shown. Hypernatremic state was achieved after a median of 1 day; however, in some instances, it took up to 5 days to reach target hypernatremia. A significant direct association ($r=0.08$, $P=0.01$) was found between the serum sodium concentrations and the Glasgow Coma Scale (GCS) score of the cohort in the first 8 days of hypertonic saline therapy. In addition, the cohort was devoid of serious adverse effects related to the hypertonic saline infusion. However, these results were heavily confounded by other variables and do not show clinical significance in terms of sustained neurological improvement [12].

A 2005 prospective randomized clinical study from Harutjunyan et al. [13] investigated the differential effects of efficacy and safety of 7.2% hypertonic saline infusion (7.2% NaCl/HES) versus 15% mannitol for 40 patients at risk of increased ICP, eight of whom had ischemic infarcts. The 40 patients were randomized to receive either 7.2% NaCl/HES 200/0.5 or 15% mannitol at a defined infusion rate halted at ICPs below 15 mmHg. Primary outcomes for the study included ICP control in the respective groups. In the collective outcomes, both drugs held capabilities to lower ICP below 15 mmHg, although 7.2% hypertonic solution showed to be more effective than mannitol. In the subgroup analysis of patients with ischemic strokes, hypertonic saline led to a faster and longer reduction in ICP compared to mannitol. However, there was no difference in mortality. Data on neurologic outcomes was not provided. The limits of the study include the absence of the rate of infusion and the non-inclusion of the targeted plasma sodium and serum osmolality levels [13].

In 2011, Hauer et al. [12] investigated the effects of continuous hypertonic saline infusion in 100 patients with a mixture of cerebrovascular diseases, including intracerebral hemorrhage, ischemic strokes, or aneurysmal subarachnoid hemorrhage. They compared patients receiving hyperosmolar therapy to a historical cohort of 115 with severe cerebrovascular disease that did not receive continuous hypertonic saline. Of these patients, 57 had ischemic infarcts. Their treatment protocol involved initiation of hypertonic saline within 72 hours of symptom onset, with adjustment of infusion rate until targets of 145–155 mEq/L and 310–320 mOsm/kg were reached for plasma sodium and serum osmolality, respectively. Primary outcomes included frequency of ICP crises and in-hospital mortality. Overall, they observed a trend of fewer ICP crises and a significant reduction in mortality in patients who received hypertonic saline compared to controls. How-

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ever, similar to the findings of Qureshi et al. [10], these improvements were not demonstrated in those with ischemic infracts. Though identical inclusion criteria were used to identify the historical control group, the control cohort was significantly older than those receiving hypertonic saline. Age is well-established independent factor in prognosis of acute stroke and may have contributed to the survival benefit in the cohort receiving hypertonic therapy. Further, this study involved a limited cohort of patients with ischemic stroke [11].

In 2017, Erdman et al. [14] conducted a two-center retrospective cohort review to assess predictors of acute kidney injury in 337 patients receiving hypertonic saline infusion for severe neurological injuries—113 with ischemic strokes. Acute kidney injury occurred in 16% of patients receiving hypertonic saline. In addition, by comparing those that developed an acute kidney injury with those that did not, the study found independent risk factors for developing acute kidney injury that included a history of chronic kidney disease ($P=0.007$), serum sodium >155 mmol/L ($P\leq0.001$), treatment with piperacillin/tazobactam ($P=0.002$), male gender ($P=0.002$), and African American race ($P=0.007$). Interestingly, multiple risk factors commonly thought to contribute to acute kidney injury were not identified as significant in this study including mannitol, diuretics, contrast media, and other antimicrobials. In addition, type of neurologic injury (acute ischemic stroke, intracerebral hemorrhage, traumatic brain injury, or other) was not an independent risk factor. The study also noted that, because sodium concentration was recorded as a categorical variable, they could not comment on the relationship between acute kidney injury and increases in sodium. In addition, the study noted that both institutions widely use hypertonic saline infusion in patients. Thus, there was no comparison to a cohort with comparable cerebral edema that was not given hypertonic saline infusion [14].

Among the five studies, a total of 186 ischemic stroke patients were studied. In studies that involved a control group, a total of 33 patients did not receive continuous hypertonic saline. Those that received hypertonic saline were found to have fewer episodes of elevated ICP and faster and greater reduction in ICP. However, there were no significant overall differences in neurological outcomes, with some contrasting data on short-term GCS. Qureshi et al. [10] found that mean GCS worsened in ischemic stroke patients given hypertonic saline (n=6), while Larive et al. [11] found a direct association between serum sodium concentrations and GCS in the first 8 days of hypertonic saline infusion (n=2). The results of Larive et al. [11] may be confounded by the fact that only 2 of 19 patients in their study had ischemic strokes so GCS improvement may not be entirely applicable to this patient population. There were no significant differences in adverse events in those studies that reported this data (Table 1).

In regards to mortality, only Hauer et al. [12] found decreased mortality with use of hypertonic saline (n=28) by 12.6% ($P=0.037$) when compared to control group (n=29 ischemic). Although Erdman et al. [14] found an increased mortality ($P=0.001$) in those that developed an acute kidney injury (16%), patients with ischemic strokes (n=113) were not at a higher risk for developing acute kidney injury. Erdman et al.'s study [14] was also the only study to report on length of stay and functional outcomes. They found an increase in length of stay with those that developed acute kidney injury but no overall difference in functional outcomes at discharge.

DISCUSSION

Malignant cerebral edema continues to be a prominent contributing factor to morbidity and mortality in ischemic stroke patients. Use of hypertonic therapy has been employed for decades for the reduction in cerebral edema and ICP. Although transient uses of this therapy have demonstrated reduction in ICP, no studies have demonstrated sustained reduction in cerebral edema or improvement in neurological outcomes.

Several studies have examined the effects in animal models with conflicting results. Toung et al. [4] demonstrated improvement in global cerebral edema with continuous hypertonic saline in rat models treated after MCA infarctions. Similarly, Zeng et al. [5] found that hypertonic saline was effective in reducing cerebral edema as compared to mannitol in rat models. However, Bhardwaj et al. [6] reported that hypernatremia worsened cortical infarct volume following transient focal cerebral ischemia in rats. Similarly, Papangelou et al. [7] found no reduction in brain water content on the ipsilateral hemisphere of an induced MCA stroke in rats and with no change in infarct volume.

Continuous use, however, has been sparsely studied in humans. In a review of hemispheric stroke management in 2011, Kimberly and Sheth [15] recommended eunatremic goals with no indication for administration of prophylactic hypertonic saline. Furthermore, in a 2008 review of hypertonic saline for neurologic injury, Forsyth et al. [16] highlight the lack of information on the effect of hypertonic therapy for stroke patients. These authors [16] cite several animal studies that showed hypertonic saline having a negative impact on the stroke penumbra, but data in humans is limited.

Recently published guidelines by the neurocritical care society also highlight the general lack of evidence when it comes to use of hypertonic saline for management of cerebral edema in ischemic

strokes [17]. In addition, most studies involve comparison of mannitol versus hypertonic saline with primary outcomes being ICP control without effectively matched cohort groups. Most of these studies indicate that transient use of hypertonic saline leads to effective ICP control even in cases of mannitol failure [13,18]. However, use of continuous hypertonic saline has only been demonstrated in a limited number of prior studies. Our literature review has demonstrated only five studies that evaluated the role of continuous hypertonic saline—all of which failed to largely demonstrate sustained and prolonged reduction in ICP and did not appear to improve overall mortality or neurological outcomes (Table 1).

Collectively, these previous studies fail to demonstrate any significant improvement in mortality or neurological outcomes. Although several of these studies do demonstrate reduction in ICP with continuous hypertonic saline, the results are not sustained and do not translate to a clinical improvement. Additionally, lack of control groups, small sample sizes, and lack of reported data on functional outcomes and length of intensive care unit/hospital stay make these studies fairly limited in terms of generalizability. Lastly, these studies did not evaluate the role of continuous hypertonic saline in preventing or delaying decompressive hemicraniectomy surgery. Most of the studies were fair quality with relatively low levels of evidence (Tables 1 and 2). Future prospective studies with matched cohorts are needed to adequately assess the effects of continuous hypertonic saline in patients with malignant cerebral edema secondary to acute ischemic infarcts.

CONCLUSION

Continuous hypertonic saline for acute ischemic infarcts has been routinely used in neurocritical centers for the management for malignant cerebral edema. However, the data supporting its use is extremely limited. We present a systematic literature review that highlights the lack of substantial evidence supporting its use and emphasizes the study flaws that make the conclusions nongeneralizable. Although the reported studies demonstrate improvement in ICP control, there are no significant differences in neurological or functional outcomes, or overall mortality.

ARTICLE INFORMATION

Ethics statement

Not applicable.

Conflict of interest

No potential conflict of interest relevant to this article.

Author contributions

Conceptualization: AJSC, BHS, SAH. Data curation: AJSC, MM, KS, AS, KO. Formal Analysis: AJSC, MM, KS, BHS, SAH. Methodology: AJSC, KS, BHS. Visualization: AJSC, BHS, SAH. Writing–original draft: AJSC, MM, KS, BHS, AS, KO. Writing–review and editing: AJSC, BHS, SAH.

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Utility of medical simulation in neurovascular critical care education

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Simulation has shown good results in medical scenarios in which the patient's problem can be solved by following protocols previously established in clinical practice guidelines. Therefore, the implementation of simulation programs in neurocritical care improves the outcomes of patients at clinical centers because a properly trained professional will be able to provide the most effective care in the shortest time possible, safeguarding the patient's life. Some learning and simulation models that can be included in medical education to improve neurocritical vascular care include task trainers, full-body mannequins, standardized patients, and computer-based simulation. Specifically, medical simulation in academic training programs in health sciences has a great impact on the development of specific skills, which could potentially reduce medical-legal and economic issues, improve care, and result in the management of clinical events. Simulation is established as an essential educational tool, allowing the instruction of knowledge from an interactive perspective and offering a broader vision when it comes to medical practice. The objective of this article is to present evidence related to the usefulness and impact of medical simulation in neurovascular critical care education.

Keywords: Simulation training; Computer simulation; Medical education; Cerebrovascular disorders; Central nervous system diseases; Health education

INTRODUCTION

In the process of medical education, there are three essential principles of knowledge that trainees must learn: know, know how, and know to be [1]. These pillars allow the development of communication skills, professional attitude, medical judgment, clinical dexterity when performing a physical examination and medical history, and technical capacity when performing a diagnostic or therapeutic procedure, orientating them towards the resolution of the patient's condition [1,2]. The acquisition and refinement of these skills comprise the core of what medical education should represent [3]. The integration, specifically of knowing how medi-

cal training allows the learner to acquire both rational and practical abilities, including the development of clinical reasoning and the capacity to formulate an integrated action plan for the management of the patient, an archetype to clinical practice. This is essential to promote the quality of healthcare professionals and the improvement of their techniques [2].

Currently, many trainees point to learning gaps in their educational processes, particularly in the practical component [1]. In neurology, this problem is more common, translating into the fear of facing cases involving neurocritical medicine. This is attributable to both the diagnostic and therapeutic challenges that they imply and the level of knowledge that one must possess to treat them [4]. Similarly, fewer and fewer people have been interested in neurosurgical and neurointensive specialties. This is a growing concern and a problem for the health system since many patients attend to the emergency room with acute neurological pathologies but the supply of medically trained personnel is limited [4]. Therefore, education models that consolidate the necessary knowledge for both students and medical professionals should be implemented to increase their confidence, security, and competence when managing cases in neurocritical care.

A solution to this issue is the incorporation of simulation-based education, which has been very well received in the educational field since its inclusion in aviation for pilot training and in medicine in 1960 through the introduction of the Rescue Annie dummy to train people in cardiopulmonary resuscitation [4]. Simulation provides an ideal, effective, and safe learning environment for medical learners when acquiring clinical knowledge and skills [5]. Hence, the objective of this review is to provide evidence related to the utility of medical simulation in neurocritical care, especially in neurovascular care.

MEDICAL SIMULATION

Simulation is a method used to recreate a situation without having to participate in a real event, and its main objective is to optimize the learning process and develop skills to improve professional performance [6-9]. This model is called experience-based learning because it offers a common practice scenario, followed by feedback and analysis of what has been learned and what could improve the results [10,11]. Although encounters with patients are an important component for learning in medicine, simulation grants previous exposure in different complex circumstances that may pose a risk to the patient, providing the trainee with a safe environment to develop their capability, acquire skills, and reflect on mistakes without putting their professional reliability at risk [6,12,13]. Furthermore, it can be used as a complement to experiences seen in patient care, providing educational opportunities that are not available in real events [6,14].

Learners are partially responsible for their education. To be able to access simulation-based learning, the apprentice must first acquire prior theoretical notions about basic sciences to confront clinical scenarios [15]. In addition, the habit obtained when treating the patient will accredit the trainee to act efficiently, professionally, and empathically, that is, to treat the patient satisfactorily [16,17]. The integration of the three aforementioned principles allows educating individuals who are capable of dealing with clinical problems with cleverness. When learners are competent, they are more confident with their abilities and proficient in correctly executing procedures because their knowledge has solid foundations [3,18].

Moreover, a responsible and well-trained instructor is in charge of participating in the improvement of the students' capacities by evaluating their performance in an impartial manner, providing information, pointing out errors, and offering support and guidance during the debriefing. All of which focus on the abilities of the evaluated person. The instructor also leads the discussion where it is necessary to fulfill the learning objectives [19,20]. Ahmed et al. [21] conducted a cross-sectional observational study to evaluate the point of view of medical professors on the integration of simulation-based medical education and found that the majority of respondents recognized that simulation is an effective tool that can benefit teaching outcomes. Furthermore, its inclusion in the curriculum is indispensable and should not be conceived as an isolated activity. Roze et al. [22] proposed a simulation exercise in which trainees represented a patient suffering a neurological syndrome, and the attending physician supervised by a tutor. Student motivation, learning, topic understanding, communication skills, and learner confidence were found to be considerably improved [22,23].

As mentioned earlier, one of the main features of simulation is feedback. In fact, it is one of the most studied and has the most evidence related to effective learning based on this method of education [14,24,25]. van de ridder et al. [26] described feedback in clinical education as a "specific information about the comparison between the performance of an apprentice and a standard, given with the intention of refining the management of the apprentice." Feedback ensures that the teaching objectives are met and provides a post-event reflection process [14]. In addition, debriefing is proposed as an exchange or discussion following the medical simulation, allowing learners to receive feedback, understand their actions, and better the results of their intervention. This helps incorporate new information into previous knowledge [19,27]. This method also enhances technical and behavioral skills [19].

Other characteristics of simulators that lead to proficient education include repetitive practice, range of levels of difficulty, diverse learning strategies, controlled environments, and individualized learning [25].

Over time, various types of simulations have been created and implemented to satisfy certain purposes, each having its own characteristics and level of complexity (Table 1) [28]. (1) Part task trainers: these consist of three-dimensional (3D) anatomical models whose objective is to represent a specific part of the human body and to educate as similar to reality as possible. With these structures, deliberate practice of regularly used procedures in the clinical setting for the acquisition of skills can be achieved [24,29]. (2) Full-body mannequins: 3D anatomical models with sizes and physiognomies very similar to a real human body. The complexity of these structures can vary depending on the age of the patient represented, ability to offer physiological responses, systemic reactions, and even present neurological signs, which can be controlled by electronic devices managed by an operator in real time or through responses programmed directly into the mannequin [29]. This type of simulator allows the development of teamwork skills, handling critical events, and offers a method for evaluation. Studies have shown that this type of simulation is helpful for learning in critical care [24]. (3) Standardized patients: this group consists of actors with previous training in the simulation of specific clinical situations. Their participation allows the trainee to obtain a real experience in their practical exercise. They are important in the training of medical learners for the acquisition of competencies, such as empathy and communication [24,29]. Professionals, amateurs, and sometimes "real" patients, called expert patients, perform this role [30]. (4) Computer-based simulation: it consists of virtual representations of specific medical situations whose objective is to develop skills in the trainee. Their level of complexity ranges from a basic computer program to virtual reality programs that permit interaction with patients [29]. This option offers the opportunity to recreate scenarios that cannot be carried out with other types of simulation, such as disaster scenarios or terrorist attacks [24]. (5) Hybrid simulators: the types of simulation previously mentioned can be combined and carried out simultaneously in a practical exercise, with the goal of enhancing the academic value of the activity and increasing the learning process for the apprentice [24,29].

SIMULATION IN NEUROCRITICAL CARE

Neurological diseases account for a large percentage of admissions to the emergency department. Consequently, the clinician who is going to perform the evaluation and management of the patient must do so optimally and quickly [31,32]. The care of patients with acute neurological disorders requires a set of techniques, skills, and aptitudes on the part of healthcare personnel because the severity of these disorders are at risk for high rates of mortality and morbidity, such as compromised motor function and disability [33].

Many physicians, residents, and students feel anxious when dealing with neurological patients, which may be related to the lack of knowledge and little contact with these specific groups of patients during their training [34]. These fears and insecurities can be observed when health personnel are unsure how to act when facing these types of situations, which has a negative impact on the health of the patient, given that the first hours in the management of neurocritical events are crucial. For this reason, proper neuroscience education is essential to avoid fatal outcomes [33-36].

Traditionally, teaching neurologic emergencies is often transmitted through lectures, assigned readings, self-study modules, or demonstration of important findings in patients with neurological diseases [10]. For instance, during their clinical practice rotations, medical learners know the basic principles of the neurological ex-

Table 1. Summary of the simulation modalities currently implemented in the learning process in healthcare education

Simulation modality	Characteristics	Example
Part task trainers	Three-dimensional anatomical structures of specific parts of the human body that allow the practice of tasks and development of skills	Synthetic leather pads to practice sutures; structures for practicing airway management/intubation
Full-body mannequins	Three-dimensional anatomical model of the human body with the ability to respond to specific situations	The SimMan 3G, HAL S3201, the Human Patient Simulator
Standardized patients	Actors with training in specific clinical situations	Trained actors, volunteers
Computer-based simulation	Computer programs allow the acquisition of medical knowledge and the practice of skills.	The Neurological Exam Rehearsal Virtual Environment, NewroSim
Hybrid simulators	Practice various types of simulation in the same scenario	Standardized patient wound simulator which can project emotions such as fear, anger, anxiety, this will reinforce practical wound management skills, communication skills, and learning to work under pressure.

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amination and its possible variations in patients with an acute event. However, this knowledge is acquired by consulting the books provided by the teacher, practicing with colleagues, and checking on patients with sequels of a previous episode. As such, they rarely confront the real situation, which can generate gaps and impede proper professional performance. In the same way, many learners report feeling incapable and uncomfortable in performing neurological examinations as a consequence of the lack of understanding of basic sciences, which decreases their efficiency and motivation. This also subsequently limits their clinical expertise in an environment where they might be in charge of providing the initial management in the future [35,37,38].

Several studies [2,3,5,6,9,13,39] have shown that "people give more significance to the knowledge they obtain from experience than to those they acquire passively." Therefore, it is necessary to implement tools that mediate the acquisition of knowledge in an active manner; in this case, instructing the trainee in a pragmatic way during their learning process [39]. However, there are situations where there is little or no opportunity to practice, such as in neurocritical events, which are characterized by the rapid deterioration of patients and the need for rapid and effective intervention by a specialized team [39]. Evidence supporting this includes the Neurocritical Care Education During Residency: Opinions (NEURON) study, which concluded that a significant number of neurology residents were concerned about training in neurocritical care, expressing that education within the neurocritical care unit is very restricted and should change to benefit the student's experience [40]. For this reason, simulation is an essential tool to recreate these types of scenarios as similar to reality as possible.

Before being exposed to real situations, the inclusion of these simulated spaces in neurocritical care offers the opportunity to learn how to communicate effectively with a team during an emergency, make quick decisions, correctly identify patients with critical neurological conditions, and implement appropriate treatment algorithms that help develop the reliability of the staff and their expertise in patient management [8,10,41]. Similarly, by incorporating simulations, the learner can experience failure and recognize the limits of their capacities, which results in the reduction of errors and better care to the patient and their loved ones [6,42].

SIMULATION IN NEUROVASCULAR CRITICAL CARE

The most frequently reported cause of neurological emergencies, and consequently, the main reason for consultation faced by neurologists on call is acute cerebrovascular disease [32,43]. According to the World Health Organization, stroke is the second leading cause of death worldwide, accounting for approximately 11% of deaths in 2019 [44,45]. Additionally, it is the leading cause of acquired physical disability in adults, the leading cause of epilepsy in older people, and the second most common cause of late-onset dementia. Likewise, cerebrovascular accidents have been ranked as the first or second most common cause of death in South American countries, which was aggravated by the poor system of care in neuroemergencies [46].

Based on the previous information, the implementation of simulation programs in neurovascular critical care can increase the life expectancy of patients who arrive at hospital centers due to stroke and other neurological conditions as it will provide them with the opportunity of better care in the hands of trained personnel, who are not necessarily specialists, for these situations. In addition, it also promotes the process of learning and education (Table 2) [46-49].

In London, simulated education has been practiced for several years and has been useful in professional stroke training and in establishing the acute stroke unit model. It has also been utilized to train first response personnel to perform thrombolysis [8]. In stroke, there is an important correlation between the time of onset of symptoms to the time of recanalization of the affected blood vessel. Simulation is used in this case as an educational technique to ensure prompt attention and assessment. Tahtali et al. [50] proposed to train the subjects based on the data collected regarding the care provided to the patient, over conferences given to the health workers and suggested that a well-structured team generally consists of a neurologist, radiologist, resident, and nurse, who

Table 2. Advantages of implementing medical simulation in neurovascular care education [46-49]

Advantage of simulation in neurovascular care
The "know-how" of the three essential principles of knowledge in medical education is put into practice.
Provides an effective and safe learning environment in the acquisition of knowledge in neurovascular critical care
Allows the acquisition of clinical reasoning skills
Improves trainees' confidence, security, and skill in the neurocritical care approach
Reduces trainees' insecurity when facing neurocritical situations
Allows the development of teamwork skills during critical events

coordinate strategies to reduce the patient waiting time for treatment.

In addition, Ospel et al. [51] conducted an international multidisciplinary survey, with the intention of determining the point of view of neurointerventionalists about the errors regularly committed in the endovascular treatment of unruptured intracranial aneurysms. They found that the faults that most regularly caused complications were related to technical execution and suggested that these faults can be prevented by strengthening the abilities of medical personnel through training in simulation settings. As a result, it would be ideal for simulation to be widely available to physicians and to become a part of the equipment in intervention centers, similar to surgical specialties that use this learning modality permanently in their academic training program [51-53].

To meet the requirements for appropriate therapy in cases of neurovascular events, educational programs and hospital centers resort to strategies that guarantee a better level of qualification, surgical success, and efficient ways to pass on knowledge to their staff. In an attempt to promote education and training in neurocritical care, the Neurocritical Care Society developed an emergency neurological life support course, which teaches health professionals the correct management of patients during the first hours of a neurological urgency [54]. The course provides a series of guidelines and protocols for the care of patients with acute neurological conditions, including acute ischemic stroke and intracerebral and subarachnoid hemorrhage, which are some of the main cerebrovascular pathologies [54].

NEUROVASCULAR SIMULATION MODALITIES

Other learning and simulation modalities that can be included in different medical schools as a strengthening method in the area of vascular neurocritical care are as follows.

Task trainers

Physical simulators are necessary for the apprentice to acquire practical experience and be able to face the critical situations of patients with neurovascular conditions. An example of this is the creation of simulated models of cerebral aneurysms that can help neurology residents and neurosurgeons gain a solid foundation of knowledge and well-developed surgical skills for the treatment of this condition [55].

Wurm et al. [56] used stereolithography and 3D printing to design aneurysms with surrounding blood vessels and the neurocranium to perform clipping surgeries. They concluded that 3D printing is the most promising technique for creating neurovascular structures [56]. Benet et al. [57] reported the fabrication of a customized aneurysm using a 3D printer for use in a human cadaver to facilitate training in the approach of complex surgical cases and interventions. Torres and De Luccia [58] developed a simulation system for endovascular aneurysm repair using a 3D printer, which improved the performance of vascular surgery residents by reducing fluoroscopy and procedure time.

Recently, in order to help train neurosurgeons in the management of aneurysms and complications during surgery, Chen et al. [59] created a physical simulator that realistically imitated the brain stem, brain lobes, cerebral arteries, and the circle of Willis, with aneurysms designed to occur in places where they are most likely to appear. This has been evaluated and supported by several studies [60-62].

Furthermore, Joseph et al. [63] designed a physical simulator based on a 3D printed model of the patient's skull, brain, and specific arteries that is capable of imitating the experience of intracranial aneurysm microsurgery. Based on the participants' evaluations, the vast majority (84%) indicated that the use of the simulator was a better alternative than conventional neurosurgical training methods, considering that this type of surgery was very limited at the time of neurosurgical residency. Therefore, simulation allows the acquisition of experience and encounter with this type of situation where practice is very scarce due to its critical component.

Other goals obtained from neurovascular simulation include improving the understanding of cerebral vascular anatomy in three dimensions, developing a detailed understanding of the neurosurgeon's view of aneurysm position and accessibility, and familiarizing the neurosurgeon with the methods and instruments used during surgery [64]. Additionally, the neurosurgeon benefits from simulation in aneurysm repair for training in both open vascular surgery (surgical clipping) and endovascular treatment [64].

Cranioencephalic trauma simulators have also been designed to teach skills necessary for the management of traumatic brain injuries, where specific pathologies, such as subdural and epidural hematomas, can be programmed [65]. Lobel et al. [65] developed a neurosurgical simulation curriculum that was presented at the 2012 Congress of Neurological Surgeons. Within this curriculum, a trauma model was designed to teach traumatic brain injury management skills and, subsequently, the residents' participation in this module. Improvements in practical knowledge were observed after the training and coaching [65,66].

Full-body mannequins

Musacchio et al. [67] incorporated a human patient simulator by

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Medical Education Technology, Inc. (METI, Sarasota, FL, USA), a multifunctional simulator that displays parameters such as blood pressure, oxygenation, cerebral perfusion, pulse, and intracranial pressure. This can also be used to perform procedures such as drug administration, intubation, mechanical ventilation, or cardiopulmonary resuscitation. In addition, it reacts to reflexes, maneuvers, and interventions performed by the examinee. The authors intended to construct scenarios capable of evaluating the response of residents and learners to the management of neurocritical pathologies, such as spinal shock, craniocencephalic trauma, cerebral vasospasm, hemorrhage, and cerebral herniation. The mannequin communicated with the trainee through a speaker that was controlled by the supervisor. Moreover, the learners underwent pre-exercise and post-exercise evaluations and a satisfaction survey. Afterward, the obtained knowledge was measured, and a substantial improvement was evidenced in most of the participants.

Standardized patients

In a study in 2011, Mehta et al. [68] added a practical component based on acute stroke simulation to the academic program for first-year neurology studentsn. Standardized patients were used for this exercise, where the actress was a nurse trained by a vascular neurology specialist, who instructed her what signs she should manifest in order to simulate stroke and make the simulation exercise as close as possible to a real case.

During the exercise, the residents were supervised by a specialist, and a report of their performance was given to them at the end of the procedure. Many residents agreed that one of the benefits of the simulation was that they were able to recognize their faults and thus correct them, allowing them to have more confidence in themselves when interacting with a real patient [68]. The results of this study allowed a notable improvement in the performance of the residents, which reduced the time of administration of treatment in stroke patients by approximately 9 minutes [68]. In stroke, every second that passes is vital for the maintenance of neuronal integrity. As such, it is of utmost importance to shorten the breach of time from the patient's arrival to the institution until the implementation of treatment to achieve the best results [69,70].

Computer-based simulation

With advances in technology, virtual spaces have been designed to allow learners to access the information that they require for their studies from their computers [71]. E-learning refers to the use of the Internet or information technologies for educational activities, offering accessibility and flexibility to control their own learning [72]. An example of this is the e-brain platform, which has more than 600 interactive and multimedia lessons, webinars, virtual case reports, and practice exams to support professional development [72,73].

Likewise, virtual reality programs have been increasingly used in simulation, leading to an immersive learning environment and advancements in the way vascular diseases are diagnosed and treated [71,74-75]. NeuroTouch is a virtual reality model through which the representation of predetermined clinical scenarios is made possible. It was developed to teach skills on the implementation of specific clinical situations, such as resection of brain tumors, restoration of hemostasis, and ultrasonic aspiration [76]. It also allows for the evaluation of several parameters in the sample case, such as the time spent in the procedure, volume of blood lost during the procedure, and the degree of force that is applied to the tissue [76]. With the correct use of this model, trainees will be able to improve their skills and their ability to quickly and efficiently visualize vascular structures and increase their confidence in the procedures, which lead to reduced complications [74].

Similarly, a virtual neurological model known as NewroSim has been developed, which has the capacity to simulate the main cerebrovascular alterations present in various pathological conditions, such as stenosis of the intracranial and extracranial arteries [77]. This equipment makes it possible to reproduce the hemodynamics of cerebral vessels and observe cerebral blood flow velocities using transcranial Doppler [24,78]. The use of NewroSim in the practice of neurological scenarios is of great help to learners as it allows them to observe the changes in cerebral perfusion and their direct impact on the neurological disorder of the patient [77,78].

On the other hand, given the increasing number of endovascular interventions for stroke treatment, simulation can play an important role in gaining experience, particularly for beginners, because any complication in this type of procedure can have serious consequences [79]. Kreiser et al. [79] found that the use of an angiography simulator allowed medical students and residents to learn about the principles of performing angiographic examinations and the necessary steps in specific interventions, such as carotid stent placement or aneurysm coiling. Likewise, Spiotta et al. [80] studied the usefulness of simulated diagnostic cerebral angiography among neurosurgical residents and fellows using an endovascular biplane angiography simulator and demonstrated that simulation facilitated the acquisition of technical angiography skills. Currently, other endovascular simulators, such as Procedicus VIST and ANGIO Mentor, allow learners to practice without the risk of harm to the patient, improving performance in a stress-free environment. When errors would occur, the simulators would generate feedback, thus facilitating learning [81].

Finally, treatment of ischemic stroke usually consists of the administration of recombinant tissue-type plasminogen activator within 4 hours of symptom onset, and its combination with mechanical thrombectomy has shown improved outcomes [82]. Simulation through virtual reality enhances learners' experience in performing mechanical thrombectomy through the use of and familiarization with endovascular devices, thrombectomy devices, catheters, and guidewires. This exercise demonstrated that apprentices who participated in simulation activities obtained better results than those who did not [82,83].

LIMITATIONS IN THE USE OF SIMULATION

There is very limited literature on the expenses incurred in the implementation of simulations in a medical setting [25]. However, the common point in most studies is the high cost, since mannequins, virtual reality simulators, and other types of simulators do not have very accessible prices. In addition, these equipment require adequate personnel for their management and maintenance, which greatly increases the costs of simulation in education [24]. Technological advances come in giant steps, and what today seems to be a great simulation equipment can quickly become obsolete. Therefore, it may not be viable to make this investment [84].

Simulation has shown good results in medical scenarios in which the patient's problem can be solved following protocols previously established in clinical practice guidelines, such as cardiopulmonary resuscitation, a common practice among health professionals [85]. However, in neurological emergencies, the most important thing is to be able to obtain a diagnosis before implementing previously established protocols. The issue is not as simple as one might think, and the solution to that problem depends on the encounter between the physician and the patient [86].

Actors are trained to represent classical patterns of a specific disease. However, in reality, patients may show nonspecific signs. Simulation may not sufficiently teach some skills since the scenario will never be the same as the real one, and no matter how hard one tries, there are certain characteristics that could never be simulated by an actor or a mannequin [86]. Hocker et al. [86] stated in their study that learners will hardly succeed in maximizing their knowledge and skills until they experience dealing with a real patient.

Therefore, although simulation is an important component of knowledge acquisition, it does not replace intimate patient contact because it is a component that ultimately determines problem-solving, decision-making, and communication skills. Hence, it is necessary to complement both simulation and practice in real situations to train competent professionals.

CONCLUSION

Medical simulation in academic training programs for health sciences has a great impact on the development of specific skills, potentially reducing medical-legal and economic complications and improving care and results in the management of clinical events. Simulation is an essential educational tool that imparts knowledge from an interactive perspective and offers a broader vision in relation to the practice of medicine. In neurocritical care, specifically neurovascular care, the visualization of these environments represents an opportunity to develop rapid and accurate decision making, allowing the maintenance of neuronal integrity and functional capacity of the patient, and ultimately reducing morbidity and mortality.

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Hiccups in neurocritical care

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REVIEW ARTICLE

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Hiccups are usually self-limiting and benign but can be distressing when they become persistent or intractable and produce significant morbidity. In the intubated patients in neurocritical care, persistent hiccups may cause respiratory alkalosis and are also associated with an increased incidence of ventilator-associated pneumonia. Several pharmacological and nonpharmacological strategies have been devised for the treatment of persistent and intractable hiccups. The evidence to support or declare any intervention as harmful is scarce. In this review, we have presented the pathophysiology and workup, and a stepwise management protocol for intractable hiccups.

Keywords: Hiccups; Intractable hiccups; Neurocritical care; Persistent hiccups; Drug therapy

INTRODUCTION

Hiccup or hiccough is known by the medical term "singultus," which is a derivative of the Latin word "singult," meaning "a gasp" or "a sob" [1]. Hiccups are characterized by involuntary, intermittent, repetitive, myoclonic, and spasmodic contractions of the diaphragm and the inspiratory intercostal muscles, leading to an abrupt and early closure of the glottis, terminating inspiration and generating the characteristic "hic" sound [2,3]. Both healthy adults and children commonly experience hiccup spells. In the fetus, hiccups play a physiological role by training the respiratory muscles for their breathing function, and as a reflex preventing amniotic fluid aspiration [4,5]. Transient episodes usually do not require medical attention unlike chronic hiccups (persistent and intractable), which can be associated with long term deleterious effects.

An accurate estimate of the burden of hiccups in the neuro-intensive care unit (ICU) leading to unfavorable outcomes and morbidity is unknown. Though persistent hiccups which are intractable and of neurogenic origin can result in hyperventilation and respiratory alkalosis, and are a risk factor for ventilator associated pneumonia in intubated and mechanically ventilated patients. Hence, meticulous evaluation and treatment of persistent or intractable hiccups (IH) in neuro-ICU patients is important, in a stepwise and protocolized manner which comprise of physical maneuvers first followed by pharmacological measures in failed or

resistant cases. Unfortunately, there are no clear guidelines applicable to the management of persistent or IH. Recently U.S. Food and Drug Administration (FDA) revoked the approval of chlorpromazine, citing its serious side effects in treating hiccups. In this article we strive to review the available literature on hiccups and provide a stepwise management protocol.

A single episode of hiccups can last from a few seconds to as long as several days. Based on the duration, hiccups can be divided into three categories: acute hiccups that last for up to 48 hours, persistent or protracted hiccups that last for more than 48 hours, and IH that last for over a month [6,7]. Most classifications use arbitrary time limits to categorize the phenomenon. Brief episodes of hiccupping are physiological. The point of transition to a pathological form is not well defined. The longer the duration of the hiccupping, the less amenable it will be to interventions. An episode lasting longer than a week is considered chronic while resistance to sequential therapy using three different drugs warrants the use of the label obstinate [8].

EPIDEMIOLOGY

Hiccups are more common in diseases affecting the gastrointestinal or central nervous system (CNS). Gender differences in hiccups frequency have not been seen in healthy subjects. Prevalence of non-CNS origin hiccups is higher in men than CNS origin hiccups [9,10]. No racial, geographic, or socioeconomic variation in hiccups has been documented. Recurrent hiccups occur in about 3% of the healthy population, compared to approximately 20% with Parkinson disease and 10% of patients with gastroesophageal reflux disease (GERD) [11]. Overall, the prevalence of hiccups in advanced cancer has been reported to be 3.9%–4.8% [12,13]. A variety of CNS pathologies cause IH. Lateral medullary infarcts (LMIs) cause 12%–36% of central hiccups cases. Keane (1961) found 56% of patients with central hiccups to primarily have LMIs, [14] and this proportion was 14% as per the report by Park et al. [15]. There is high preponderance of developing IH following an ischemic insult to the brainstem including pons or involvement of posterior inferior cerebellar artery [16,17]. Vascular lesions of CNS are the most common cause of IH followed by infective (meningitis, encephalitis), structural lesions, such as a multitude of space occupying lesions like cavernous angiomas or tuberculomas, and inflammatory and demyelinating conditions such as multiple sclerosis and neuromyelitis optica [18].

PATHOPHYSIOLOGY

The mechanism of hiccups is not very clear and the neuroanatomical center for hiccups has not been identified, though few hiccups provoking hypothesis have been proposed [19,20]. Bailey [21] first proposed the "reflex arc" in 1943 responsible for generating hiccups. The afferent impulse in this proposed arc is carried by the vagus nerve, phrenic nerves, or sympathetic nerve fibers (thoracic outflow T6–T12). Upper spinal cord (C3–C5), medulla oblongata near the respiratory centers, the reticular formation, and the hypothalamus appear to be the CNS centers involved in the hiccup response. Dopaminergic and gamma-aminobutyric acid (GABA)ergic neurotransmitters are involved in the modulation of this central mechanism [22]. The efferent response of the reflex is carried by the phrenic nerve to the diaphragm. Accessory nerves activation lead to the contraction of the intercostal muscles as well. Recurrent laryngeal nerve causes the reflex closure of the glottis, completing the sequence of events during a hiccup [22,23]. Davis concluded that hiccup generation was a supraspinal mechanism involving interplay between behavioral and chemical respiratory influences at the spinal level, independent of inspiratory centers [24]. Suppression of inhibitory influences on a supraspinal hiccup center could lower the threshold and cause hiccups to start. This mechanism may explain the persistent hiccups seen in multiple sclerosis or metabolic disorders. Hassler [25] propounded that hiccups may be generated at the pontomedullary level of the triangle of Guillain-Mollaret (inferior olivary nucleus, dentate nucleus, and red nucleus). Denervation super sensitivity of the inferior olivary complex, nucleus ambiguus, and adjacent reticular formation of medullary oblongata have also been hypothesized to give rise to hiccups [26-28]. Nucleus raphe magnus with its GABA-containing inhibitory cells has been shown to be the likely source of inhibitory inputs to the hiccup reflex arc [29]. Various neurotransmitter pathways of the brainstem and medulla, including those involving dopamine, serotonin, opioids, calcium channels, and GABA are possibly involved in mediating hiccups [30] (Fig. 1).

ETIOLOGY

Any process that affects the peripheral afferent, central, or efferent components of the proposed reflex arc can trigger hiccups [22]. The most common benign reason being large meals or carbonated drinks causing stomach distension. Hot and spicy foods, alcohol, smoking, and other substances irritating the gastrointestinal or pulmonary tracts can also trigger the reflex. Over-excitement or anxiety, when accompanied by hyperventilation or air swallowing (aerophagia) can trigger hiccups as well.

The causes of persistent hiccups can be classified into central and peripheral (Table 1). Central hiccups could occur with any le-

Table 1. Causes of hiccups

Cause of hiccups	
1. Central nervous system lesion	
Vascular pathology	Stroke, infarct, aneurysms
Neoplasm	Astrocytoma, cavernoma, brain stem tumors
Inflammation	Neuromyelitis optica, multiple sclerosis
Trauma	Traumatic brain injury
Infection	Encephalitis, meningitis
2. Peripheral cause	
Thoracic	Mediastinal lesions, diaphragmatic tumors
Heart	Ischemic heart disease, pericarditis, thoracic aneurysm
Gastrointestinal tract	Gastroesophageal reflux disease, *Helicobacter pylori* infection, esophageal tumors
Pulmonary	Bronchitis, pneumonia, tuberculosis, asthma
Miscellaneous	Ascites, intestinal obstruction, pelvic tumors
3. Surgical	Bronchoscopy, tracheostomy, thoracic or abdominal surgeries, central venous catheterization
4. Drug induced	Chemotherapy, anti-Parkinsonian drugs, dexamethasone, opioids, benzodiazepines, macrolides, anti-psychotic medications
5. Psychosomatic	Anxiety, stress, fear, excitement

sions along the pathway from the CNS to the phrenic nerve, especially with lesions of the brain stem, such as tumors and ischemic stroke [15,17,18,31]. Peripheral hiccups can be caused by diseases at the phrenic nerve level involving diaphragmatic irritation, such as gastric distention, subdiaphragmatic abscess, or hepatosplenomegaly.

CNS lesions

The dorsal area of the medulla is commonly associated with hiccups as it incorporates a number of complex structures which conciliate the reflex arc, including the vagus nerve, respiratory center, solitary nucleus, nucleus ambiguus, central sympathetic tract, and spinal tract of trigeminal nucleus. Chronic hiccups have been reported following hemorrhagic and ischemic strokes, cerebellar aneurysms, and neuromyelitis optica [32-38].

Peripheral nervous system lesions

Involvement of the hiccup reflex arc in conditions like sarcoidosis, diaphragm tumors, or other causes of abdominal distension may lead to persistent hiccups.

Gastrointestinal and abdominal causes

GERD is commonly associated with persistent hiccups and is responsive to treatment with proton pump inhibitors [39,40]. *Helicobacter pylori* infection may lead to persistent hiccups secondary to increased acid production causing irritation of esophageal vagal afferents [41].

Hiccups under anesthesia

Hiccups can occur during administration of general or regional anesthesia [42], particularly under lighter plane of anesthesia especially with the usage of short acting barbiturates and during intubation, patient positioning, or visceral manipulation during surgery. Surgeries in thorax and abdomen often lead to hiccups in the postoperative period probably due to gastroparesis [43]. Anesthetic drugs like propofol induced hiccups [44]. Hiccups following epidural anesthesia have been reported with possible mechanism of action being deafferentation of sensory nerves in the viscera coupled with increased diaphragmatic stimulation secondary to interruption of phrenic nerve motor reflex [45,46].

Cancer patients

Hiccups are frequently seen in patients with cancer either due to involvement of any portion of the hiccup reflex arc by the tumor, or as a secondary response to chemotherapy. Cisplatin is most commonly implicated [47].

Drug-induced hiccups

Steroids have been implicated in chronic hiccups. Dopamine agonists may induce bouts of hiccups in Parkinsonism patients owing to their high affinity towards D3 receptors. Macrolides like azithromycin and psychiatric medications like aripiprazole have also been known to be associated with persistent hiccups. In essence, it is imperative to thoroughly review the medication history and identify and stop the offending drugs inducing hiccups [48].

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Instrumentation-associated hiccups

Atrial pacing, catheter ablation of atrial fibrillation, and central venous catheter placement have been reported to cause hiccups presumably due to mechanical irritation of right phrenic nerve which is in close proximity to the right atrium [49-51]. Esophageal instrumentations like stenting induces hiccup by stimulating the reflex arc afferent component [52].

Psychogenic causes

Hiccups are seen in patients with acute anxiety, stress, fear, or excitement. In cases where behavioral therapy has been successful in ameliorating hiccups, a diagnosis of hysterical hiccups has been made [53].

Miscellaneous causes

Dyselectrolytemias, tuberculosis, ethanol abusers, diabetes mellitus, and chronic renal failure (due to uremia) [54] can all cause persistent hiccups. Electroencephalogram findings in patients with epilepsy suggest that chronic hiccup can be the result of seizure activity. Certain antiepileptic drugs have shown a beneficial role in the treatment of hiccups mainly due to their GABAergic effects. However, in many patients, chronic hiccups occur without the presence of cerebral dysfunction and diazepam, a potent anti-convulsant drug, can precipitate or exacerbate hiccups in such conditions [55].

EFFECTS OF PERSISTENT HICCUPS

Persistent hiccups have the capacity to induce major disabling impact on general health and cause exhaustion, sleep deprivation, malnutrition, dehydration, depression, wound dehiscence, and even death in extreme cases [2,56]. It has a detrimental effect on rehabilitation as shown by prolonged hospital stay in a study done by Kumar and Dromerick [16]. Sleep cycle is affected by hiccups with literature showing that it persists during sleep disrupting both non-rapid eye movement (NREM) and REM sleep. Chronic hiccups lead to sleep deprivation [57].

EFFECTS OF HICCUPS ON RESPIRATION

The occurrence of hiccups in a patient receiving mechanical ventilation causes desynchronization and possible respiratory alkalosis leading to lung damage and hemodynamic alterations [58]. It can be prevented by close monitoring of respiratory parameters and prompt correction, especially in patients with brain stem damage. The strong inspiratory effort does not result in a large change in lung volume due to reflex glottic closure, and, therefore, in normal subjects the ventilatory effects of hiccups are minimal. In intubated or tracheostomized patients, hyperventilation and respiratory alkalosis may happen resulting in hiccups [59].

Marinella [2] were able to demonstrate that the left hemi-diaphragm was the side of hiccup origin in 80% of their cohort of patients with advanced malignancy. Persistent and IH are a risk factor for ventilator-associated pneumonia in intubated patients. Employing continuous positive airway pressure and pressure support ventilation can stop hiccups in such patients. Salem et al. [60] demonstrated that increasing PIP to 30–40 cmH_2O immediately stopped the development of hiccup during a surgical procedure.

EVALUATION

A thorough and detailed history is warranted focusing on trigger factors for chronic hiccups along with frequency, duration, progression, and aggravating and relieving factors. Relevant history should be elicited regarding the chronology of hiccup episodes, relationship with sleep, and any physical maneuver or pharmacological treatment the patient is undergoing with their effectiveness on the condition and any side effects experienced. A comprehensive enquiry should be made regarding the prescribed medications the patient has been administered along with over-the-counter medications and various addictive habits, such as smoking and alcohol consumption. An underlying organic pathology should be ruled out in patients with chronic hiccups.

A detailed physical examination should be done along with a systemic one focusing on the respiratory, nervous, and gastrointestinal systems. An electrocardiogram may help rule out atypical myocardial infarction especially in the beginning of a hiccup attack. Routine blood workup should be done including complete blood count, electrolytes, blood urea nitrogen, creatinine, calcium, liver function tests, and amylase/lipase. Investigation to rule out GERD is important and includes an upper gastrointestinal endoscopy, esophageal manometry, and a 24 hour–pH-impedance reflux study [61]. In patients where no organic cause can be found or those not responding to routine treatment, imaging studies like computed tomography scan and magnetic resonance imaging of head and neck are warranted [62]. Stepwise management protocol is given in flow diagram (Fig. 2).

TREATMENT

The treatment approach of persistent hiccups is mostly based on observational reports and case series, and clear-cut guidelines are lacking. The treatment is mainly directed at treating the underlying cause when the illness causing hiccups has been identified

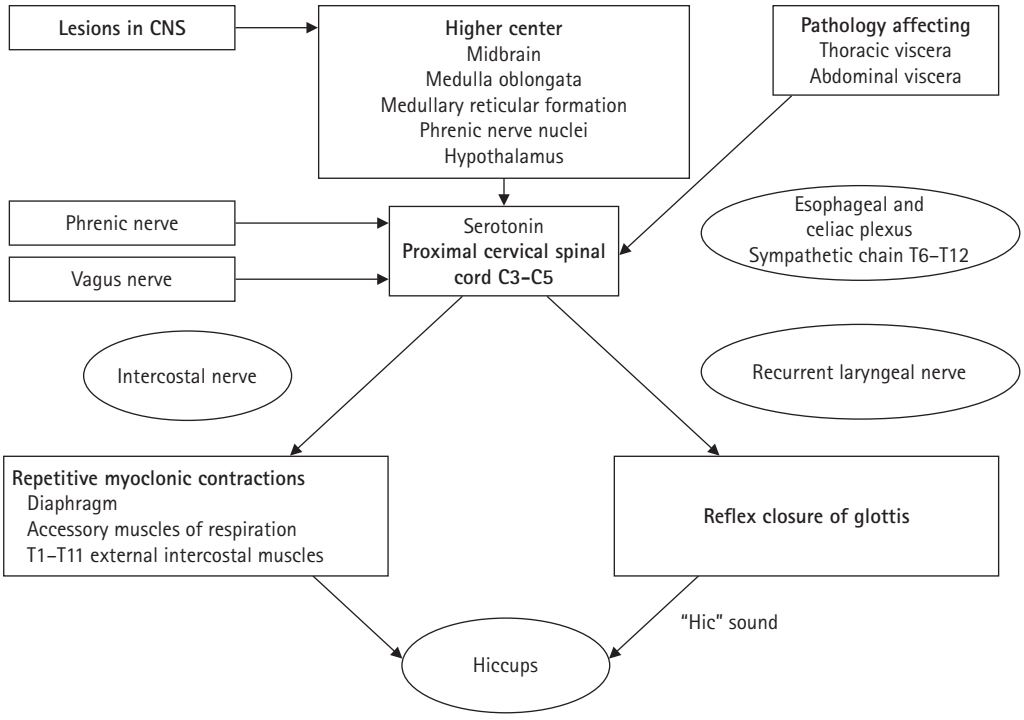

Fig. 1. Hiccup reflex arc. Activation of "hiccup center" by lesions in the central nervous system (CNS) or periphery triggers hiccups mediated via phrenic and intercostal nerves, leading to myoclonic repetitive contractions of the diaphragm and accessory muscles. The characteristic "hic" sound is produced due to reflex closure of the glottis via recurrent laryngeal nerve.

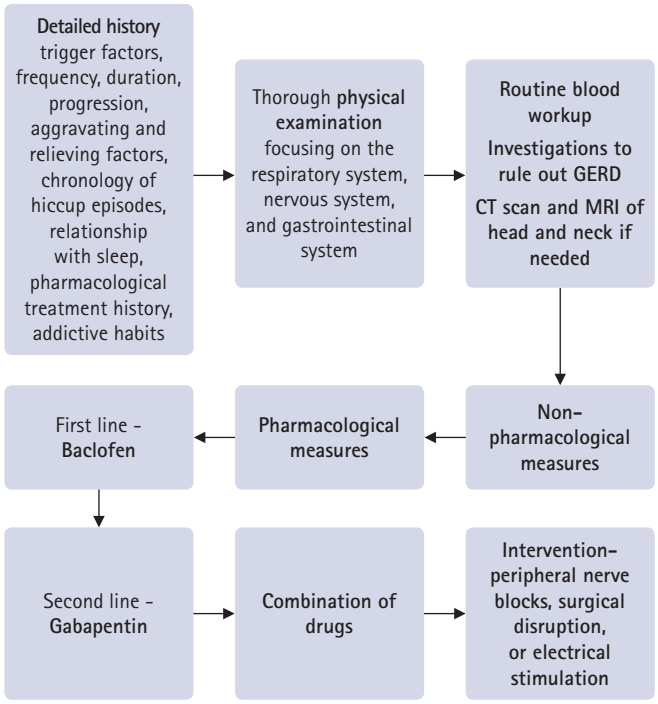

Fig. 2. Stepwise management protocol. GERD, gastroesophageal reflux disease; CT, computed tomography; MRI, magnetic resonance imaging.

[2,22,23]. In majority of the cases, no cause is found and the treatment is mainly empirical to ameliorate the symptoms. Table 2 shows the anecdotal and nonpharmacological treatment methods. Physical maneuvers such as interrupting normal respiratory function (e.g., breath holding, Valsalva maneuver), stimulating nasopharynx or uvula (e.g., sipping cold water, gargling with water, swallowing a teaspoon of dry sugar), increasing vagal stimulation (e.g., pressing on the eyeballs), and countering irritation of the diaphragm (e.g., pulling knees to chest, leaning forward to compress the chest) are first-line treatments for hiccups. The basic principle of the various physical maneuvers employed is to interrupt or suppress the reflex arc [7]. These, at best, provide a transient relief in cases of persistent or IH. Drug therapy should be reserved for treatment of hiccups when physical maneuvers have failed [63,64].

Pharmacological

There is inadequate data to formulate treatment guidelines for persistent hiccups [57]. A complete medical history regarding the ongoing medications and comorbid conditions should be available, and the possible drug interactions and probable side effects should be kept in mind before the choice of medication is made. Combination therapy for IH has also been proposed in certain case reports [65]. The drug therapy could be tapered out or dis-

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continued if hiccups cease, and alternative drug or treatment modality could be considered in case of IH. The pharmacological treatment is summarized in Table 3.

Chlorpromazine

Chlorpromazine, a dimethylamine derivative of phenothiazine, is a centrally acting dopamine antagonist which acts at the hypothalamus. The concerns pertaining to long-term neurological side effects along with hypotension, urinary retention, glaucoma, or delirium associated with the use of chlorpromazine has led to its U.S. FDA approval recently being withdrawn. The suggested dose has been 10–25 mg orally or intravenously; if no response then up to 25–50 mg three times a day can be used [66]. Other neuroleptics, like haloperidol or olanzapine, though effective are limited by their untoward effects such as such as dizziness, mood disturbance, and sedation.

Haloperidol

It alleviates hiccups by its dopamine antagonism in the hypothalamus. The major side effect is extrapyramidal symptoms. Recommended dosage is 5–10 mg/day orally or 2 mg intramuscularly [67].

Olanzapine

Postsynaptic serotonergic receptors augment phrenic motoneuronal activity and play a role in the generation of hiccups. Olanzapine is proposed to act as an antagonist at these postsynaptic receptors, thereby, attenuates phrenic excitability and relieves hiccups. Alderfer and Arciniegas [68] reported that a maintenance dose of 2.5 mg once daily led to remission of IH secondary to brain injury.

Benzodiazepines

High-dose benzodiazepines can alleviate treatment-resistant hiccups by suppressing the repetitive, myoclonic contractions of the diaphragm. Midazolam is used via continuous infusion at the rate of 10–60 mg/24 hr in patients with terminal hiccups, in the context of refractory delirium or agitation [69].

Muscle relaxants

Baclofen

Baclofen, a GABA-B agonist, inhibits transient relaxations of the lower esophageal sphincter and diaphragm with its peripherally and centrally mediated effect on vagal nerves. It also affects the esophago-gastric junction and suppresses reflux after meals. Concerns with its use include ataxia, confusion, and sedation especially in elderly patients with renal failure. Dose is 5 mg per 12 or 8 hours to start with, progressively increased by 15 mg every 3 days to a maximum daily dosage of 75 mg till optimal dose is reached [70-72]. Treatment should be slowly tapered over several days and never abruptly stopped.

Anti-epileptic drugs

Anti-convulsant medications are used as a second line treatment of persistent hiccups. They block the excitatory neural sodium channels (e.g., phenytoin, carbamazepine), enhance the release of GABA, and decrease the release of excitatory neurotransmitters in the CNS.

Gabapentin

Gabapentin modulates diaphragmatic excitability by increasing the endogenous GABA-mediated inhibition of inspiratory muscles and reducing calcium influx through inhibitory effects on voltage-operated calcium channels in the presynaptic terminals of respiratory muscles. It also increases serotonin levels in the nucleus raphe magnus of the medulla, which is the most likely source of GABAergic inhibitory inputs to the hiccup reflex arc. Gabapentin either alone or in combination with other medications has been

Table 2. Anecdotal and nonpharmacological treatment methods

Treatment	Method
Anecdotal treatments [52]	Fast drinking of a large glass of water, application of ice on epigastrium, nasal and pharyngeal stimulation, pressure on bridge of nose, gargling with water, carbonated beverages, swallowing granulated sugar or crushed ice, massage of hard/soft palate junction, digital rectal examination acupuncture, meditation, bilateral pressure on external auditory meatus
Nonpharmacological treatment of hiccup [45]	
Respiratory maneuver	Breath holding with neck extended, coughing, Valsalva maneuver, rebreathing in a bag, compression of the diaphragm by drawing legs up or leaning forward, compression of thyroid cartilage
Psychiatric treatment	Behavioral therapy and hypnosis
Gastric distension relief	Fasting for 24 hours, gastric aspiration, lavage, induced vomiting, pulling out Ryle's tube by few centimeters
Phrenic nerve disruption	Local anesthetic injection, compression of phrenic nerve at the neck, phrenic nerve stimulation

Table 3. Summary of pharmacological treatment

Drug	Action mechanism	Recommended dose	Considerable side effect
Chlorpromazine [66]	Dopamine antagonist that acts at the hypothalamus	10–25 mg orally or intravenously Max: 25–50 mg three times a day	Hypotension, urinary retention, glaucoma, or delirium
Haloperidol [67]	Dopamine antagonism in the hypothalamus	5-10 mg/day orally or 2 mg/day intramuscularly	Extrapyramidal symptoms, dizziness, mood disturbance, and sedation
Olanzapine [68]	Postsynaptic serotonergic receptors antagonist, attenuates phrenic excitability	2.5 mg once daily	Dizziness, mood disturbance, and sedation
Benzodiazepines [69]	In high doses suppresses the repetitive, myoclonic contractions of the diaphragm	Midazolam: continuous infusion at the rate of 10–60 mg/24 hr in patients with terminally hiccups in the context of refractory delirium or agitation	Sedation, respiratory depression
Muscle relaxant			
Baclofen [70-72]	GABA-B agonist	5 mg per 12 or 8 hours to start with, and progressively increased by 15 mg every 3 days to a maximum daily dosage of 75 mg	Ataxia, confusion, and sedation especially in elderly patients with renal failure
Anti-epileptic drug			
Gabapentin [73]	Increasing the endogenous GABA-mediated inhibition modulates diaphragmatic excitability	300 mg three times daily orally and titrated according to response, or 400 mg three times daily for 3 days, then 400 mg once daily for 3 days and then stopped.	
Carbamazepine [74]		200 mg every 6 hours given orally	
Valproic acid [75]	Increases the GABA transmission centrally	200–500 mg orally (15 mg/kg/24 hr in divided doses)	Gastrointestinal bleeding and hepatic toxicity
Others			
Metoclopramide [76,77]	D3 antagonist and 5-HT4 agonist; central anti-emetic and peripheral prokinetic properties with lower esophageal sphincter tightening effect	10 mg intravenously three to four times a day	Tardive dyskinesia
Domperidone [65]	Dopamine antagonist	10 mg three to four times a day	QT interval prolongation, cardiac dysrhythmias
Cisapride [78]	5-HT4 agonism	10 mg three times a day orally	Insomnia, anxiety, nervousness
Nifedipine [79]	Calcium channel blocker; interrupts the reflex arc by reversing the abnormal depolarization	10 mg orally three times a day with concurrent fludrocortisone 0.5-1 mg orally	Hypotension
Methylphenidate [80]	Inhibition of dopamine and norepinephrine reuptake	5 mg orally (maintenance 5–10 mg twice daily)	Insomnia, increased blood pressure, headache, nervousness
Nefopam [81]	Dopamine antagonist	0.25 mg/kg over 10 sec intravenously (10 mg intravenously four times daily for 2 days)	Dizziness, light headedness, hallucinations, nervousness, confusion, pink discoloration of urine
Carvedilol [82]	Acts on the afferent sympathetic component of the reflex arc	6.25 mg four times daily	Dizziness, light headedness, shortness of breath, slow heartbeat
Lidocaine [83-85]	Effect on the irritant sensory afferents	1 mg/kg loading dose followed by infusion of 2 mg/min 3 cm^3 of 4% topical lidocaine nebulized in a standard small-particle nebulize	Neurological and cardiovascular toxicities with intravenous drug; short-term loss of the gag reflex with nebulized drug
Amantadine [86]	N-methyl-D-aspartate subtype of glutamate receptors antagonist, anticholinergic activity	100 mg once daily	Dizziness, light headedness, dry mouth, constipation, insomnia

GABA, gamma-aminobutyric acid.

recommended especially in patients with hiccups secondary to brain tumors. Gabapentin dosage is 300 mg three times daily orally and titrated according to response, or 400 mg three times daily for 3 days, then 400 mg once daily for 3 days, and then stopped [73]. Porzio et al. [12] in their retrospective study evaluated gabapentin's efficacy in patients with advanced cancer having severe chronic hiccups and concluded that gabapentin can be used as a next line therapy to chlorpromazine. It has a favorable side effect profile compared to other anti-epileptic drugs.

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Carbamazepine
The recommended dosage of carbamazepine is 200 mg every 6 hours taken orally [74].

Valproic acid
Valproic acid increases the GABA transmission centrally and interrupts the hiccup stimuli. It is associated with serious side effects like gastrointestinal bleeding and hepatic toxicity. Recommended dosage is 200–500 mg orally (15 mg/kg/24 hr in divided doses) [75].

Metoclopramide
It is a D3 antagonist and 5-HT4 agonist with a chemical structure similar to neuroleptic drugs. It has both central anti-emetic and peripheral prokinetic properties with a lower esophageal sphincter tightening effect. Its efficacy in hiccups is due to gastric emptying because of its prokinetic property, which reduces gastric distension and GERD. Recommended dose is 10 mg intravenously three to four times a day [76,77]. Wang and Wang [77] in their randomized study demonstrated its benefit on terminating hiccups. Long-term dosing is associated with risk of tardive dyskinesia.

Domperidone
The drug is devoid of neurological side effects associated with metoclopramide as it does not cross the blood-brain barrier. It has a better risk profile over a longer period of time but there are concerns with its propensity to cause QT interval prolongation and cardiac dysrhythmias. The dosage is 10 mg three to four times a day [65].

Cisapride
It has 5-HT4 agonism and an effect comparable to metoclopramide. Dosage is 10 mg three times a day, taken orally [78].

Nifedipine
It is a calcium channel blocker and interrupts the reflex arc by reversing the abnormal depolarization, with the major side effect being hypotension. Recommended dosage is 10 mg orally three times a day with concurrent fludrocortisone 0.5–1 mg orally [79].

Methylphenidate
It terminates hiccups through inhibition of dopamine and norepinephrine reuptake. In the case report published by Maréchal et al. [80], methylphenidate was effective in terminating hiccups in a patient with metastatic small cell lung cancer with a dose of 5 mg orally (maintenance 5–10 mg twice daily).

Nefopam
It is a non-opioid analgesic with reported efficacy in terminating refractory hiccups with intravenous medication at a dose of 0.25 mg/kg over 10 seconds (10 mg intravenously four times daily for 2 days) [81].

Carvedilol
Carvedilol suppresses hiccups by acting on the afferent sympathetic component of the reflex arc. Stueber and Swartz [82] reported that it was effective in treating hiccups in a patient with tardive dyskinesia and compulsive self-induced hiccups and vomiting, at doses of 6.25 mg four times daily.

Lidocaine
Lidocaine nebulization is found to be effective in treating hiccups due to its effect on irritant sensory afferents. The safety profile with this is considerably better as compared to intravenous route which is fraught with neurological and cardiovascular toxicities [83,84]. Kaneishi and Kawabata [85] reported a case of hiccups, resistant to haloperidol, effectively treated by lignocaine.

Amantadine
Amantadine is an antagonist at the NMDA receptors with anticholinergic activity and anti-Parkinsonian effect and possible anti-hiccup action. There are case reports regarding the onset of hiccups following administration of dopamine agonists in a patient with Parkinson disease [86].

Combination therapy for IH
Combination therapy for IH has also been proposed in certain case reports [65].

Cisapride, omeprazole, and baclofen (COB)
Petroianu et al. [87] studied oral treatment with cisapride 10 mg three times daily, omeprazole 20 mg once daily, and baclofen 15 mg three times daily in patients with IH and concluded that COB is an effective empirical therapy.

Cisapride, omeprazole, baclofen, and gabapentin
In another study, Petroianu et al. [88] proposed that the addition of gabapentin should be considered in patients for better results.

CONCLUSION

Hiccups are usually innocuous and frequently ignored. Patients presenting with chronic hiccups require a meticulous evaluation focusing on history and physical examination. Persistent hiccups

are more often than not associated with an underlying organic pathology which requires a comprehensive workup. Pharmacological therapy should take into account the risk of long-term side effects and FDA recommendations. Considering the present literature on hiccup pharmacotherapy, baclofen may be considered as a first line therapy followed by gabapentin. Large multicenter trials are the need of the hour along with the development of robust guidelines.

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Not applicable.

Conflict of interest
No potential conflict of interest relevant to this article.

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Contribution of pupillary light reflex assessment to Glasgow Coma Scale for prognostication in patients with traumatic brain injury

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Background: Glasgow Coma Scale (GCS) and the pupillary light reflex (PLR) are important prognostic tools for traumatic brain injury (TBI). This study compared the predictability of GCS, GCS plus manual PLR (GCS-P), GCS plus Neurological Pupil index (GCS-NPi), and average NPi (avgNPi) in predicting discharge outcome in patients diagnosed with TBI.
Methods: Data were obtained from a multicenter prospective registry that included 175 subjects with TBI. A nonlinear mixed model (NLMIXED) approach was used to determine which of the following independent variables (GCS, GCS-P, GCS-NPi, and avgNPi) is a better predictor of modified Rankin Scale (mRS) at discharge by fitting four predictive models for comparison.
Results: The NLMIXED model for longitudinal data determined that GCS, GCS-P, GCS-NPi, and avgNPi were all significant predictors of mRS at discharge (P<0.001). Age was a significant predictor of the discharge mRS (P<0.001). There was a strong significant correlation between the four predicting variables (P<0.05). The maximum likelihood estimation (MLE) of GCS was –0.17 (P<0.001), MLE of GCS-P was –0.17 (P<0.001), MLE of GCS-NPi was –0.17 (P<0.001), and the MLE of avgNPi was –0.39 (P<0.001).
Conclusion: Our findings suggest that any of the four variables (GCS, GCS-P, GCS-NPi, and avgNPi) could be used as a potential predictor of discharge mRS in a patient with TBI. This warrants future investigations to explore the combination of pupillary reactivity scores and NPi with GCS for prognostication in patients with TBI.

Keywords: Pupil; Pupil disorders; Reflex, Pupillary; Critical illness; Traumatic brain injury

INTRODUCTION

Patients with traumatic brain injury (TBI) experience several methodological challenges related to outcome assessment due to the limited availability of prognostic tools for predicting outcomes. The Glasgow Coma Scale (GCS) was developed as a tool to assess the "depth and duration of impaired consciousness and coma [1]." Although, GCS is the most widely used prognostic tool for predicting outcomes in patients with TBI, the availability of other online prognostic calculators such as the international mission for prognosis and clinical trials in traumatic brain injury (IMPACT) and corticoid randomisation after significant head in-

jury (CRASH) prognostic models may also aid in estimating the 6-month outcomes in patients with moderate to severe TBI in addition to providing support to decision making and clinical judgment for determining the treatment goals and care in TBI [2,3]. In 2014, Teasdale et al. [4] cautioned that the GCS should not be used as a prognostic instrument except when used in conjunction with multivariate modeling. The development of the international Curing Coma Campaign heralds a renewed interest in prognostication and assessment of patients with disorders of consciousness [5]. The most recent adaption to the GCS, the GCS-pupil (GCS-P) adjusts for findings based on a subjective assessment of the pupillary light reflex (PLR). However, both the GCS and GCS-P predate the adoption of automated infrared pupillometry (AIP) [6-8]. Therefore, the purpose of this study is to explore the contribution of PLR assessment to prognostication in patients with TBI.

The rates of unfavorable outcomes after TBI can exceed 20%, and up to 15% of TBI patients with mild injury will have post-concussive symptoms [9,10]. Prevention of secondary brain injury relies heavily upon the ability to provide an accurate assessment of the patient at baseline, and subsequent serial assessments [11,12]. The GCS evaluates three components of responsiveness (eye-opening, motor, and verbal responses) [13]. Each component is evaluated and scored separately; component scores are then summed; ranging from 3 to 15 (higher scores represent the best responsiveness). The PLR has been examined both historically, and recently, as a prognostic variable of both morbidity and mortality [14-16]. Previous work by Perel et al. [3], Marmarou et al. [2], and Brennan et al. [17] suggest that a combination of GCS and PLR may serve as good predictors to predict outcome in patients with TBI.

Traditionally, the PLR was a subjective assessment performed using a flashlight or penlight. This method of assessment has been found to be unreliable and imprecise [18,19]. The PLR is a summary assessment that begins by evaluating the size of the pupil at rest, providing a light stimulus, and observing the degree to which the pupil constricts in response to that stimulus [20]. AIP is an emerging technology that has high reliability, precision, and reproducibility as compared to the standard pen-light examination to examine the pupillary response. It provides an objective measurement of pupillary size, symmetry, and reactivity to light [20]. The assessment of PLR by pupillometry has recently emerged as a useful tool for assessing pupillary reactivity and triaging patients for expediting care in patients with neurological diseases [21]. The NPi-200 pupilometer assesses pupillary reactivity and provides a summary score called the Neurological Pupil index (NPi) [22]. The NPi is a standardized way to assess the PLR using a hand-held pupilometer. Values range from 0 to 5 (NPi $\geq$ 3.0 is considered normal, and $<$ 3.0 is considered abnormal). Even though recent literature has indicated the usefulness of pupillometry due to its high accuracy and reliability, there is a lack of research to determine the usefulness of NPi in combination with GCS score for predicting outcome in patients with TBI.

In patients with TBI, the modified Rankin Scale (mRS) has been used to assess the degree of disability by providing a score, ranging from 0 (fully independent) to 6 (dead) to determine the functional outcome in patients [23,24]. Even though GCS is a simple and powerful prognostic tool, it has its limitations as an independent prediction tool of mortality and unfavorable outcomes [2,17,25]. Previous studies have combined GCS with PLR to predict the functional outcome in patients with TBI. But, to our knowledge, no study has examined the predictive ability of GCS in combination with NPi, or using NPi alone to predict mRS outcome in patients with TBI.

METHODS

The Establishing Normative Data for Pupillometer Assessments in Neuroscience Intensive Care (ENDPANIC) registry is a multi-center international registry of pupillary assessments and acute care data points (NCT02804438). The registry was open in 2014; a full report of the methods and additional data can be found in a previous publication [26]. Data were obtained from 175 adults (over 18 years of age) patients diagnosed with TBI who had admission GCS and AIP data linked to discharge mRS. PLR analysis was done via commercial pupilometer (NPi 200; Neuroptics Inc., Irvine, CA, USA). Pupillometry was performed and pupillometry data were collected throughout the patients' hospital stay, based on the frequency of neurological assessments ordered by the physician. This is usually every hour for the first few days, with the interval being increased subsequently once the patient is felt to be neurologically stable and not at a high risk of neurological deterioration. Data on demographic characteristics and length of hospital and ICU stay were obtained from the registry. For the GCS-P, pupillary reactivity was derived by the AIP values wherein, an NPi of 0 was scored as non-reactive and an NPi value above 0 was scored as reactive. In this manner, the GCS-P score (range, 1–15) was derived by subtracting the number of non-reactive pupils (0, 1, or 2) from the GCS (range, 3–15) [17]. Discharge mRS scores were abstracted from the discharge notes in the electronic medical record as assessed by the discharge therapist and/or physician.

The GCS-NPi score (range, 1–15) was created by subtracting points from the GCS based on NPi. We subtracted 0 points if the NPi of both eyes was $>$ 3.0; and subtracted 0.5 point if the NPi of one eye was $>$ 3.0 and the other eye was 0.1–2.9; subtracted 1

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point if the NPi of both eyes was between 0.1 and 2.9; subtracted 1.5 points if NPi of one eye was between 0.1 and 2.9 and the other eye NPi was 0; and subtracted 2 points if the NPi of both eyes was 0. The NPi values from the left and right eye were summed and divided by 2 to provide the average NPi (avgNPi).

Statistical analysis

Summary statistics and statistical models were developed using SAS ver. 9.4 (SAS Institute, Cary, NC, USA). Patient characteristics such as age, sex, race, and ethnicity were summarized at baseline. The continuous variables such as age and avgNPi were summarized as mean and standard deviation while categorical variables such as sex, ethnicity, race, PLR response, were described as frequencies and percentages. Ordinal variables were described using median and interquartile range (IQR).

To ascertain which of the measures (GCS, GCS-P, GCS-NPi, or avgNPi) is a better predictor of mRS, four separate predictive models were fitted. Because the relationship between mRS and each predictor is unlikely to be linear, and also, to take into consideration the repeated nature of the data, a random effect nonlinear mixed model (NLMIXED) was fitted for each of the potential predicting variables of mRS [27,28]. This model was fitted after the proportional odd assumption of ordinal logistic regression was violated [29]. Even though this model does not assume a linear relationship between the dependent and independent variable, both models take the dependency between observations based on the same cluster repeated measure per subject into account by introducing one or more random effects. This procedure fits multiple models by identifying the maximum likelihood estimation (MLE) and maximizing the approximate integrated likelihood by adaptive Gauss-Hermite quadrature. In this model, we controlled for age analyzed as a continuous confounder, sex analyzed as a binary confounder, and ethnicity as a binary predictor. A similar NLMIXED was employed to compute the correlation matrix for each of the four predictors.

RESULTS

One hundred seventy-five subjects met inclusion criteria. As shown in Table 1, the majority of the patients were male (n = 116, 66.29%), White (n = 102, 58.29%) and non-Hispanic (n = 164, 93.71%). The mean (standard deviation [SD]) was 56.4 years (22.3) for age, 6.8 days (7.7) for ICU length of stay, and 16.4 days (24.1) for hospital length of stay. The median (IQR) was 13 (6–15) for GCS, 12 (6–15) for GCS-P, and 12 (6–14.5) for GCS-NPi. The mean (SD) was 3.74 (0.11) for the left eye, 3.72 (0.11) for the right eye, and 3.73 (1.31) for the left and right eye averaged together (avgNPi). Of 175 patients, 158 patients (90.3%) had both pupils reactive. The median (IQR) was 4 (2–5) for discharge mRS (where an mRS of 0 indicated that the patient was absent of neurological symptoms).

Table 1. Patient baseline characteristics

Variable	Value (n=175)
Age (yr)	56.41±22.3
Sex	
Male	116 (66.29)
Female	59 (33.71)
Race	
African American	3 (1.71)
Asian	61 (34.86)
Caucasian	102 (58.29)
Other	9 (5.14)
Ethnicity	
Hispanic	11 (6.29)
Non-Hispanic	164 (93.71)
GCS	
Eye score	4 (1–4)
Verbal score	4 (1–5)
Motor score	6 (4–6)
GCS total	13 (6–15)
GCS-P	12 (6–15)
GCS-NPi	12 (6–14.5)
avgNPi	3.73±1.31
Pupillary reactivity	
Both reactive	158 (90.29)
One reactive	3 (1.71)
Neither one reactive	14 (8.00)
NPi-right	3.72±0.11
NPi-left	3.74±0.11
Pre-morbid mRS	0
mRS at discharge	4 (2–5)

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
GCS, Glasgow Coma Scale; GCS-P, GCS plus manual pupillary light reflex; GCS-NPi, GCS plus Neurological Pupil index; avgNPi, average NPi; mRS, modified Rankin Scale.

Of the 175 patients, 149 (85.14%) survived and 26 (14.86%) died (mRS = 6). Table 2 displays the calculated MLE, standard error, 95% confidence interval (CI), and P-value for the four parameters; GCS, GCS-P, GCS-NPi, and avgNPi and for the covariates (age, sex, and ethnicity) in the NLMIXED model procedure after successful convergence. The MLE (95% CI) of total GCS was –0.17 (–0.22 to –0.12, $P < 0.001$), for GCS-P was –0.17 (–0.22 to –0.12, $P < 0.001$), for GCS-NPi was –0.17 (–0.22 to–0.12, $P < 0.001$), and for avgNPi was –0.39 (–0.57 to –0.22, $P < 0.001$). If the total GCS changes by 1 unit then the mRS score at dis-

Table 2. Parameter estimates for total GCS, GCS-P, GCS-NPi, and avgNPi from non-linear mixed procedure

Parameter	Maximum likelihood estimate	Standard error	95% CI	*P*-value
Total GCS	−0.169	0.025	−0.218 to −0.120	<0.001
Sex[a]	−0.045	0.238	−0.514 to 0.424	0.850
Age	0.020	0.005	0.010 to 0.030	0.001
Ethnicity[b]	0.243	0.454	−0.653 to 1.138	0.594
GCS-P	−0.169	0.024	−0.216 to −0.122	<0.001
Sex[a]	−0.058	0.235	−0.522 to 0.406	0.806
Age	0.020	0.005	0.010 to 0.029	0.001
Ethnicity[b]	0.226	0.449	−0.660 to 1.112	0.615
GCS-NPi	−0.169	0.024	−0.215 to −0.122	<0.001
Sex[a]	−0.057	0.235	−0.520 to 0.407	0.809
Age	0.02	0.005	0.010 to 0.030	<0.001
Ethnicity[b]	0.231	0.449	−0.655 to 1.116	0.608
avgNPi	−0.394	0.090	−0.571 to −0.217	<0.001
Sex[a]	0.099	0.252	−0.398 to 0.596	0.695
Age	0.018	0.005	0.007 to 0.028	0.001
Ethnicity[b]	0.166	0.485	−0.790 to 1.123	0.732

GCS, Glasgow Coma Scale; GCS-P, GCS plus manual pupillary light reflex; GCS-NPi, GCS plus Neurological Pupil index; avgNPi, average NPi; CI, confidence interval.
[a]Male vs. female; [b]Hispanic vs. non-Hispanic.

charge will change by −0.17. If the GCS-P changes by 1 unit, the mRS score at discharge will change by −0.17. If the GCS-NPi changes by 1 unit, the mRS score at discharge will change by −0.17. A 1-unit change in avgNPi will result in a change in the discharge mRS score by −0.39. Thus, increasing the GCS, GCS-P, GCS-NPi, and avgNPi scores will significantly decrease the mRS score ($P < 0.001$). Therefore, based on the four fitted models for each of the predictors (GCS, GCS-P, GCS-NPi, and avgNPi), all four predictors were good in predicting discharge mRS, with very similar MLEs. Age was also a significant independent predictor of mRS at discharge ($P < 0.001$) whereas, sex and ethnicity were not predictors of mRS at discharge ($P > 0.05$).

Table 3 shows results from the analysis of the absolute correlation between these four independent variables. These results revealed a strong significant correlation ($P < 0.05$) between these four predicting variables suggesting that any of these predictor variables can be used to predict mRS at discharge. The weakest correlation was seen between GCS-P and total GCS (correlation, 19%) while the strongest correlation was observed between avgNPi and total GCS (correlation, 94%). Furthermore, the correlations between GCS-NPi and total GCS (correlation, 78%), and GCS-P and GCS-NPi (correlation, 76%) were moderately strong.

Table 3. Correlation matrix of parameter estimates for the predicting variable

Parameter	Total GCS	GCS-P	GCS-NPi	avgNPi
Total GCS	1.000			
GCS-NPi	0.776		1.000	
GCS-P	0.185	1.000	0.763	
avgNPi	0.940	0.260	0.788	1.000

GCS, Glasgow Coma Scale; GCS-NPi, GCS plus Neurological Pupil index; GCS-P, GCS plus manual pupillary light reflex; avgNPi, average NPi.

DISCUSSION

This study compared the ability of GCS, GCS-P, GCS-NPi, and avgNPi to predict mRS outcome at discharge in a patient with TBI. Our findings show no statistical difference between the four variables and all of the variables were good predictors of mRS outcome at discharge in patients with TBI ($P < 0.001$). Although the pupilometer is more reliable and accurate than the manual pupillary evaluation (performed using a penlight), combining NPi with GCS did not predict mRS outcome at discharge better than using GCS alone, GCS-P, nor avgNPi for predicting outcome. Therefore, any of these predictor variables may be used to predict mRS outcome, due to the high correlation between them ($P < 0.05$). However, the correlations (weak to moderately strong) between total GCS, GCS-P, GCS-NPi, and avgNPi indicate that it would not be appropriate to use any pair of these variables to predict mRS at discharge because they are highly related and will result in multi-collinearity.

The present study is the first to examine the difference between the four predictor variables in predicting mRS outcome at dis-

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charge in patients with TBI. Previous studies have compared GCS alone with GCS-P, Simplified Acute Physiology Score (SAPS) II, Acute Physiology and Chronic Health Evaluation (APACHE) II, Full Outline of UnResponsiveness (FOUR) score, and Kampala Trauma score in predicting the mortality among patients in neurocritical care or general critical care [30-32]. In a study by Brennan et al. [17] that compared GCS alone with GCS-P in predicting mortality, it was found that GCS-P was significantly better than GCS in predicting mortality as increasing the GCS-P was associated with a decrease in mortality which is similar to the results of our study that also indicate that a 1 unit change in GCS-P is associated with a –0.17 units change in mortality. Of note, in our study, GCS-P was derived was using AIP, an objective measure of PLR, given that AIP is more reliable than subjective assessment [19,22]. GCS-P in our sample is likely more representative of true GCS-P than previously reported.

A similar study in the past compared the FOUR score and GCS and also compared their inter-rater reliability but found no statistical difference ($P > 0.05$) between the two scores in predicting 28-day mortality among patients in general critical care however, the interrater reliability of the FOUR score was better than the GCS [31]. The FOUR score was developed with one of the assessments being pupillary examination [31]. Another study conducted in the past studied the predictive power of SAPS II, APACHE II, and GCS found no significant difference between the four variables in predicting mortality in neurosurgical patients, which isn't entirely similar to our study, but the results from our study also indicated no difference between the four variables in predicting mRS outcome in patients, with TBI [30].

As no significant difference is seen between the predictive ability of the four variables, using any of these tools to predict the functional outcome in patients at discharge after TBI will be equally useful. While there was no significant difference between GCS and the other predictor variables, using NPi alone has the advantage of being an objective measure and may be clinically more relevant than using GCS alone. Further, to be accurate, the GCS must be performed in the absence of a sedative or hypnotic effect [33]. Patients with TBI may have pharmaceutical effects as a result of treatment (e.g., the need for sedation to facilitate care), and this may impair the ability to perform an accurate GCS [34]. Although ocular instillation of medications is known to affect the PLR [35], the currently available evidence supports that the most common sedatives used in TBI care do not impair the PLR [21].

We believe that NPi, alone or combined with GCS may be clinically more reliable and useful than GCS alone due to the high interrater reliability of the pupilometer that measures the NPi in a few seconds [18,19]. However, small sample size is one of the limitations of our study. Although our sample was drawn from four U.S. hospitals and one hospital from Japan, and this increases the generalizability of the study. Our data is also limited in that we did not have TBI subtypes identified (e.g., open, closed, concussive, epidural, subdural, etc.). A recent study found that abnormal NPi was a strong predictor of the need for neurosurgical intervention after severe closed TBI [36]. There is still a need for a more reliable and objective tool for predicting functional outcomes in patients with TBI. Although the combination of GCS and NPi may be clinically more reliable and useful, it is not yet integrated into practice. Therefore, the addition of NPi to other prognostic models such as IMPACT and CRASH prognostic calculators that are easily available and accessible to all clinicians may be tested in prospective research studies to quantify prognosis in patients with TBI and for supporting clinical research and practice. We believe that future studies including a large sample size are required to study the differences in the predictive ability of the GCS-NPi in comparison to GCS, GCS-P, and avgNPi as well as to study the additional role of NPi to the prognostic models approach for predicting the mRS outcome in patients with TBI should be tested.

Our study concludes that any of the four predictors (GCS, GCS-P, GCS-NPi, and avgNPi) could be used as potential predictors in predicting mRS outcome at discharge among the study population. These findings suggest that the combination of PLR and GCS is not superior to NPi alone in predicting discharge mRS. Additional studies including a large study population is required to determine whether the combination of GCS and measures of the PLR improve prognostication.

ARTICLE INFORMATION

Ethics statement

The Establishing Normative Data for Pupillometer Assessments in Neuroscience Intensive Care (ENDPANIC) registry is approved by the Institutional Review Board of the University of Texas Southwestern Medical Center (IRB No. STU_2015) and is granted waiver of consent.

Conflict of interest

No potential conflict of interest relevant to this article.

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Treatment of patients with severe traumatic brain injury: a 7-year single institution experience

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ORIGINAL ARTICLE

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Background: This study was designed to compare the efficacy of multimodality monitoring and goal-directed therapy protocol (MM&GDTP), in patients with Glasgow Coma Scale (GCS) scores ≤8 with the conventional intracranial pressure (ICP)-cerebral perfusion pressure (CPP) treatment.

Methods: The study was divided into two time periods, a 2-year historic period in which severe traumatic brain injury (sTBI) patients were treated with an ICP-CPP targeted strategy and a 5-year intervention period during which MM&GDTP was utilized. Patients with unsurvivable brain injuries were excluded. Variables of interest included mechanism of injury, age, sex, hemodynamics, GCS score, abbreviated injury score–head (AIS-H), Marshall Class, injury severity score, decompressive craniectomy, ventilator/intensive care unit days, length of stay, predicted mortality by corticosteroid randomization after significant head injury model, functional outcome, and mortality.

Results: The study group comprised 810 sTBI patients, aged 14–93 years, admitted during a 7-year period; of these patients, 67 and 99 AIS-H≥4 and Marshall Class ≥III were included in control and intervention groups, respectively. The control group was treated with an ICP-CPP targeted approach, while the intervention group with an MM&GDTP. At presentation and after resuscitation, patients in the intervention group required a higher CPP to reach the endpoints of therapy. The MM&GDTP decreased mortality from 34.3% to 23.2%, yielding a 32.3% improvement in overall survival and improved functional outcome as measured by Glasgow Outcome Scale >3 (MM&GDTP vs. ICP-CPP: 50/99 vs. 15/67, *P*=0.003).

Conclusion: Institution of MM&GDTP targeted to threshold-defined values improves functional outcomes and may reduce mortality among patients with sTBI compared to that of patients receiving an ICP-CPP–based treatment.

Keywords: Traumatic brain injuries; Severe; Treatment; Multimodality monitoring and goal-directed therapy protocol; Mortality

INTRODUCTION

The treatment of patients with severe traumatic brain injury (sTBI) remains controversial. There is a wide range of perspectives on the value of foregoing intracranial pressure (ICP) monitoring and treating patients based solely on clinical and radiological findings versus utilizing either an intracranial pressure-cerebral perfusion pressure (ICP-CPP) targeted approach or a multimodality monitoring and brain tissue oxygen tension (ICP-$PbtO_2$) targeted treatment aimed at optimizing cerebral blood flow and brain tissue oxygenation. Regardless of modality employed, studies have confirmed that short periods of brain hypoxia with CPP < 60 mmHg are associated with decreased survival and compromised functional recovery at 6 and 12 months, respectively [1-3]. The Brain Oxygen Optimization in Severe TBI, Phase 2 (BOOST2) trial suggested a potential benefit of an ICP-$PbtO_2$ targeted treatment over an ICP-CPP targeted approach as the latter can reduce the duration and depth of brain hypoxia; however, it did not document a survival advantage for patients [4]. Following these findings, the BOOST-3 prospective randomized trial was initiated to further demonstrate whether an ICP-$PbtO_2$ targeted treatment is superior to an ICP-CPP targeted approach from the standpoint of overall mortality and functional outcome; this study is ongoing [5]. At this time, there is no evidence to support the use of ICP-$PbtO_2$ targeted treatment for all patients with sTBI.

Following the recruitment of two of the authors of this study (MFS and CPM), a multimodality monitoring and goal-directed therapy protocol (MM&GDTP) was implemented in our Level I Trauma Center in 2011. The protocol includes a set of interventions aimed at preventing secondary brain injury and maintaining functional brain metabolism during the first 5 days following injury. It uses a tiered intervention strategy to treat isolated increases in ICP and decreased cerebral blood flow identified with near-infrared spectroscopy (NIRS) regional cerebral oxygen saturation (rSO_2) using cerebral microdialysis (CMD) data to detect brain tissue hypoxia. Our initial experience with MM&GDTP showed an improved survival compared to that predicted by the corticosteroid randomization after significant head injury (CRASH) model, but we did not compare contemporary outcomes with those of historical controls from our own institution [6,7]. Therefore, this study compared the mortality and functional outcomes of patients with sTBI who were treated during a pre-MM&GDTP control period of 2 years with a subsequent 5-year period, during which the MM&GDTP was implemented.

METHODS

This study involved a retrospective chart review, and an informed consent waiver was granted. This study compared the outcomes of patients (age range, 14–93 years) with sTBI treated at a single institution over a period of 7 years. It was divided into two time periods: a historic control period that extended from January 1, 2009 to December 31, 2010 and an intervention period from April 1, 2011 to December 31, 2015, during which patients with sTBI were treated with a 5-day MM&GDTP. The decision to limit the control group to those treated during these 2 years was based on the presence of a different group of neurosurgeons before that period. Patients excluded from the analysis included those treated between January 1, 2011 and March 31, 2011 because not all components of the MM&GDTP were available until April 1, 2011. Patients with one or more of the following criteria, after resuscitation, physiological stabilization, and a period of observation who were deemed to have suffered an unsurvivable brain injury were excluded from the study: (1) Glasgow Coma Scale (GCS) score 3 with dilated and fixed pupils, (2) GCS score 3 with pupils unreactive to light, (3) GCS score 3 and brain injury observed on a computed tomography (CT) scan of the head expected to result in permanent loss of all brain function above the brain stem, and (4) brain perfusion CT scan showing absence of cerebral blood flow.

Multimodality monitoring included monitoring of ICP, CPP, which was defined as the difference between the mean systemic blood pressure and ICP, $PbtO_2$ (Integra Licox Brain Tissue Monitoring; Integra LifeSciences, Princeton, NJ, USA) in mmHg; rSO_2 by NIRS (Medtronic & Covidien, Minneapolis, MN, USA); and hourly CMD data. The goal-directed therapy protocol included maintenance of normothermia (37°C) with dry water immersion (Arctic Sun 5000 Temperature Management System, Medivance-Bard, Louisville, CO, USA), $PbtO_2$ ≥ 20 mmHg, ICP ≤ 20 mmHg, CPP ≥ 70 mmHg, rSO_2 ≥ 55%, CMD lactate/pyruvate ratio (LPR) < 40, nutritional support targeted to ensure a respiratory quotient between 0.83 and 0.87 by indirect calorimetry on days 3 and 5, with calories adjustment as needed based on the day 3 respiratory quotient, and positive nitrogen balance by day 7. To achieve the threshold CPP value required to keep $PbtO_2$ and CMD LPR above the critical values, when needed, patients received a limited amount of normal saline (NS) (1,000 mL) and norepinephrine infusion at a dose of 0.1 to 0.2 μg/kg/min. Post-pyloric peptide-based enteral nutrition was initiated upon completion of the resuscitation phase. All patients were sedated to synchrony with the ventilator, avoidance of cough and a modified Ramsey score of 2 achieved with midazolam and propofol infu-

sion. Patients were treated using a 2-tier approach based on their classification (Fig. 1). Osmotherapy included administration of 3% saline and the addition of either low- or high-dose mannitol when appropriate. Burst suppression, monitored with continuous electroencephalography, was initiated with an infusion of midazolam at a dose up to 15 mg/hr and propofol at a dose up to 100 μg/kg/min when ICP, low $PbtO_2$, or low rSO_2 were not responsive to first-tier therapy. The anti-shivering protocol used during the normothermic approach involved the use of a Bair Hugger set at 4°C with administration of a combination of acetaminophen, buspirone, fentanyl, midazolam, and propofol, and when needed, the addition of cisatracurium.

Indications for immediate craniotomy included symptoms of uncal herniation syndrome, midline shift > 1 cm, epidural hematoma volume > 30–40 mL, presence of subdural hematoma with thickness > 0.5 cm extending over the hemispheres or > 30–40 mL volume with a significant mass effect, and intraparenchymal hemorrhage > 30 mL in the temporal lobe or cerebellum with a significant mass effect. A large fronto-temporoparietal (≥ 12 × 15 cm) decompressive craniectomy was employed for patients with late refractory ICP that did not respond to second-tier treatment modalities. All intracranial monitors were inserted within 2–4 hours of sTBI diagnosis, except for patients who went directly to the operating room for evacuation of mass lesions and had monitors placed after the craniotomy.

A multi-channel monitor (Moberg ICU Solutions, Ambler, PA, USA) provided continuous online recording of all multimodality monitoring minutes of brain flow and oxygen variables. CMD was

Type A

ICP ≤20 mmHg, CPP ≥70 mmHg, rSO_2 >55%, $PbtO_2$ ≥20 mmHg, CMD LPR <40
No further therapy needed.

Type B

Sustained ICP >20 mmHg, CPP ≥70 mmHg, NIRS >55%, $PbtO_2$ ≥20 mmHg, CMD LPR <40
Therapy aimed at decreasing ICP
Tier 1:
- Elevate the head of the bed by 30°
- Maintain normothermia (37°C)
- Drain CSF
- Adjust sedation with midazolam/propofol
- 3% NS to sNa 155–160 mEq/L
- Mannitol 0.25–0.50 g/kg IV bolus to 320 mOsm/kg/H_2O or Osm gap <20

Tier 2: ICP >20 mmHg for >15 minutes despite tier 1 therapy
- Increase RR to keep PCO_2 32–35 mmHg
- High-dose mannitol 1.0–1.5 g/kg IV bolus if Osm <320 mOSm/L
- Repeat CT scan of the head to assess mass lesion progression
- If increased mass, proceed with decompressive craniectomy.

Type C

ICP <20 mmHg, CPP ≥70 mmHg, rSO_2 <55%, $PbtO_2$ <20 mmHg, CMD LPR >40
Therapy aimed at increasing $PbtO_2$ and decreasing LPR
Tier 1:
- Increase CPP to 100 mmHg with infusion NE if ICP decreases by ≥3 mmHg with increasing CPP
- Optimize sedation
- Increase FiO_2 100 then keep at 60%
- Increase PEEP to 10 cm H_2O

Tier 2:
- Increase midazolam to 10–15 mg/hr and propofol to 75–100 μg/kg/min
- Setup cEEG to 3–4 bursts/screen
- Drain CSF <15 mmHg
- If Hg <7 g/dL transfuse 3 units of PRBCs less than 7 days old
- CT scan for lesion progression
- If lesion progression observed on CT scan, proceed with decompressive craniectomy.

Fig. 1. Treatment algorithm. ICP, intracranial pressure; CPP, cerebral perfusion pressure; rSO_2, regional cerebral oxygen saturation; $PbtO_2$, brain tissue oxygen tension; CMD, cerebral microdialysis; LPR, lactate/pyruvate ratio; NIRS, near-infrared spectroscopy; CSF, cerebrospinal fluid; NS, normal saline; sNa, seum sodium; IV, intravenous; RR, respiratory rate; CT, computed tomography; NE, norepinephrine; PEEP, positive end-expiratory pressure; cEEG, continuous electroencephalogram; Hg, hemoglobin; PRBC, packed red blood cell.

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performed via a dual lumen catheter inserted concurrently with the Licox catheter. CMD data that were measured included levels of glucose (normal value, 14.4–46.8 mmol/L), lactate (2.0–3.8 mmol/L), pyruvic acid (119–213 μmol/L), glutamate (0.0–32.0 μmol/L), and glycerol (38.0–126 μmol/L) and LPR. CMD data and mean values of the measurements were averaged hourly. All patients with a GCS score < 10 on day 5 underwent tracheostomy with placement of a subglottic suctioning tracheostomy tube and percutaneous endoscopic gastrostomy between days 5 and 7.

Treatment during the control period included maintenance of CPP ≥ 60 mmHg and ICP monitoring with external ventricular drainage, control of increased ICP with drainage of CSF, infusion of 3% NS titrated to a serum sodium concentration of 155 mEq/L, and the infusion of mannitol titrated to 320 mOsm/L or an osmolar gap < 20 as rescue therapy for increased ICP. The timing and performance of the decompressive craniectomy were at the discretion of the individual neurosurgeon. $PbtO_2$ monitoring and CMD were not performed, and normothermia was not protocolized. Hyperthermia was controlled on an individual basis, and enteral nutrition was administered at the discretion of the individual neurosurgeon. Indirect calorimetry and nitrogen balance measurements were not monitored. The timings of tracheostomy and percutaneous endoscopic gastrostomy were decided by the individual neurosurgeon.

Data acquired included mechanism of injury; age; sex; hemodynamics; GCS scores on admission and upon completion of the resuscitation phase and a period of physiological stabilization and observation; abbreviated injury score-head (AIS-H); Marshall Class; injury severity score (ISS); performance of decompressive craniectomy; ventilator and intensive care unit days; length of stay; predicted mortality (PM) by the CRASH model; and actual mortality. The GCS score obtained after completion of the resuscitation phase and a period of physiological stabilization and observation was used for statistical analysis because of its improved prognostic value over the GCS score acquired on admission. Continuous data are presented as means with standard deviation, and nonparametric data are presented as medians with interquartile range (IQR). Statistical analysis was limited to the comparison of the 99 patients who underwent treatment with the MM&GDTP with a control group of 67 patients who underwent conventional ICP-CPP treatment. Of note, all but one (MFS) of the neurosurgeons treating the patients during the two study intervals remained the same; however, during the intervention period, the neurosurgeons agreed to treat the patients with the MM&GDTP. Analysis of continuous data was performed with an unpaired *t*-test, and analysis of categorical data was performed with a chi-square or Fisher's exact test. Medians were compared using a nonparametric Mann-Whitney *U*-test. Stepwise logistic regression analysis was performed to identify variables predictive of outcome. The inverse probability of treatment weighted adjusted logistic regression models (SAS ver. 9.4; SAS Institute, Cary, NC, USA) were used to study the effect of MM&GDTP on mortality and functional outcomes. Statistical significance was accepted to correspond to a *P*-value less than 0.05.

RESULTS

A total of 810 patients with sTBI were admitted to our Level I Trauma Center between January 1, 2009 and December 31, 2015. One hundred and twenty-three patients died between days 1 and 2 or progressed to brain death from unsurvivable brain injury, and 316 patients with AIS-H < 4 were excluded; therefore, 371 patients were included for further analysis. An additional 205 patients with AIS > 0 in other body regions were excluded to limit the analysis to patients with isolated sTBI. Of the 166 remaining patients, 67 (control group) were treated with an ICP-CPP targeted approach following the Brain Trauma Foundation guidelines, whereas the 99 patients in the intervention group were treated with the MM&GDTP (Fig. 2); the patients were matched for sex,

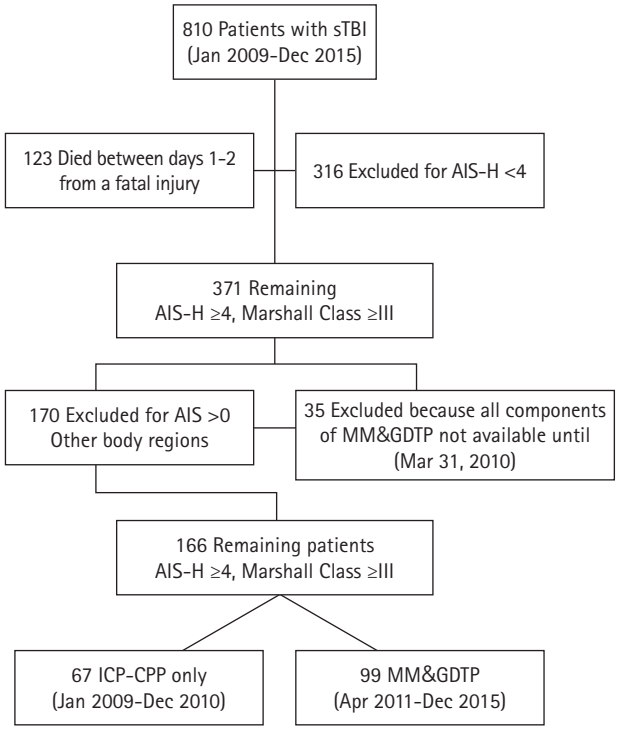

Fig. 2. Study design flowchart. sTBI, severe traumatic brain injury; AIS-H, abbreviated injury score–head; MM&GDTP, multimodality monitoring and goal-directed therapy protocol; ICP-CPP only, intracranial pressure-cerebral perfusion pressure targeted approach.

Table 1. Patients characteristics

Variable	All patients (n=166)	MM&GDTP (n=99)	ICP-CPP only (n=67)	*P*-value
Age (yr)	56±23	59±22	51±23	0.02
Male:female	121:45 (72.9/27.1)	70:29 (70.7/29.3)	51:16 (76.1/23.9)	0.48
SBP (mmHg)	143±30	146±31	138±28	0.08
GCS score	3 (3–5)	3 (3–3)	3 (3–6)	1
AIS-H 4	84	53 (53.5)	31 (42.3)	0.42
AIS-H 5	82	46 (46.5)	36 (57.7)	0.42
ISS	20.4±4.5	20.0±4.5	20.8±4.5	0.89
DC	35 (21.0)	21 (21.2)	14 (20.9)	1
Marshall Class III	53 (31.9)	32 (32.3)	21 (31.3)	1
Marshall Class IV	34 (20.4)	20 (20.2)	14 (20.9)	1
Marshall Class V	35 (21.0)	21 (21.2)	14 (20.9)	1
Marshall Class VI	44 (26.7)	26 (26.3)	18 (26.9)	1
DC mortality	16/35 (45.7)	9/21 (42.8)	7/14 (50)	0.73
PM CRASH (%)	52±26	55±26	50±26	0.22
Hospital mortality	46 (27.7)	23 (23.2)	23 (34.3)	0.15
GOS score	3 (1–4)	4 (2–4)	2 (1–3)	0.01
GOS score >3	65 (39.2)	50 (50.5)	15 (22.4)	0.003

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
MM&GDTP, multimodality monitoring and goal-directed therapy protocol; ICP, intracranial pressure; CPP, cerebral perfusion pressure; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; AIS-H, abbreviated injury score–head; ISS, injury severity score; DC, decompressive craniectomy; PM, predicted mortality; CRASH, corticosteroid randomization after significant head injury; GOS, Glasgow Outcome Scale.

Table 2. Covariates by weight

Characteristics	Unweighted			Weighted by inverse probability of treatment		
	ICP-CPP	MM&GDTP	SMD	ICP-CPP	MM&GDTP	SMD
Age	59±22	51±23	–0.367	57±37	56±30	0.063
ED SBP (mmHg)	138±28	146±31	–0.275	143±45	143±40	–0.003
ED GCS	3.7±1.5	4.4±1.9	–0.417	4.1±3.0	4.1±2.3	0.023
Sex			0.023			–0.043
Male	51 (76.1)	70 (70.7)		125 (74.6)	120 (72.6)	
Female	16 (23.9)	29 (29.3)		43 (25.4)	45 (27.4)	
AIS-H			–0.166			–0.043
4	31 (46.3)	53 (53.5)		82 (48.4)	84 (50.5)	
5	36 (53.7)	46 (46.5)		87 (51.6)	82 (49.5)	
Decompressive craniectomy			0.008			–0.003
0	53 (79.1)	78 (78.8)		131 (77.8)	129 (77.9)	
1	14 (20.9)	21 (21.2)		37 (22.2)	36 (22.1)	
Logit of the propensity score			0.650			–0.024

Values are presented as mean±standard deviation or number (%). SMD were used to assess the balance of the covariates before and after inverse probability of treatment weighting between the ICP-CPP and MM&GDTP groups. An SMD value <0.1 was accepted to correspond to adequate balance.
ICP, intracranial pressure; CPP, cerebral perfusion pressure; MM&GDTP, multimodality monitoring and goal-directed therapy protocol; SMD, standardized mean difference; ED, emergency department; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; AIS-H, abbreviated injury score–head.

GCS score, ISS, AIS-H, Marshall Class, decompressive craniectomy, and PM by the CRASH model.

The pre- and post-propensity matching variables for the two groups are shown in Tables 1 and 2. Before propensity matching, patients in the intervention group were significantly older than those in the control group. As shown in Table 1, there was an almost equal distribution of patients with Marshall Class III to VI between the two groups. The patients in the intervention group required a higher CPP of 83 ± 6 mmHg to achieve a rSO_2 > 55% with a $PbtO_2$ ≥ 20 mmHg and a CMD LPR < 40 with pyruvate < 120 mmol/L and glucose < 8 mmol/L, compared to patients in the control group, which required a mean of 66 ± 4 mmHg to stay

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within the target CPP of 60–70 mmHg and ICP ≤20 mmHg. The percentage of patients who required decompressive craniectomy did not differ between the two study periods. As seen in Table 3, there were no differences in age, sex distribution, GCS score, ISS, and PM between the patients in the two groups undergoing decompressive craniectomy, but more patients in the intervention group had an AIS-H 5 compared to that in the control group. While there was a lower mortality in the patients who underwent decompressive craniectomy during the MM&GDTP period, the difference did not achieve statistical significance.

The patients in the intervention group had a lower mortality rate than that of patients in the control group (23/99 [23.2%] vs. 23/67 [34.3%], respectively). However, the difference was not statistically significant. Nevertheless, there was a 32.4% reduction in mortality when patients treated during the two intervals were compared. Time to death was not significantly different between the two periods, 10 days (IQR, 7–16 days) as opposed to 8 days (IQR, 6–14 days), control versus intervention period, respectively ($P>0.05$). The analysis of mortality, stratified by Marshall Class, suggested a statistically significant improvement in mortality in patients with Marshall Class V pathology (Table 4). The mortality of patients with sTBI during the intervention interval was ascribable to sustained severe metabolic crisis defined by an LPR >40 in patients with a pyruvate level <120 μmol/L and a glucose level <8 mmol/L in the CMD effluent, despite the achievement of target levels for brain flow variables in some of the patients.

Functional outcome

Patients treated with the MM&GDTP had a statistically significant improvement in functional outcome (Glasgow Outcome Scale [GOS] score >3) at the time of transfer to different TBI rehabilitation centers compared to patients treated with the ICP-CPP targeted approach. Fifty of 99 patients (50.5%) treated as per the MM&GDTP, as opposed to 15 of 67 (22.4%) patients treated with the ICP-CPP targeted approach, had a GOS score >3 at a median of 18 days (IQR, 12–27 days) and 23 days (IQR, 16–36 days) ($P<0.05$). As seen in Table 5, the improved functional outcome was observed mostly in the group of patients treated with the MM&GDTP who did not undergo decompressive craniecto-

Table 3. Characteristics of patients who underwent decompressive craniectomy

Variable	Historic control group (n=14/67, 20.9%)	MM&GDTP group (n=21/99, 21.2%)	*P*-value
Age (yr)	48±14	51±22	0.65
Male sex	113	156	0.71
SBP (mmHg)	137±32	140±28	0.77
GCS score	3 (3–3)	3 (3–3)	1
ISS	22±4	22±4	1
AIS-H 4:5	5:9 (35.7:64.3)	6:15 (28.6:71.4)	0.22
GOS score >3	4 (28.6)	5 (23.8)	0.49
Vent-day	10 (6–21)	8 (4–16)	1
LOS (day)	19 (8–31)	17 (10–24)	0.45
PM (%)	59±21	55±25	0.62
Mortality	7 (50.0)	9 (42.8)	0.73

Values are presented as mean±standard deviation, median (interquartile range), or number (%).
MM&GDTP, multimodality monitoring and goal-directed therapy protocol; SBP, systolic blood pressure; GCS, Glasgow Coma Scale; ISS, injury severity score; AIS-H, abbreviated injury score–head; GOS, Glasgow Outcome Scale; Vent-day, number of ventilator days; LOS, length of hospital stay; PM, predicted mortality.

Table 4. Mortality stratified by Marshall Class

Marshall Class	Number	Overall mortality	ICP-CPP alone mortality	MM&GDTP mortality
III	53 (31.9)	7/53 (13.2)	1/21 (4.7)	6/32 (18.7)
IV	34 (20.5)	7/34 (20.2)	4/14 (28.6)	3/20 (15.0)
V	35 (21.1)	10/35 (28.6)	8/14 (57.1)	2/21 (9.5)[a]
VI	44 (26.5)	22/44 (50.0)	10/18 (55.5)	12/26 (46.1)
Total	166	46/166 (27.7)	23/67 (34.3)	23/99 (23.2)

Values are presented as number (%).
ICP, intracranial pressure; CPP, cerebral perfusion pressure; MM&GDTP, multimodality monitoring and goal-directed therapy protocol.
[a] $P<0.05$.

Table 5. Functional outcome stratified by decompressive craniectomy status

Group	GOS score >3		
	No decompressive craniectomy	Decompressive craniectomy	Total
ICP-CPP	11/53 (20.7)	4/14 (28.6)	15/67 (22.4)
MM&GDTP	45/78 (57.7)	5/21 (23.8)	50/99 (50.5)

Values are presented as number (%).
GOS, Glasgow Outcome Scale; ICP, intracranial pressure; CPP, cerebral perfusion pressure; MM&GDTP, multimodality monitoring and goal-directed therapy protocol.

my. In contrast, patients in the ICP-CPP group showed similar functional outcomes, independent of the performance of decompressive craniectomy. Of note, AIS-H and age were the only two variables predictive of functional outcome and mortality with the following odds ratios (OR) with 95% confidence intervals (CI): 5.12 (2.80–9.33) and 1.02 (1.01–1.04), respectively ($P < 0.001$). The inverse probability of treatment weighted logistic regression models with the following covariates: age (in years), systolic blood pressure, sex, GCS score (3–15), AIS-H (4–5), and decompressive craniectomy for the two dependent outcome variables, death and functional outcome (GOS score > 3), showed that the MM&GDTP did not improve mortality (OR, 0.66; 95% CI, 0.40–1.07; $P = 0.089$) but improved functional outcome by 3.5 fold (OR, 3.56; 95% CI, 2.22–5.70; $P < 0.001$) compared to the ICP-CPP treatment strategy.

DISCUSSION

The treatment of patients with sTBI remains controversial from the standpoint of the best monitoring modalities and approach to reach specific endpoints of targeted therapy. This is a result of the conflicting conclusions of clinical trials, some of which showed that for patients with sTBI care based on clinical monitoring and imaging alone is as effective as maintaining monitored ICP ≤ 20 mmHg. However, other studies have showed a potential benefit for an ICP-$PbtO_2$ targeted treatment over an ICP-CPP targeted strategy from the standpoint of reducing duration and depth of brain hypoxia but without a survival advantage. Moreover, some studies have shown a survival advantage at 6 months from decompressive craniectomy in patients with refractory intracranial hypertension but a higher rate of vegetative state, lower and upper severe disability than that seen with medical care; nevertheless, these have not shown any difference in the rates of moderate disability and good recovery between patients treated with decompressive craniectomy and those treated with medical therapy alone [4,8,9].

Our approach for the treatment of patients with sTBI has evolved over time from an initial ICP-$PbtO_2$ targeted therapy to one that includes maintenance of normothermia, early achievement of adequate nutritional support targeted to a positive nitrogen balance by day 7 using indirect calorimetry, in addition to reaching specific endpoints of brain flow and cerebral metabolism assessed using $PbtO_2$, rSO_2, and CMD data.

We have previously studied the effectiveness of the MM&GDTP for the treatment of patients with sTBI by comparing our mortality rate to that predicted by the CRASH model [6]. We believe that this approach for analyzing our results led us to prematurely conclude about the superiority of our approach over the more conservative ones owing to the overestimation of mortality rate by the CRASH model and failure to compare our cohort to a historic control group of patients [7]. For this reason, we decided to assess the efficacy of our recent MM&GDTP by comparing patients treated with this protocol to a historical group of patients treated in the same institution by the same neurosurgeons but without the new protocol. We limited our comparison to patients with the most severe form of isolated TBI, namely, AIS-H ≥ 4 and Marshall Class ≥ III. While we still used the CRASH model to compare the mortality rate to the predicted one, we were interested in assessing whether the introduction of the MM&GDTP would improve the mortality and functional outcome of patients with sTBI compared to those of a recent historical group of patients matched for the severity of TBI and treated by the same group of neurosurgeons with excellent results.

The implementation of the MM&GDTP decreased the mortality rate among patients with sTBI, from 34.3% to 23.2%, yielding a 32.3% reduction. However, the difference in mortality was not statistically significant. The treatment of patients using the MM&GDTP provided a statistically significant benefit in functional outcome, as measured by the GOS. This improvement in functional outcome was observed mostly in the group of patients treated with the MM&GDTP who did not undergo decompressive craniectomy. Patients treated with the MM&GDTP who underwent decompressive craniectomy did not have improved functional outcome when compared with their counterparts in the ICP-CPP treated group. We believe that the failure of decompressive craniectomy to offer a benefit in functional outcome in both groups can be attributed to several reasons, such as the assessment of functional outcome at discharge from the hospital and at 6 months after discharge may be a premature endpoint for patients with sTBI. The outcomes of decompression continue to improve beyond 6 months, and possibly even beyond 12 months. Additionally, while decompressive craniectomy decreases ICP and improves brain compliance and cerebral blood flow, it may not pro-

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vide a benefit to patients with devastating structural brain lesions, such as those in the brainstem that may have not been detected on CT and instead could have been identified before decompression by magnetic resonance imaging. Another important reason why patients in the intervention group who underwent decompressive craniectomy did not have an improved mortality rate and favorable functional outcome could be because the secondary decompressive craniectomy was performed for "early" refractory ICP elevation, defined as an increased ICP >20 mmHg for >15 minutes not responsive to tier 2 therapy (Fig. 1). Early secondary decompressive craniectomy is no longer recommended for improving mortality and favorable outcomes [10].

Since there was no difference in the severity of the brain injury as per GCS score, AIS-H, and Marshall Class between the patients during the two intervals, we that the outcomes experienced by patients during the control period were due to the limitations of the ICP-CPP targeted approach, particularly the inability to identify a suboptimal $PbtO_2$ leading to cerebral metabolic crisis despite the achievement of adequate ICP and CPP. In 2005, Stiefel et al. [11] demonstrated that the use of both ICP and brain tissue PO_2 monitors and therapy directed at brain tissue PaO_2 were associated with reduced patient death following sTBI. Subsequently, in 2006, the same investigators, in a study of 25 patients undergoing neurocritical care monitoring, demonstrated that 47% of patients had a $PbtO_2$ <20 mmHg despite a CPP and an ICP ≥60 and <25 mmHg, respectively, highlighting the limitations of the ICP-CPP approach for the treatment of patients with sTBI [12]. In 2010, Spiotta et al. [13] corroborated the beneficial impact of $PbtO_2$-guided therapy on the outcome of patients with sTBI. They reported a decrease in mortality from 45% in 53 patients whose therapy was guided by the ICP-CPP to 25% in 70 patients whose therapy was guided by CPP-$PbtO_2$.

We hypothesize that the poor functional outcomes of patients treated before the implementation of the MM&GDTP is likely the result of the suboptimal information provided by ICP, as opposed to the additional information available from the $PbtO_2$ and CMD data during the intervention period. Another reason for the poor outcomes during the control period may be related to the maintenance of CPP to values between 60 and 70 mmHg, which, based on the data provided by CMD, is often associated with metabolic crises and may lead to adverse outcomes, if sustained. The additional information available from the $PbtO_2$ and CMD data can be used to optimize the individual level of CPP and, therefore, may limit the number of metabolic crisis events, which in turn may yield better outcomes.

The improved mortality experienced in the setting of a Level I trauma center already performing at an observed to expected ratio less than one for patients with sTBI may be attributed to the implementation of this MM&GDTP since this was the only difference between the treatments of patients with sTBI in the two study intervals. It appears that the addition of more advanced monitoring methods, which can identify cerebral blood flow and brain oxygen crisis events, added to the armamentarium of a group of very competent neurosurgeons and surgical intensivists , provides a more sensitive methodology to monitor and minimize the number and duration of cerebral metabolic crises. This may in turn improve 30-day survival for patients with sTBI and, more importantly, their functional outcome.

ICP may represent a non-specific marker that highlights the dynamic changes occurring in the brain, and both waveform data and cerebrovascular reactivity index values can be derived from ICP monitoring, which may help guide therapy. However, a therapeutic strategy that uses ICP monitoring and CPP as endpoint of therapy may be less sensitive to the identification of brain oxygen crises related to brain flow and cerebral metabolism when compared to $PbtO_2$ monitoring and the metabolic data provided by CMD to the identification of brain oxygen crises related to brain flow and cerebral metabolism [14].

As noted in our results, patients treated with the MM&GDTP required a much higher CPP to provide the cerebral blood flow needed to avoid the development of cerebral metabolic crisis compared with the CPP of the patients treated with the ICP-CPP targeted therapy. However, despite the higher CPP, some of the patients who died during the intervention interval suffered several episodes of severe metabolic crisis, which were ultimately responsible for their death. As previously reported, severe metabolic crisis can occur even in the presence of adequate CPP, rSO_2, $PbtO_2$, and ICP, although the number of these events and their duration is significantly lower in survivors than in non-survivors, who typically experience on average more than 2 hours of severe metabolic crisis when CPP and $PbtO_2$ are less than 60 and 20 mmHg, respectively [7].

Some authors have reported an increased incidence of acute respiratory distress syndrome (ARDS) in patients with sTBI treated with hypervolemia to increase CPP [15,16]. Our patients did not experience any episode of ARDS despite our approach targeting CPP values much higher than previously reported. The method used to increase CPP may have played a role in the difference in the incidence of ARDS. The use of norepinephrine instead of large amounts of crystalloids to raise CPP may explain the difference between our results and those reported by other authors. It is likely that in the setting of a capillary leak syndrome triggered by trauma, as it occurs in sTBI, the infusion of a large volume of crystalloids to raise CPP may lead to a higher incidence of ARDS as

opposed to the incidence seen with an alternate approach that uses a vasoconstrictive agent to achieve a higher CPP to maintain $PbtO_2 \geq 20$ mmHg and CMD LPR < 40 mmHg.

Based on our institutional experience, we believe that the "optimal" CPP threshold is higher than the recommended 60–70 mmHg in patients with a $PbtO_2 < 20$ mmHg and $rSO_2 < 55\%$. Additionally, the ICP response to increased CPP in patients with intact autoregulation is characterized by a significant decrease in ICP; therefore, attempts should be made for each individual patient with intact autoregulation to identify the "optimal" CPP. Targeting the treatment of patients with sTBI to this individualized "optimal" CPP may be more effective than the treatments targeting existing consensus-based guideline thresholds. Two prospective pilot studies evaluating CPP-optimized tailored therapies in different settings have demonstrated an improvement in patient physiology and outcomes [17,18].

Our study has many limitations that prevent us from suggesting that our conclusions are generalizable. First, it represents a single institution's 7-year experience, with the control group being limited to those treated only during 2 years, and it is possible that the results are affected by the difference in the number of patients between the two study periods. The second limitation is the inability to identify which of the several threshold target values included in the MM&GDTP may have affected the improvement in mortality and functional outcome, and whether the observed improvements were due to a Hawthorne effect during the intervention period of the study. Third, the inherent increased complexity of the MM&GDTP compared to the ICP-CPP targeted treatment may have led to a much more intense overall monitoring and treatment and, possibly, fewer episodes of hypoperfusion during the intervention period compared to that during the historic control period. The fourth limitation is the absence of 6- and 12-month data regarding the overall functional outcome of the surviving patients in both groups.

The results of our study suggest that a therapeutic strategy based on a MM&GDTP targeting threshold-defined values may reduce the mortality and improve the functional outcome of patients with sTBI, compared to those seen with an ICP-CPP treatment strategy, by enhancing cerebral oxygenation and brain metabolism through the optimization of cerebral blood flow. However, we believe that much larger studies are needed to understand the role of the MM&GDTP as a whole and of each individual component to reveal the patient-specific brain injury pattern in order to formulate an individual optimal treatment plan. Monitoring devices themselves will not improve outcomes; they are needed to identify specific physiological patterns of survivorship and improved functional outcomes that can be used for the timely implementation of individualized treatment for patients with sTBI.

ARTICLE INFORMATION

Ethics statement

The New York Medical College Institutional Review Board approved the study design and methodology (L-11,356). This study is a retrospective chart review, and as such, there is no need for an informed consent.

Conflict of interest

No potential conflict of interest relevant to this article.

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Author contributions

Conceptualization: CPM, MFS. Data curation: CPM. Formal analysis: CPM. Methodology & Project administration: CPM, PP. Visualization: CPM, MFS. Writing–original draft: CPM, PP. Writing–review & editing: CPM, PP, JMcN, EL, AL, MFS.

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Refractory brainstem encephalitis mimicking progressive cerebral infarction: infliximab and methotrexate as a salvage immunotherapy

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CASE REPORT

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Background: Brainstem encephalitis is a rare, severe, and potentially life-threatening inflammation of the central nervous system, exhibiting various treatment responses and outcomes owing to multiple etiologies.
Case Report: We describe the favorable outcome of salvage immunotherapy using a combination of infliximab and methotrexate in a 62-year-old woman with refractory brainstem encephalitis. The patient was initially presumed to be at a subacute stage of medullary infarction but showed progressively worsening conditions involving cervical myelopathy, despite having completed the schedule of subsequent immunotherapy with intravenous methylprednisolone, immunoglobulin, and rituximab. After completion of four sessions of weekly rituximab injection, she was treated with 5 mg/kg of infliximab, scheduled at 0, 2, and 6 weeks, along with methotrexate (weekly 12.5 mg). After completion of infliximab injection and maintenance with methotrexate treatment, she showed an improving course of quadriplegia.
Conclusion: This case report provides evidence for the potential efficacy of infliximab with methotrexate in cases of refractory brainstem encephalitis.

Keywords: Brainstem encephalitis; Subacute cerebral infarction; Infliximab; Immunotherapy

INTRODUCTION

Brainstem encephalitis is a rare, severe, and potentially life-threatening inflammation of the central nervous system that exhibits various treatment responses and outcomes owing to multiple etiologies [1]. However, owing to the risk of surgical biopsy of vulnerable structures such as the brainstem, the etiological evaluation of neuroinflammatory and immune-mediated brainstem lesions has been limited [2]. There is a need for detailed clinical assessment and investigations using magnetic resonance imaging (MRI) for detection of lesion location, distribution, and morphology, and cerebrospinal fluid (CSF) and serum studies for detection of infectious sources, autoimmune and paraneoplastic antibodies, and others [3].

Besides the difficulty in differential diagnosis of various inflammatory diseases in the brainstem, determining the ideal candi-

dates for therapeutic management of brainstem encephalitis is difficult and a serious concern, especially in worsening cases where the causative pathogen has not been detected. Thus, conventional immunotherapy using intravenous steroids and immunoglobulin has been considered for empiric immune therapy because of the lack of controlled trials for the treatment of related disorders [4]. Furthermore, recent studies have suggested that autoimmunity is an emerging and common etiology of cryptogenic encephalitis [5]. Based on this estimation, early intensive immunotherapies are recommended in cases without evidence of infectious causes and in those where specific antibodies are not detected [6].

We describe a 62-year-old woman who presented with a catastrophic and rapid deterioration resulting in quadriplegia, which was initially suspected due to refractory cerebral infarction to the intensive stroke management. This was further aggravated despite subsequent immunotherapy with intravenous methylprednisolone, immunoglobulin, and rituximab under the assumption of cryptogenic brainstem encephalitis with cervical spinal cord involvement, until the completion of infliximab treatment as salvage immunotherapy.

CASE REPORT

A 62-year-old woman without any previous history of atherosclerotic risk factors or vascular and autoimmune disease was transferred to our center presenting with sudden onset of hiccups and paresthesia on the right face and limbs 5 days prior. Baseline laboratory tests revealed no definite evidence of systemic inflammation or infection. Brain MRI showed an increased diffusion-weighted image (DWI) sequence at the right medial medulla with a combination of an increased T2-weighted and T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence signal intensity and normal apparent diffusion coefficient (ADC) sequence (Fig. 1). Under the assumption of a subacute stage of infarction related to small vessel occlusion due to nonremarkable angiography, she was administered oral aspirin 100 mg, clopidogrel 75 mg, and atorvastatin 40 mg, and intravenous fluid maintenance.

However, by day 5 of hospitalization, the episode of paresthesia on the right face and limbs became more frequent and worse, accompanied by fluctuating motor weakness in the left limbs and hoarseness. Therapeutic-induced hypertension and triple anti-platelet agents including Cilostazol 200 mg were additionally administered, otherwise these problems were still worsening. Transfemoral cerebral angiography revealed no definite evidence of vascular abnormalities such as dissection, arteriovenous malformation, or fistula in the vertebrobasilar and spinal artery; intra-arterial and intravenous tirofiban treatment was then provided.

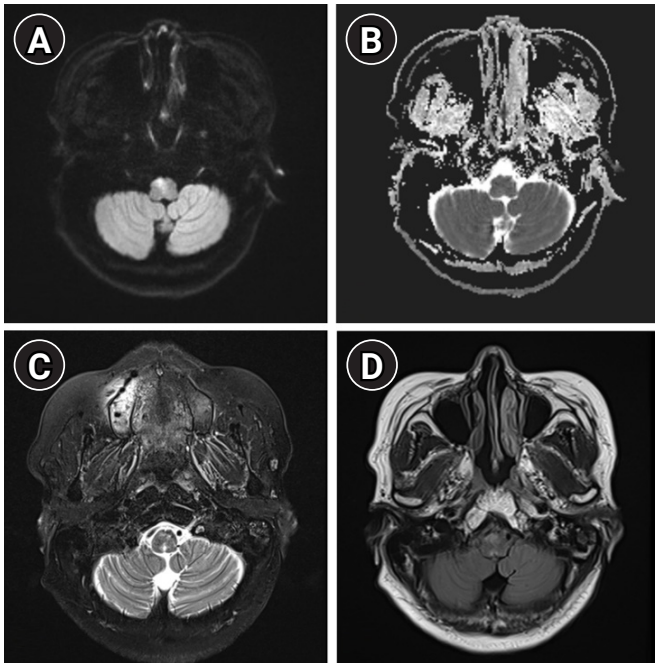

Fig. 1. Magnetic resonance imaging (MRI) findings at admission. Baseline brain MRI revealing increased signals on the diffusion-weighted imaging sequence on the right anteromedial medulla (A) with a subtle signal change on apparent diffusion coefficient sequence (B) and increased signal intensity on T2-weighted (C) and T2-weighted fluid-attenuated inversion recovery (D) sequences.

On day 13 of hospitalization, neurological deficits worsened further, and follow-up MRI of the brain and spine revealed a persistent signal change on the DWI sequence with an aggravated perilesional T2-weighted and T2-weighted FLAIR signal intensity and enhancement in the medulla oblongata with expansion to the C1 level of the spinal cord, without evidence of intraventricular and periventricular ependymal lesions (Fig. 2). At this stage, we considered brainstem encephalitis based on the aggravated MRI findings compatible with vasogenic edema and performed a workup for etiological diagnosis before immunotherapy. She denied any previous history of autoimmune diseases such as recurrent oral or genital ulcers, skin problems, ophthalmoplegia, ophthalmodynia or visual acuity problem, and limb paresthesia, and had normal findings on fundoscopic and visual field tests on ophthalmologic evaluation. Serum anti-aquaporin-4 antibodies were absent; we did not perform further evaluation of the myelin oligodendrocyte glycoprotein (MOG) and HLA-B51 test focusing on the possible diagnosis of Bechet disease or anti-MOG associated inflammatory demyelinating diseases.

CSF analysis was unremarkable, except for lymphocytic pleocytosis: cells 19/μL, protein 41.0 mg/dL, glucose 64 mg/dL, and

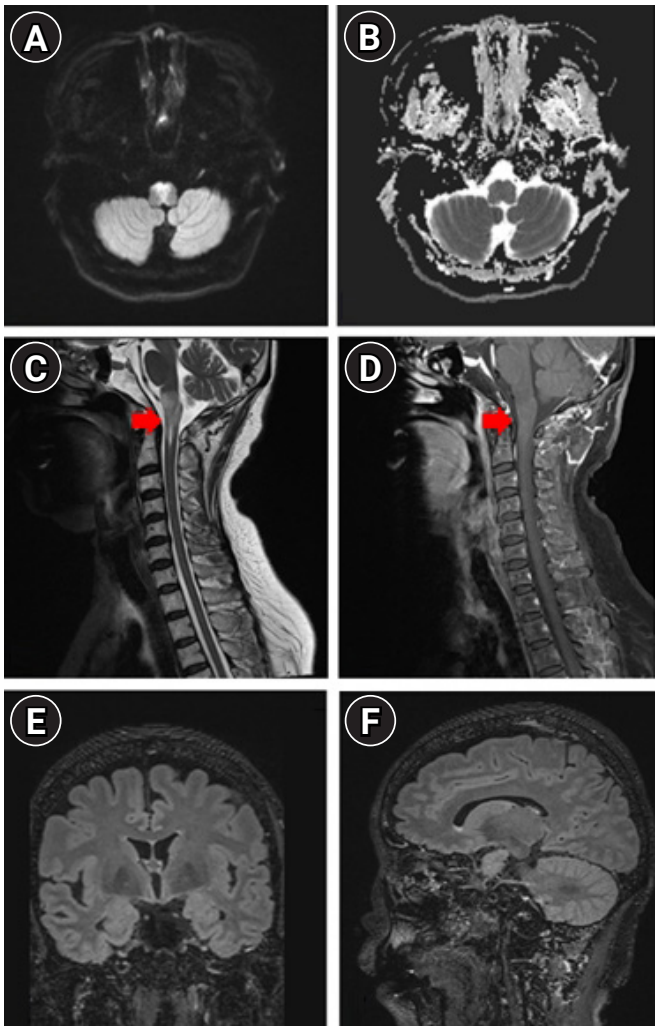

Fig. 2. Magnetic resonance imaging (MRI) findings at 2 weeks of hospitalization during management for infarction. Follow-up brain spine MRI revealing further increased signals on the diffusion-weighted imaging sequence on the bilateral anteromedial medulla (A) with a subtle signal change on apparent diffusion coefficient sequence (B) and increased signal intensity on T2 sequence within C1 level of the medullar oblongata and spinal cord with increased enhancement (red arrows; C, D, respectively) during the therapeutic-induced hypertension and anti-thrombotic treatment, including triple anti-platelet agents and tirofiban infusion without evidence of intraventricular and periventricular ependymal lesions (E, F).

lactate dehydrogenase below 50 IU/L. Oligoclonal bands were absent with mild elevation of albumin (31 mg/dL) and immunoglobulin G (5.45 mg/dL) in CSF. CSF stain and culture, and polymerase chain reaction test results for the detection of a wide range of bacteria, tuberculosis, fungi, and viruses, and cytospin tests for the detection of malignant cells were negative. Test results for the detection of serum influenza virus A/B antigen, antibodies (e.g., herpes simplex, varicella zoster, Hantaan, Leptospira, tsutsugamushi, Toxocara, and mycoplasma), blood culture, autoimmune tests (e.g., anti-nuclear, anti-double-stranded DNA, anti-thyroid peroxidase, anti-thyroglobulin, and anti-neutrophilic cytoplasmic antibodies, rheumatoid factor, and lupus anticoagulant), and immunofixation were negative. The serum angiotensin-converting enzyme levels were within the normal range. Tests for the detection of anti-ganglioside antibodies, including GQ1b, were negative in the serum. Computed tomography of the chest and abdomen and whole-body positron emission tomography revealed no definite evidence of malignancy. Test results for the detection of autoimmune encephalitis antibodies (NMDAR, AMPA1, AMPA2, LGI1, CASPR2, and GABA-B) and paraneoplastic antibodies (Hu, Yo, Ri, Ma2, CV2/CRMP5, amphiphysin, recoverin, SOX1, and titin) were negative.

Under the assumption of cryptogenic brainstem encephalitis, she received sequential treatment with 5 days each of 1,000 mg of intravenous methylprednisolone and 0.4 g/kg of intravenous immunoglobulin. However, she showed deteriorated quadriparesis with grade 2 on the Medical Research Council (MRC) scale accompanied with painful spasms and spasticity. She was then retreated with intravenous methylprednisolone for 5 days, followed by 375 mg/m^2 of rituximab treatment. However, despite completion of 4 weeks of weekly rituximab injection, neurological deficits worsened further to quadriplegia with grade 0 on the MRC scale accompanied with frequent spasms at intervals of several minutes resistant to multiple anti-epileptic drugs. Repeated examination of serum and CSF including all of the above-mentioned profiles revealed no significant difference compared to baseline findings, and follow-up brain MRI showed further expansion of diffusion-restricted lesions with increased perilesional signal intensity on T2-weighted and T2-weighted FLAIR sequences (Fig. 3). At this stage, we decided to treat her with 5 mg/kg of infliximab scheduled at 0, 2, and 6 weeks according to the manual for intractable Crohn disease with a combination of methotrexate (weekly 12.5 mg) for modulation of cell-mediated immunity to complement the prior immunotherapies mainly focusing on humoral immunity. After completion of infliximab injection with maintenance with methotrexate treatment, she showed an improving course of quadriparesis with grade 2 on the MRC scale and decreased frequency of spasms. Repeated CSF measurements showed an improving course of pleocytosis (from 19, 17, 11 to 2/μL) with persistently elevated protein (from 41.3, 46.9, 59.6 to 61.3 mg/dL) at baseline, 1 month (after completion of intravenous immunoglobulin and methylprednisolone), 2 months (after completion of rituximab treatment), and 3 months (after completion of the 2nd injection of infliximab). After 7 months of onset (3 months after completion of infliximab treatment), she was able to sit alone with further improvement of quadriparesis with grade 4

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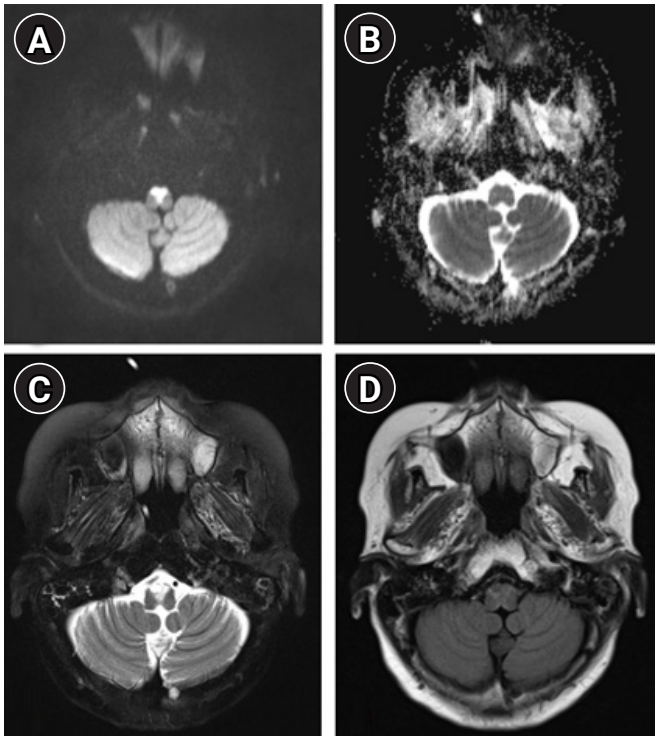

Fig. 3. Magnetic resonance imaging (MRI) findings at 2 months of hospitalization after completion of conventional immunotherapy. Follow-up brain MRI revealing expansion of diffusion-restricted lesions on the diffusion-weighted image sequence to both the anteromedial medulla (A) with a subtle signal change on apparent diffusion coefficient sequence (B) and increased perilesional signal intensity on T2-weighted (C) and T2-weighted fluid-attenuated inversion recovery (D) sequences, after completion of immunotherapy including intravenous methylprednisolone and immunoglobulin following completion of four sessions of weekly rituximab treatment.

on the MRC scale. Follow-up brain MRI revealed a decreased extent of abnormal T2-weighted and T2-weighed FLAIR high signal intensity in the bilateral anteromedial medulla and cervical spinal cord with normalized DWI and ADC sequences (Fig. 4).

DISCUSSION

We describe the favorable outcome of salvage immunotherapy using infliximab in combination with methotrexate in a 62-year-old female with refractory brainstem encephalitis, who was initially presumed to be at a subacute stage of medullary infarction with progressively worsening conditions despite having completed the schedule of subsequent immunotherapy with intravenous methylprednisolone, immunoglobulin, and rituximab.

Until now, the etiologies of brainstem encephalitis have been poorly studied; although several entities, such as Listeria rhombencephalitis, Bickerstaff's brainstem encephalitis, paraneoplastic

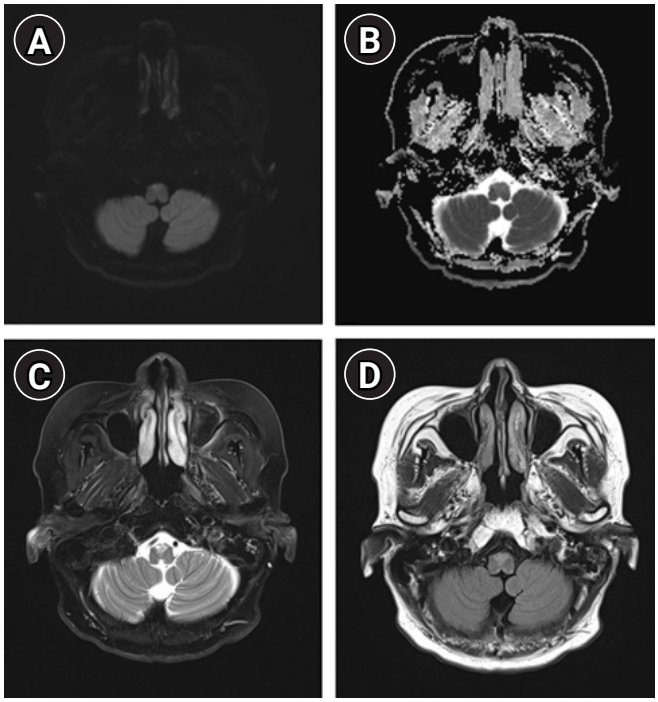

Fig. 4. Magnetic resonance imaging (MRI) findings at 10 months after symptom onset. Follow-up brain MRI revealing a normalized diffusion-weighted image (A) and apparent diffusion coefficient (B) sequence on both the anteromedial medullar and cervical spinal cord with decreased perilesional signal intensity on T2-weighted (C) and T2-weighted fluid-attenuated inversion recovery (D) sequences, 6 months after completion of infliximab treatment.

encephalitis, and neurosarcoidosis have been suggested as possible causes [2,7], the spectrum of causes and outcomes of brainstem encephalitis are unclear [1,8]. In our case, we failed to reveal the possible etiologies despite the broad investigation of CSF and serum with repeated measurements, due to lack of results from the high-risk needle biopsy of the upper cervical medulla oblongata. Furthermore, we also failed to achieve a therapeutic response with rituximab as adjunctive immunotherapy in addition to the conventional immunotherapy based on the current concept for the management of broad-spectrum encephalitis; several recent systematic reviews have recognized that early intensive immunotherapy is associated with better outcomes in autoimmune encephalitis [5]. Our case also showed a unique course of gradual aggravation of neurological deficit to complete quadriplegia until 14 weeks after symptom onset, and then achieved a gradual improvement of neurological deficit for 14 weeks after completion of intravenous immunotherapy with a maintenance of oral methotrexate (Fig. 5).

Thus, considering refractory brainstem encephalitis, including intractable myelopathy, we recognized that neurosarcoidosis was the most common etiology of cryptogenic cord problems based

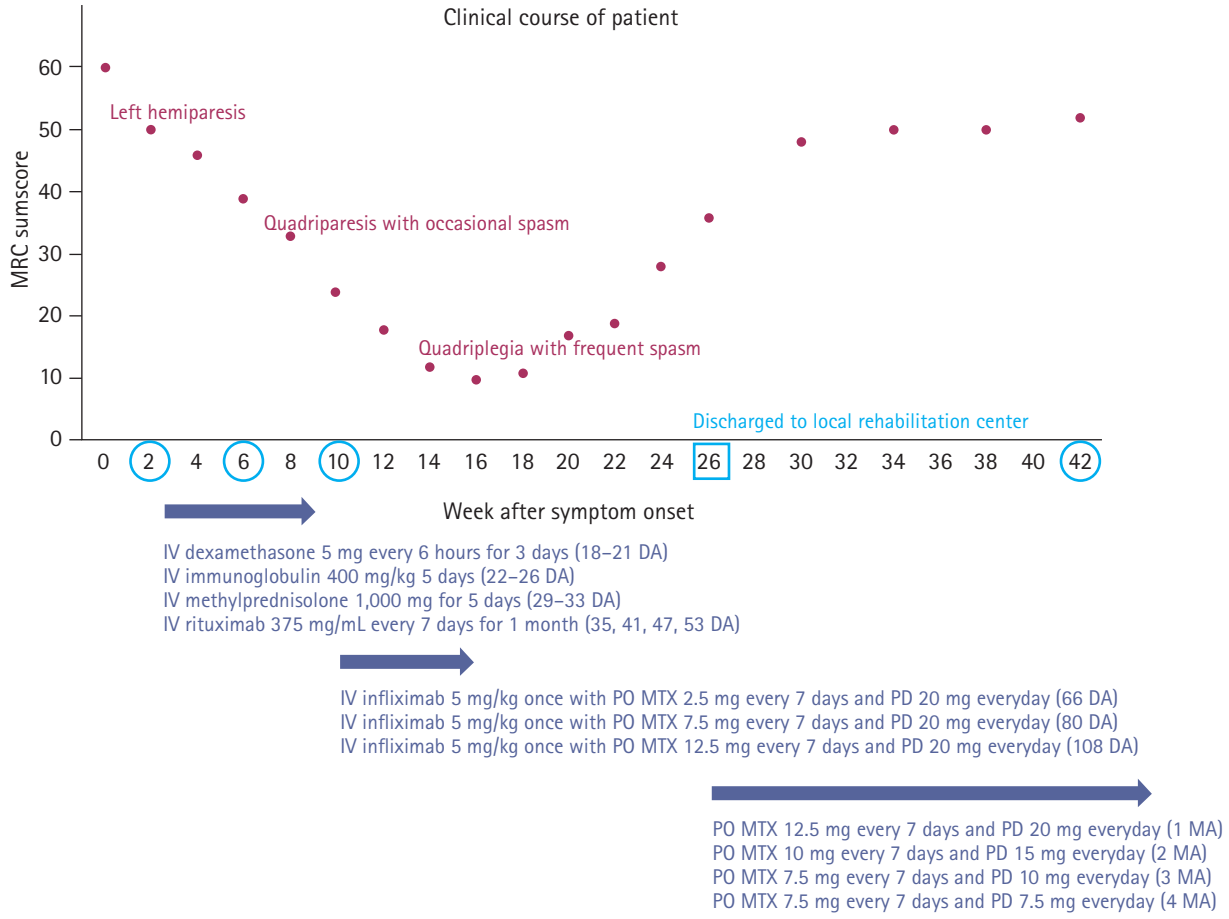

Fig. 5. Clinical course of patient. The patient's neurological deficit (measured by Medical Research Council [MRC] sumscore) and magnetic resonance imaging findings (blue circle) worsened until 18 weeks and gradually improved after completion of the scheduled escalation of immunotherapy until 16 weeks and maintenance of PO MTX and PD, following gradual tapering after discharge (blue square) at 26 weeks after symptom onset. MRC sumscore evaluates global muscle strength including manual strength of six muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion) on both sides using the MRC scale. Summation of scores gives MRC sumscore, ranging from 0 to 60 (0–36, quadriplegia to severe quadriparesis; 36–48, mild quadriparesis; 48–60 [max], normal strength). IV, intravenous; DA, days after onset; PO, per oral; MTX, methotrexate; PD, prednisolone; MA, months after discharge.

on biopsy results [9,10], and management with global immunosuppressant agents in combination with immunomodulatory monoclonal antibodies, such as infliximab, was considered to demonstrate effective management [11,12]. Infliximab can be considered as salvage immunotherapy in addition to rituximab, considering the different mechanisms of immunomodulation. It is a chimeric monoclonal antibody against tumor necrosis factor-α (TNF-α) and has emerged as a treatment option in refractory and steroid-dependent patients with neurosarcoidosis [12] as TNF-α is a cytokine critical for granuloma formation and maintenance in human sarcoidosis granulomas [11]. In contrast, rituximab is a monoclonal antibody against CD20-positive B cells and induces B-cell depletion, and consequently leads to suppression of autoimmune neurological disorders via modulation of immunity [13], with relative safety in terms of infectious adverse effects. Therefore, despite the lack of biopsy results, we attempted to treat the patient using infliximab as an adjunctive salvage immunotherapy and achieved gradual improvement in clinical features, as well as in findings of radiographic (mainly perilesional vasogenic edema) and CSF (pleocytosis) examinations. In addition, methotrexate has been well-documented for its efficacy in the treatment of rheumatoid arthritis and wide range of autoimmune diseases, showing the ability of modulation for inflammation; evidence favors the notion that the endogenous anti-inflammatory autocoid adenosine mediates the anti-inflammatory effects of methotrexate [14]. Intrathecal methotrexate has been considered for salvage immunotherapy in autoimmune encephalitis patients who failed to respond to first-line immunotherapy. However, although intrathecal injection of methotrexate may be reasonable with consideration of the poor penetration of the immune modulators such as

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intravenous immunoglobulin, steroids, and rituximab across the blood-brain barrier, methotrexate-induced neurotoxicity via intrathecal injection is still a concerning issue [15]. Thus, future studies are needed to confirm the efficacy and safety of the maintenance of oral methotrexate in combination with infliximab treatment. This case report provides evidence of the potential efficacy of infliximab with maintenance of methotrexate in certain cases of refractory cryptogenic brainstem encephalitis.

ARTICLE INFORMATION

Ethics statement

This study was approved by the Research Ethics Committee of Pusan National University Yangsan Hospital, and Informed consent was obtained from the patient to publish her case.

Conflict of interest

Dr. SH Ahn is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Conceptualization: SHA, SKB, JHS. Data curation: KNW, HSK. Formal analysis: SHA, KNW, HSK, JHS. Funding acquisition: SHA. Methodology: JR, SKB. Project administration: JHS. Visualization: JR, SKB. Writing–original draft: SHA. Writing–review & editing: all authors.

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Paralytic rabies mimicking Guillain-Barré syndrome: the dilemma still prevails

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CASE REPORT

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Background: Paralytic rabies lacks the hallmark signs of rabies at presentation and is often misdiagnosed as Guillain-Barré Syndrome (GBS). Sensitive antemortem diagnostic criteria for rabies is lacking, and the diagnosis is confirmed posthumously by demonstrating Negri bodies on brain biopsy. Antemortem brain and spine magnetic resonance imaging findings have recently been reported for paralytic rabies.
Case Report: We report a case of paralytic rabies in a young boy who was initially misdiagnosed with GBS. In this case, brain and spine magnetic resonance imaging (MRI) findings pointed towards paralytic rabies, which was confirmed by the presence of anti-rabies antibodies in the serum and cerebrospinal fluid analysis, and posthumously by Negri bodies on brain biopsy.
Conclusion: In patients with GBS, paralytic rabies should be considered as an alternative diagnosis, especially in regions where rabies is endemic, and early MRI of the brain and spine should be considered for the antemortem diagnosis of paralytic rabies.

Keywords: Paralytic rabies; Guillain-Barré syndrome; Magnetic resonance imaging

INTRODUCTION

Rabies leads to nearly 59,000 human deaths annually in over 150 countries [1]. Despite rabies being a fulminant problem with a high fatality rate, diagnosis of rabies, especially atypical or paralytic rabies, remains a challenge. This could be due to lack of hallmark signs of aerophobia/hydrophobia, autonomic disturbances, and initial presentation as acute flaccid paralysis (AFP) mimicking Guillain-Barré Syndrome (GBS) [2]. Further, lack of exposure history (cryptogenic) adds to the diagnostic problem [2]. We present a case of cryptogenic paralytic rabies mimicking GBS, thus delaying the diagnosis.

CASE REPORT

An 18-year-old boy presented with a history of fever for the past 7 days, weakness in the lower limbs for the last 5 days, and weakness in the upper limbs and difficulty in swallowing for the past 3 days. The patient was drowsy, but followed commands. He was unable

to lift his head and had a poor cough reflex and shallow respiration. The single breath count (an estimate of vital capacity; normal range, 25–30) was 5. Neck rigidity was not observed. Patient was areflexic, with mute plantar responses. The Medical Research Council grade for motor power was 2/5 and 0/5 for upper limbs and lower limbs, respectively, with normal sensory examination. Pupils were equal, reactive to light, and the fundus was normal upon examination. Laboratory investigations were normal except for serum sodium, which was 121 mmol/L (normal, 135–147 mmol/L). There was no history of dog bite, bat bite, or recent vaccination. A preliminary diagnosis of GBS was made, and large-volume plasmapheresis (LVPP) was planned.

Drowsiness was attributed to hyponatremia, and correction with 3% NaCl was initiated. Although the patient's sensorium improved by the next day, he became quadriplegic. The patient underwent tracheal intubation, and mechanical ventilation was initiated. The patient received four cycles of LVPP on alternate days. Cerebrospinal fluid (CSF) analysis revealed six cells; protein, 26 mg/dL; glucose, 82 mg/dL; and chloride, 113 mmol/L (normal CSF contains 0–5 white blood cells, 15–45 mg/dL protein, 40–70 mg/dL glucose, 118–132 mmol/L chloride). The chronic meningitis workup was also normal. Nerve conduction studies were planned but could not be performed due to logistic reasons. On the sixth day, the patient became drowsy and developed hypothermia and hypotension, requiring external forced air warming and noradrenaline infusion. Computed tomography of the brain revealed normal findings. Furthermore, extraocular movements became restricted in all directions, and the patient developed vertical nystagmus and pupillary asymmetry with sluggish reaction to light. In view of these signs, diagnosis was reconsidered to be either acute demyelinating encephalomyelitis (ADEM) or viral encephalitis; therefore, intravenous methylprednisolone 30 mg/kg/day and acyclovir were started on day 9. Simultaneously, magnetic resonance imaging (MRI) of the brain and spine was performed, and serum samples were sent for antibody testing to investigate infectious causes, such as Herpes simplex virus encephalitis, Japanese encephalitis, chikungunya, syphilis, hepatitis B, dengue, or rabies.

MRI of the brain (T2 weighted and fluid-attenuated inversion recovery) and spine (plain and contrast) revealed the involvement of cerebral cortical gray matter, midbrain, optic chiasma, hypothalamic region (Fig. 1), and central gray matter of the spinal cord in the lower dorsal and lumbar region with intense post-contrast enhancement of nerve roots of the cauda (Fig. 2), respectively. MRI findings were suggestive of paralytic rabies. Subsequently, the patient became deeply comatose, with pupils dilated, fixed, and unreactive to light. The patient died on day 15. Salivary polymerase chain reaction (PCR) for rabies viral RNA was negative on day 12. However, the rabies antibodies test by rapid fluorescent focus inhibition technique (RFFIT) came out positive on day 13 with a serum titer of 4,096 IU/mL (normally titers are not detectable if the patient is not vaccinated for rabies). The patient's father later confirmed a history of dog bite 2 years back on his left leg in the school (as told by his friends). The patient had not informed about this at home and was not vaccinated for rabies. The patient's parents refused an autopsy but agreed for transnasal brain biopsy and lumbar puncture. Post-mortem CSF-PCR for rabies virus was negative. However, the CSF-RFFIT titer for antibodies was < 16 IU/mL (detectable titers in the CSF is considered as positive for rabies irrespective of the vaccination status), and brain biopsy showed Negri bodies, confirming the diagnosis of rabies.

DISCUSSION

Our patient initially presented with rapidly progressing AFP, mimicking GBS, without any preceding history of animal bite (positive history surfaced just a day prior to his death). Although GBS is the most common cause of AFP, it is important to consider rabies as a differential diagnosis at the earliest, even in the absence of a history of animal bite, especially in regions where rabies is endemic [1,2]. In one of the largest retrospective studies, involving 34 patients with paralytic rabies over 30 years, authors reported that the most common misdiagnosis was GBS (17/34) followed by ADEM (10/34) based on the patients' initial clinical presentation [2]. There are also a few similar case reports [3-5]. Gadre et al. [2] observed that the incubation period between the time of animal bite and onset of rabies symptoms ranged from 7 days to 4 years. Paralytic rabies frequently presents as GBS, leading to a diagnostic dilemma. Furthermore, due to the lack of antemortem diagnostic criteria for rabies, the diagnosis remains challenging. Clinically, the presence of progressive paralysis with high-grade fever, bladder involvement, paraesthesia, rapid progression to cranial nerve palsies, altered mental status, deep coma, and the absence of albumin-cytological dissociation in CSF on laboratory examination, should raise the suspicion of paralytic rabies [2]. Major difference in the clinical course of paralytic rabies and furious rabies is attributed to the host immune response to the virus, which is defective in paralytic rabies and heightened in a furious form [6]. If we treat paralytic rabies with plasma therapy or immunoglobulins on the pretext of GBS, the possibility of protracted clinical course of the paralytic rabies and delayed encephalitic manifestations cannot be ruled out. It has been observed that immunotherapy and post-exposure prophylaxis can sometimes delay rabies manifestations and can present as paralytic rabies mim-

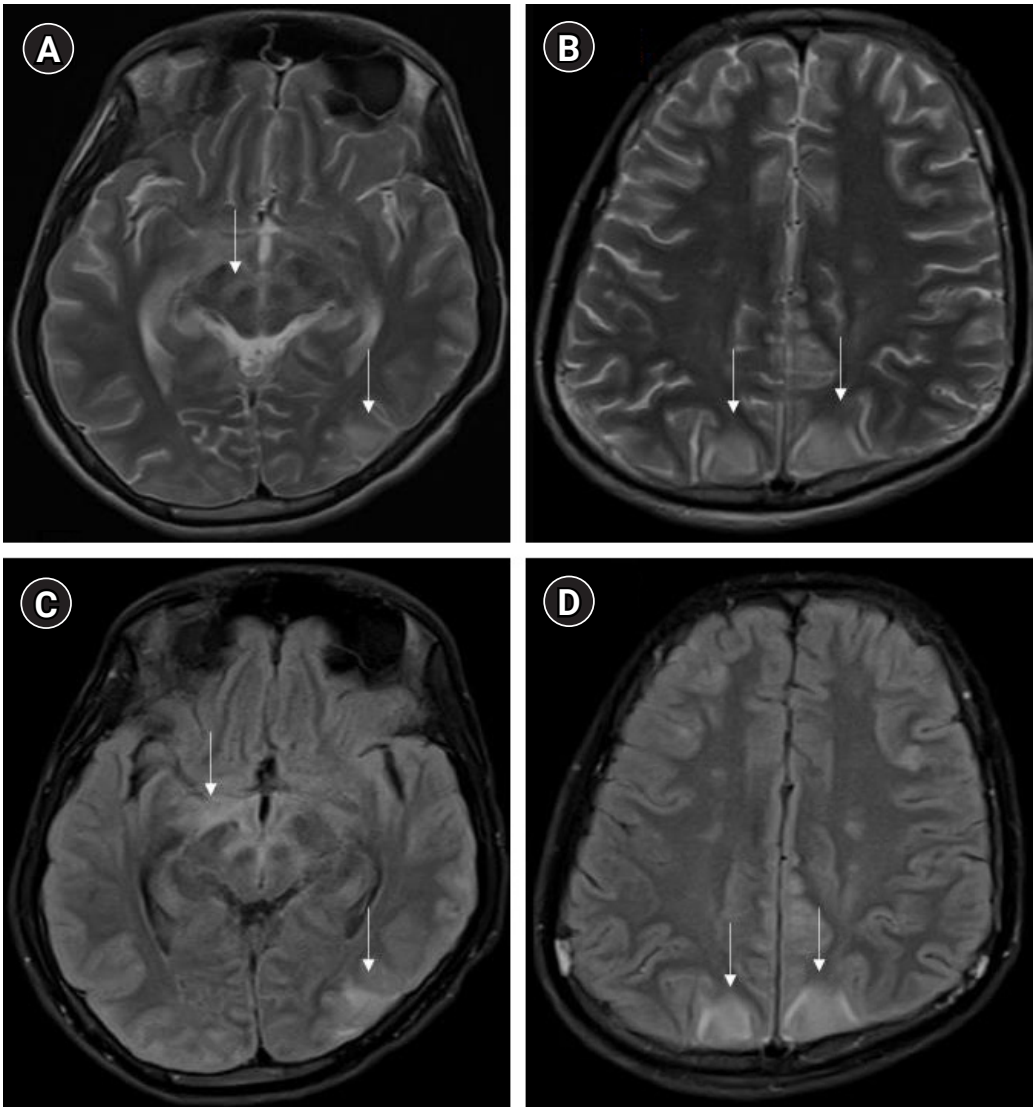

Fig. 1. Magnetic resonance imaging brain-T2 weighted axial image at the level of midbrain shows hyperintensity along the substantia nigra, mesial temporal structures, and left parieto-occipital region involving cortex and underlying white matter (A), at a higher level shows bilateral parieto-occipital hyperintensities involving the cortex and underlying white matter; subtle hyperintensities are also noted in centrum semiovale bilaterally (B). On fluid-attenuated inversion recovery axial images, the hyperintensities are better appreciated in the similar regions and additional hyperintensities are noted in the optic tracts and hypothalamic region (C) and bilateral frontal region (not apparent on T2) (D). Pathological changes are highlighted by vertical arrows.

icking GBS [7].

Antemortem diagnosis of rabies requires detection of viral RNA (in CSF, saliva, or skin) or neutralizing antibodies (in CSF or serum) by various methods, which are specific but have their own limitations with respect to sensitivity, turn-around time, availability, and affordability [8]. MRI findings in rabies have been found to be promising for diagnosing and distinguishing it from other common forms of AFP. As per available literature, MRI of paralytic rabies shows its predilection for specific areas, such as spinal cord, thalamus, hypothalamus, basal ganglia, brainstem, and hippocampus, which shows hyperintensity on T2 and fluid-attenuated inversion recovery [2-4]. In GBS, imaging findings are limited to nerve root enhancement in the cauda equina, sparing the brain parenchyma [9]. Imaging in ADEM predominantly involves white matter, although there can be cortical and deep gray matter involvement [10]. On the other hand, the hallmark of rabies is cerebral cortical and spinal gray matter involvement with relative sparing of the white matter, which may help differentiate rabies encephalitis from demyelinating disorders. Rabies encephalitis and paralytic rabies have similar MRI findings, although spinal cord and medullary involvement is more commonly observed in the paralytic form [11]. In our case, we found involvement of

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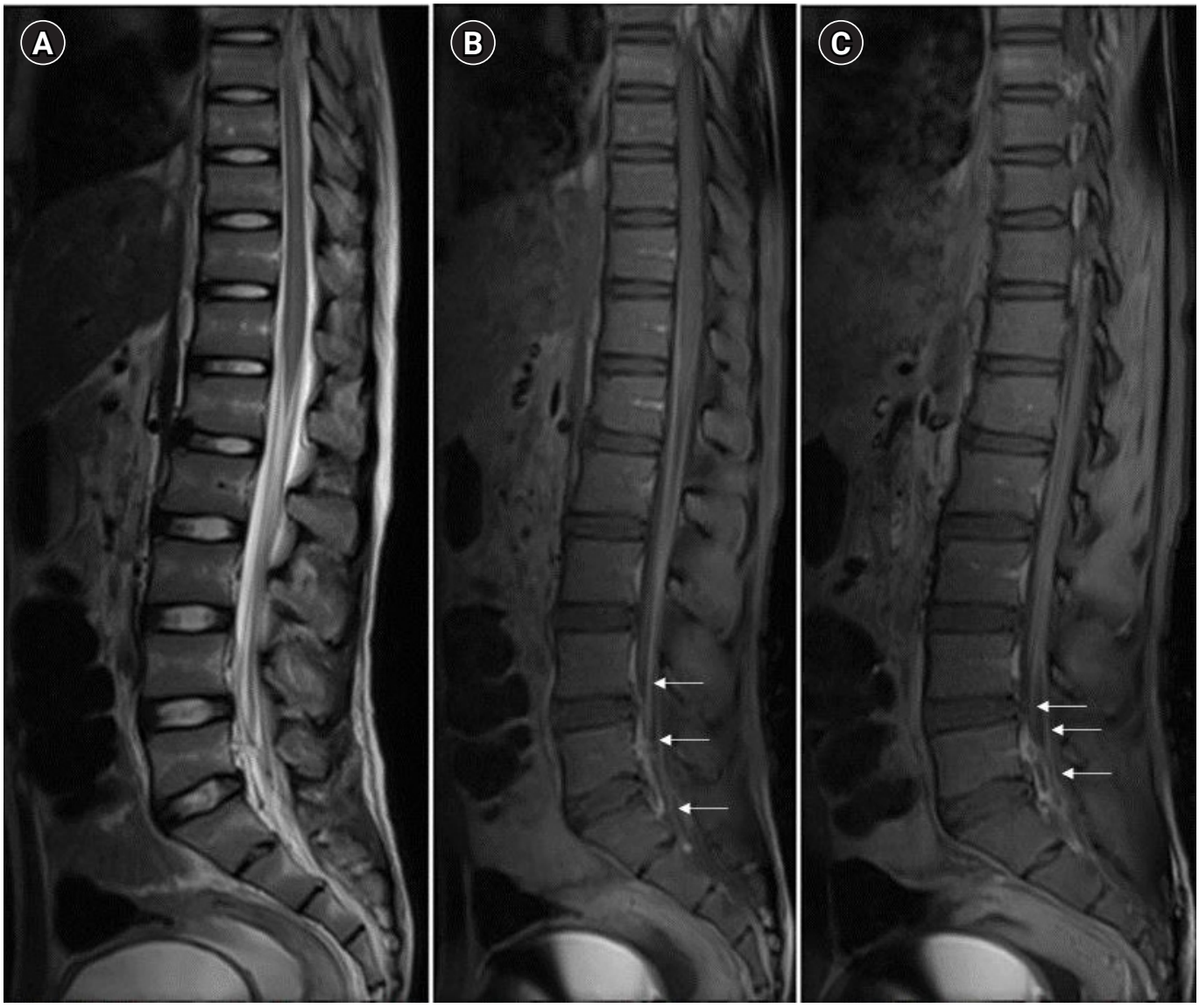

Fig. 2. Magnetic resonance imaging spine-T2 weighted sagittal image of the conus-cauda region shows subtle hyperintense signal changes in the conus and nerve roots of the cauda are slightly thickened (A). Post-contrast T1 fat saturation image shows intense enhancement of the cauda nerve roots along with conus enhancement (B) and nerve roots enhancement noted at parasagittal level (C), as indicated by horizontal arrows.

the mid brain, optic chiasma, hypothalamic region, and gray matter of the spinal cord with nerve root enhancement. Our MRI findings resonate with the existing literature on MRI in paralytic rabies.

Early diagnosis of paralytic rabies is crucial to prevent unnecessary treatment on the lines of GBS or other demyelinating disorders and to explain the prognosis to the family. This will enable us to take appropriate infection control measures. In addition, with the emerging cases of rabies survivors, early diagnosis can give an impetus in trying newer treatment modalities in addition to supportive care [11,12]. To prevent neuronal damage following viral infiltration and subsequent immune response, various treatment protocols have been tried in the past, which include induction of therapeutic coma or hypothermia, but they were not found to be effective [13]. Sedatives, such as barbiturates, ketamine, or midazolam, and other medications, such as amantadine, antiviral (ribavirin), high dose immunoglobulins, and interferon alpha, also did not show promising results [13,14]. Newer therapeutic approaches include the use of newer antivirals such as favipiravir, molecular engineering of rabies antibodies for passive immunity, exogenous cytokines, and more recently silencing RNA and artificial microRNAs are being investigated and need further exploration to test the possible protocol that will work in rabies management [13].

In a patient diagnosed with GBS, paralytic rabies should be

considered as a potential differential diagnosis, even in the absence of a history of animal bite, especially if the patient belongs to a rabies endemic region. To facilitate early antemortem diagnosis of rabies, MRI of the brain and spine should be considered along with the antemortem rabies-specific tests.

ARTICLE INFORMATION

Ethics statement

This case was reviewed and approved by the Institute Ethics Committee (IEC) of National Institute of Mental Health and Neurosciences (No. NIMHANS/IEC/2020-21 dated 02.12.2021). Written informed consent was obtained from the patient's father.

Conflict of interest

No potential conflict of interest relevant to this article.

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Conceptualization: RMS. Data curation: RMS. Formal analysis: RMS, HSP. Writing–original draft: RMS. Writing–review & editing: all authors.

Additional contributions

We thank the deceased patient's father for providing consent to publish this case report.

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Pneumococcal meningitis complicated by otomastoiditis and pneumocephalus confounding an acute ischemic stroke diagnosis

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CASE REPORT

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Background: Approximately one-fourth of admissions to stroke centers are diagnosed with non-stroke conditions or stroke mimics. Differentiating between these diagnoses and acute ischemic stroke is an important and time-sensitive task. The decision of whether or not to administer thrombolytic therapy is also a critical component, and its safety has been studied numerous times.
Case Report: This case presents a patient with pneumococcal meningitis initially diagnosed as an acute ischemic stroke treated with thrombolytic therapy before further imaging.
Conclusion: Many stroke mimics such as migraines, infections, and seizures exist. Time is of the essence for the treatment of an acute ischemic stroke. The safety profile of tissue plasminogen activator has been studied numerous times in stroke mimics and shown to be relatively safe indicating if the patient has no contraindications for stroke intervention, treatment of stroke should not be extensively delayed to rule out stroke confounders.

Keywords: Meningitis; Ischemic stroke; Stroke; Cerebrovascular accident; Acute stroke

INTRODUCTION

Stroke continues to be one of the leading causes of morbidity and mortality in the United States. Guidelines from the American Stroke Association emphasize the importance of quickly recognizing and initiating treatment. The National Institutes of Health Stroke Scale (NIHSS) is one of the measures used to identify characteristics of strokes such as deficits in language, motor, and sensory functions. Intravenous (IV) tissue plasminogen activator (tPA) is a treatment option utilized in acute ischemic strokes (AISs) with a window of time of 3 hours that can be extended to 4.5 hours from the initiation of symptoms [1]. Clinical outcome measures have identified a door-to-needle time of 60 minutes or less defined as the time from when the patient enters the hospital to when treatment is administered. This necessitates a rapid identification of AISs [2]. While IV tPA remains the standard of care for AIS, new studies have demonstrated the benefits of endovascular intervention along with intraarterial tPA administration and mechanical thrombectomy [3]. Several conditions confound and mimic stroke symptoms including seizures, syncope, conversion

disorder, metabolic disorders, infections, and migraines [4]. These conditions can cause misidentification and the initiation of ineffective treatments. This case is an example of such a confounder in a patient who presented with aphasia, dysarthria, and confusion and was treated as an AIS but further imaging indicated otomastoiditis, pneumocephalus, and pneumococcal meningitis. This case highlights the safety of tPA in a stroke mimic case with a patient who required surgery for an intracranial process diagnosed after tPA administration and did not suffer any complications due to thrombolytic therapy administration. Written consent was obtained from the patient before the publication of this case report.

CASE REPORT

A 65-year-old female with a past medical history of end-stage renal disease (ESRD) on daily peritoneal dialysis, hypertension, rectal cancer, chronic variable immunodeficiency with a history of receiving subcutaneous immunoglobulin infusions, history of rheumatic fever, history of non-ST elevated myocardial infarction, asthma, hypothyroidism, gastroesophageal reflux disease, and recent 1-month history of otitis media treated with an 8-day course of cephalexin presented to an outside hospital with expressive aphasia, confusion, dysarthria, and decreased level of consciousness. She presented to the hospital approximately 3 hours after the onset of symptoms. Initial NIHSS was 7. The patient received a computed tomography head performed at the outside hospital, which was negative for intracranial abnormality, per report. The patient's symptoms began waning while being managed in the emergency room; however, the decision to administer a 15 mg IV tPA bolus followed by an infusion was made. This was administered approximately 4 hours and 17 minutes after the onset of symptoms. Before transfer, her NIHSS was 3.

Upon arrival to our facility, NIHSS was 2 for expression aphasia and confusion with Glasgow Coma Scale of 14 with no noted cranial nerve abnormalities. An emergent computed tomography angiography of the head and neck was performed which indicated no hemorrhage, mass, infarct, or vascular occlusion. However, the scan did note complete opacification of left mastoid air cells and left temporal pneumocephalus suspicious for acute otomastoiditis (Fig. 1). Following the report of this scan, a magnetic resonance imaging of the head was ordered which noted nonsuppression of fluid-attenuated inversion recovery around the left temporal and occipital lobes suspicious for meningitis. (Fig. 2) Consults to infectious disease and otolaryngology were placed immediately. Upon further exam of bilateral ears, the patient was noted to have left ear opacification with purulent effusion with Weber tuning fork test lateralizing to the left ear indicative of left

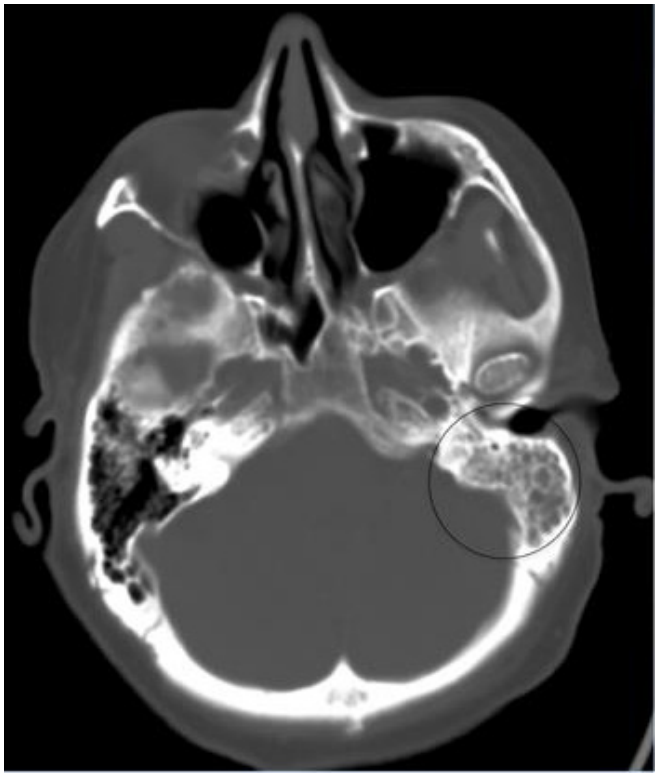

Fig. 1. Computed tomography angiography of the head and neck demonstrates complete opacification of the left mastoid air cells as well as left temporal pneumocephalus (circle) suspicious for acute otomastoiditis.

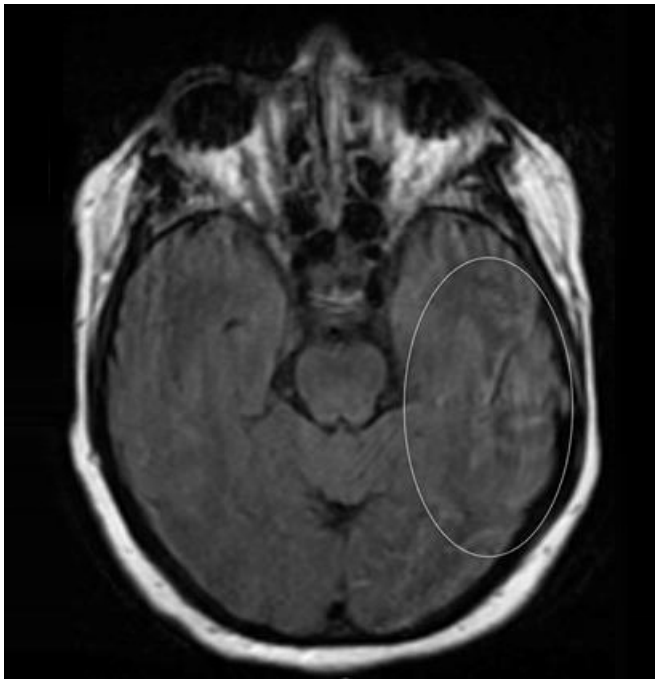

Fig. 2. Magnetic resonance imaging of the head demonstrates non-suppression of fluid-attenuated inversion recovery signal (circle) around the left temporal and left occipital lobes suspicious for meningitis.

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bone conduction greater than air conduction.

On the day of admission, the patient was started on renally dosed vancomycin and 1 g IV cefepime every 24 hours. There was no leukocytosis nor elevated temperatures throughout the hospital admission. A lumbar puncture was unable to be obtained due to the timing of IV tPA administration. In addition, 20 g IV immunoglobulin was administered since the patient had not received subcutaneous immunoglobulin for 10 months before presentation due to ESRD. Tympanomastoidectomy and myringotomy with tube placement and Penrose drain placement were performed on hospital day 2. Granulation tissue was noted through the middle ear as well as mastoid and tegmen dehiscence. Cultures collected indicated numerous (20–50/oil immersion field) white blood cells, moderate (5–10/oil immersion field) Gram-positive cocci in pairs, which were later identified as *Streptococcus pneumoniae*. Antibiotics were adjusted to renally dosed vancomycin and 2 g ceftriaxone every 12 hours on the day of surgery. The patient's neurologic status returned to baseline after surgery, and no neurological deficits were present on discharge. The Penrose drain was removed on postoperative day 2 and ciprofloxacin otic drops were initiated in the left ear for 1 week. The patient underwent a procedure for Hickman catheter placement in order to receive outpatient antibiotic treatment and was discharged from the hospital on a 2-week course of ceftriaxone 2 g IV every 12 hours and vancomycin 1.25 g every 72 hours.

DISCUSSION

This case involves pneumococcal meningitis presenting with symptoms resembling an AIS. The leading cause of bacterial meningitis in adults is *S. pneumoniae* [5]. In a review by Durand et al. [5], only two-thirds of patients exhibited the triad of fever, change in mental status, and nuchal rigidity characteristic of bacterial meningitis. Headache, neck stiffness, altered mental status, temperature > 38°C were the most common symptoms of presentation; however, seizures, tachycardia, hypotension, and focal neurological abnormalities were also reported in a large prospective cohort study by Weisfelt et al. [6]. Aphasia, one of the presenting symptoms in our case, was present in 34% patients in this study. Otitis and sinusitis were the most common predisposing condition manifesting in 43% of patients [6]. Uncommon symptoms have been shown to manifest in the elderly and immunocompromised. Otitis intracranial complications have been shown in adult patients to mimic stroke symptoms with symptoms such as hemiparesis and decreased level of consciousness [7].

Pneumocephalus is defined as air within the intracranial compartments. Otogenic pneumocephalus, which was described in our case, is a rare and severe manifestation of pneumococcal meningitis, which has been described previously in several case reports [8,9]. In a study by Cuinat et al. [10], the meningeal disease was found to be the diagnosis in 1.7% of patients presenting with stroke symptoms while 25.3% of the patients overall were found to have a non-stroke diagnosis.

Many confounders and stroke mimics exist clouding a stroke diagnosis. Dawson et al. [4] found that 24.2% of patients admitted to a stroke center were diagnosed as stroke mimics. Among these, headaches, seizures, sepsis, and syncope were the most common symptoms [4,11]. Other confounders include metabolic disorders such as hypoglycemia, neuropathy, drug intoxication, conversion disorder, dementia, or brain masses [11]. The concern over these confounders is two-fold involving diversion of stroke care resources and facilities to non-stroke conditions and the inappropriate treatment of non-stroke conditions with thrombolytics [12]. In addition, there has been concern that with the number of stroke mimics, actual stroke diagnoses will be missed in favor of a non-stroke diagnosis. Stroke mimics along with stroke chameleons, defined as strokes with unusual presenting symptoms, could be harmful because of the delay in or lack of administration of stroke medications and interventions [12]. Two cases describing both the medical and legal consequences of strokes misdiagnosed as mimics leading to severe medical and legal outcomes are described by Moore et al. [13].

Due to the concern of treating patients who may end up being diagnosed as a stroke mimic, several studies involving the safety of tPA have been conducted. In a study described by Chernyshev et al. [14], 14% of patients who received tPA at their facility ended up being diagnosed with a stroke mimic diagnosis. However, none of these patients were found to have a symptomatic intracranial hemorrhage (sICH) as a complication of the thrombolytic therapy while patients diagnosed with an AIS in this study exhibited a 6% risk of an sICH as a complication of tPA therapy [14]. In a large multicenter cohort study, Ali-Ahmed et al. [15] found that 3.5% of patients who received tPA were stroke mimics. The rate of sICH was found to be 0.4% in the stroke mimic group and 3.5% in the AIS group [15]. The patient in our study initially received tPA before further imagining revealing otomastoiditis, pneumocephalus, and pneumococcal meningitis and did not have an sICH as a complication. The patient's symptoms did improve after IV tPA from NIHSS 7 to NIHSS 2 indicating that this patient may have experienced a thrombotic event secondary to the inflammation from mastoiditis/meningitis which was amenable to IV tPA. These studies demonstrate that although risks of administering thrombolytics are not nonexistent, therapy should not be delayed for an extended time in order to confirm stroke diagnosis

and rule out stroke mimics.

Stroke mimics include diagnoses such as migraines, infections, and seizures which present with stroke-like symptoms. Our case highlights such a mimic in a patient who presented with aphasia, dysarthria, and confusion and initially was diagnosed as an AIS receiving tPA therapy. While obtaining a history, physical, and imaging are critical to the diagnosis of a patient presenting with stroke-like symptoms, time is of the essence for treatment. Several studies have indicated the relatively safe profile of tPA in stroke mimics indicating if the patient has no contraindications for stroke intervention, treatment of stroke should not be extensively delayed to rule out stroke confounders [14,15].

ARTICLE INFORMATION

Ethics statement

Approval for this study was waived in accordance with The University of Kansas policies because this study is a case report of a single patient and did not include protected health information, data analysis, or testing of a hypothesis, and was de-identified. Written consent was obtained from the patient before the publication of this case report.

Conflict of interest

No potential conflict of interest relevant to this article.

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Author contributions

Conceptualization: MM, JP. Formal analysis: MM, JP. Investigation: MM, JP. Supervision: JP, FL. Writing–original draft: all authors. Writing–review & editing: all authors.

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Delayed cerebral infarction due to cerebral venous air emboli after cardiac arrest

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IMAGES IN NEUROCRITICAL CARE

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A 63-year-old woman had a sudden cardiac arrest while undergoing tooth scaling. After 4 minutes, the return of spontaneous circulation (ROSC) was achieved. She was stuporose, but other neurological examinations were within normal limits. The patient had a history of meningitis, and she had undergone ventriculoperitoneal shunt surgery for hydrocephalus in her 20s. Brain computed tomography performed immediately after ROSC showed cerebral air emboli (Fig. 1A). Brain magnetic resonance imaging (MRI) after 5 hours showed no acute lesions (Fig. 1B). Targeted temperature management was performed. Her consciousness improved to a drowsy state, but left hemiparesis was observed. Brain MRI performed on the 6th day showed gyriform infarction in both frontoparietal cortices that were consistent with air emboli (Fig. 1C-E).

Cerebral air embolism can lead to arterial and venous infarctions [1,2]. They can lead to blood flow obstruction and induce an inflammatory reaction with the breakdown of the blood-brain barrier [3]. In this case, the delayed cerebral infarction was detected by follow-up brain imaging. Cerebral venous air emboli can cause delayed cerebral infarction because the collateral circulation in the cerebral venous system allows for compensation. Even if the initial MRI is negative, repeated brain MRI may help detect cerebral infarctions caused by cerebral venous air emboli.

ARTICLE INFORMATION

Ethics statement

This case was reviewed and approved by the Institutional Review Board of Dong-A University Hospital (IRB No. DAUHIRB-21-105). Informed consent was waived by the Board.

Conflict of interest

Dr. Jeong JH is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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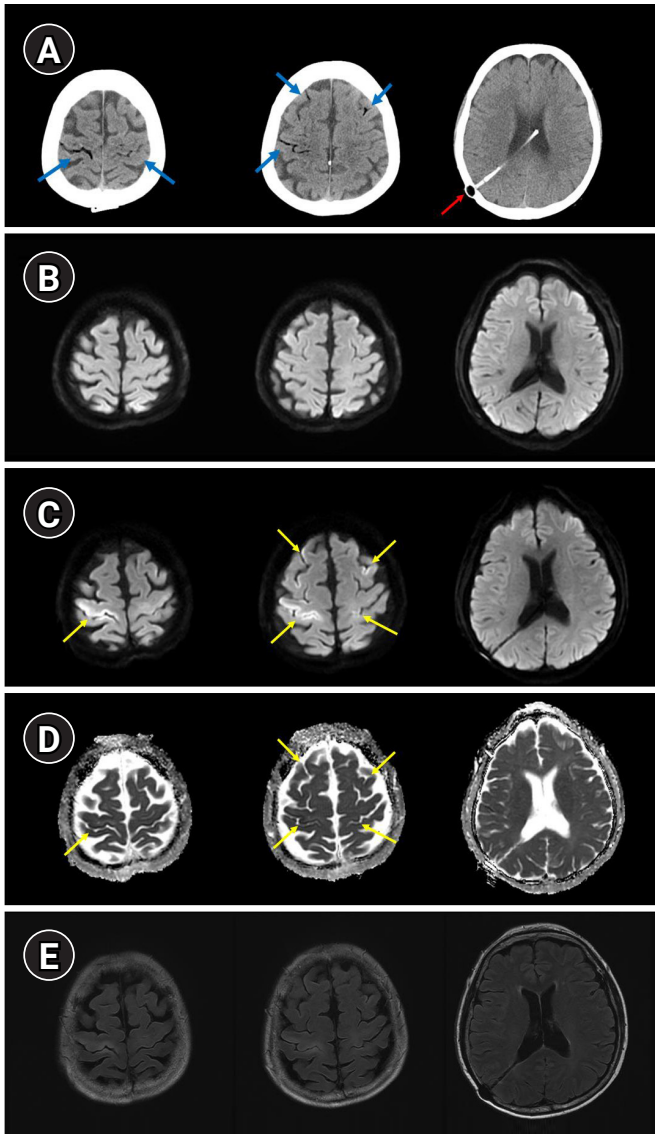

Fig. 1. Brain computed tomography and magnetic resonance imaging (MRI). (A) Non-contrast computed tomography of the head performed immediately after the return of spontaneous circulation (ROSC) showing air bubbles in the frontoparietal sulci (blue arrow). A ventriculoperitoneal shunt catheter was inserted in the right lateral ventricle (red arrow). (B) Diffusion-weighted brain MRI 5 hours after ROSC showing no acute lesions. (C-E) A follow-up brain MRI was performed on the 6th day after ROSC. Diffusion-weighted images and apparent diffusion coefficient images showed focal gyriform infarction in both frontoparietal cortices, especially in the right motor cortex (yellow arrows). Fluid-attenuated inversion recovery images showed high signal intensities in the same area.

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Author contributions

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Journal of Neurocritical Care

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