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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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Refractory and super-refractory status epilepticus and evidence for the use of ketamine: a scope review

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REVIEW ARTICLE

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Status epilepticus (SE) is a neurological emergency with serious consequences for neuronal tissues, therefore, it is considered the most serious manifestation of epilepsy. The response to treatment, its evolution time and duration, and the need to use one or more antiseizure drugs define SE as refractory or super-refractory. Ketamine has been used in SE management since the 90s when an article describing its use in treating SE was published. Since then, at least 24 publications have reported the use of ketamine for the treatment of SE in both adult and pediatric patients. This scoping review seeks to synthesize information on the use of drugs in super-refractory SE, specifically ketamine. Twenty articles were chosen for the final document construction. Few studies have investigated the use of ketamine in refractory status epilepticus (RSE) and super-refractory status epilepticus (SRSE). Most of the information comes from retrospective case series studies, mostly with small sample sizes, and although the information is heterogeneous, it points to the efficacy of ketamine as a third-line drug in RES and SRSE, in controlling seizures.

Keywords: Ketamine; Anticonvulsants; Epileptic status; Treatment; Diagnosis

INTRODUCTION

The incidence of status epilepticus (SE) ranges from approximately 5 to 40 per 100,000, based on several population-based studies across the US [1,2], and the incidence of super-refractory status epilepticus (SRSE) is 0.7 per 100,000. The response to treatment, its evolution time and duration, and the need to use one or more antiseizure drugs define SE as refractory or super-refractory. In 2015, the Task Force of the International League Against Epilepsy defined SE as a prolonged seizure that exceeded the intrinsic termination mechanisms at a certain point in time from the onset of the seizure (t₁) and persisted beyond a second

point in time (t₂), the latter being the time at which cortical damage occurs. It also defines refractory status epilepticus (RSE) as one that persists beyond t₂ time point despite treatment with first- and second line antiseizure drugs. It also defines SRSE as an SE that persists for more than 24 hours after the addition of a third-line drug, generally an intravenous anesthetic [1].

These definitions and their determinant aspects have clinical and therapeutic implications and dimension the consequences of the status, which forces the implementation of treatment with a certain "aggressiveness" and is a quick start to try to limit neuronal damage and improve neurological and clinical results [2-4]. The incidence of refractory and SRSE is approximately 40% among

patients presenting with SE, depending on the cause, with mortality approaching 50% [5].

Ketamine, a drug derived from phencyclidine, was synthesized in 1960 and reached peak popularity in the 1970s. In 1982 it was reported that it could have another possible mechanism of action by agonism of μ , δ , and γ opioid receptors [6]. Another possible mechanism of action is the inhibition of monoamine oxidase, which prolongs the half-lives of serotonin, dopamine, and norepinephrine [7,8]. In a study published in 2011, a decrease in the production of interleukin (IL)-6, IL-8, IL-10, and tumor necrosis factor-alpha was found in patients undergoing cardiopulmonary surgery who received ketamine, which gives it certain anti-inflammatory properties [9]. Another study in 2015 observed that it caused a decrease in calcium concentration at the cytosolic level in cardiac myocytes, and thus counteracted its effect in states of hypoxia, ischemia, oxidative stress, and hypertrophic cardiomyopathy [10]. Ketamine occurs in two forms: the S isomer, which is three times more active than its opposite, the R-enantiomer. The most widely used pharmacological presentation is a racemic mixture of both molecular forms [11-13]. Despite its widespread use as an anesthetic during surgical procedures, it was not until the 1990s that an article was published showing its use in treating SE [14,15].

Glutamate receptors (pharmacological targets of ketamine) are classified into two types: metabotropic receptors (mGluRs), which promote the activation of second messengers via the activation of transmembrane G proteins, and ionotropic receptors, which are coupled to an ion channel and allow the entry of various ions, mainly calcium [16,17] (Fig. 1). Ionotropic receptors are divided according to the affinity of their specific agonists; here, N-methyl-D-aspartate (NMDA) receptors belong to this family.

Excitotoxicity is characterized by neuronal death induced by the excessive release of glutamate and overactivation of its receptors [18]. This event is associated with various disease states of the central nervous system, including epilepsy, hypoxia, ischemia and trauma. This overstimulation increases intracellular calcium concentrations; promotes lipid peroxidation of the cytoplasmic membrane, endoplasmic reticulum, and mitochondria and causes cell death [19,20].

METHODS

This scoping review seeks to synthesize available information from different domains of drug use in SRSE, specifically ketamine. No specific questions were raised and the definitions and variables used in different publications on the use of ketamine in SE were explored. Two researchers searched for articles using key-

words in the PubMed, Embase, SciELO, Bireme, Latindex, and Google Scholar databases, and medRxiv was explored for gray literature. The words that were used to construct the search strategy were "status epilepticus," "refractory," and "ketamine."

RESULTS

A search of seven bibliographic databases identified 38 articles related to the terms of interest published between 1990 and 2022. Articles in English or Spanish were selected based on their titles or abstracts. After filtering by content and relevance, 20 articles were selected for the final document construction (Fig. 2). The extraction results were synthesized and presented as a qualitative description of the information and synthesis in quantitative data tables.

Pharmacokinetic profiles of ketamine

Table 1 shows the main causes of SE, including head trauma, cerebrovascular disease, infections, tumors, autoimmune disorders, and hypoxic-ischemic encephalopathy. The etiology of SE and SRSE is particular and suggests that both conditions are more likely to develop due to acute neurological damage associated with a persistent inflammatory state, but not specifically with the presence of epilepsy, an underlying pathology.

To initiate the pharmacological treatment of SE, it is crucial to understand the mechanism by which seizures become refractory.

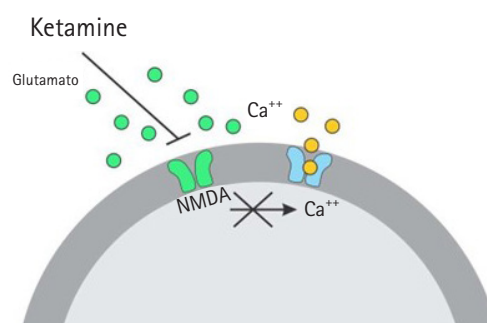


Fig. 1. N-methyl-D-aspartate (NMDA) receptors regulate, through a complex mechanism, calcium entry into the cell from the extracellular compartment. The entry of this cation translates into calcium-dependent intracellular excitability mediated by second and third messengers. Ketamine antagonizes NMDA receptors which are located at the medullary, thalamic, limbic, and cortical levels. Thanks to the multiplicity of NMDA receptors, ketamine interferes with the sensory afferent flow to the central nervous system's higher centers, affecting pain, emotional responses, and memory, which is why it is referred to as a "dissociative anesthetic." Ketamine also has some side effects on opioid receptors which helps propagate its analgesic effect, as well as in alpha- and beta-adrenergic receptors, which gives it some cardiovascular actions.

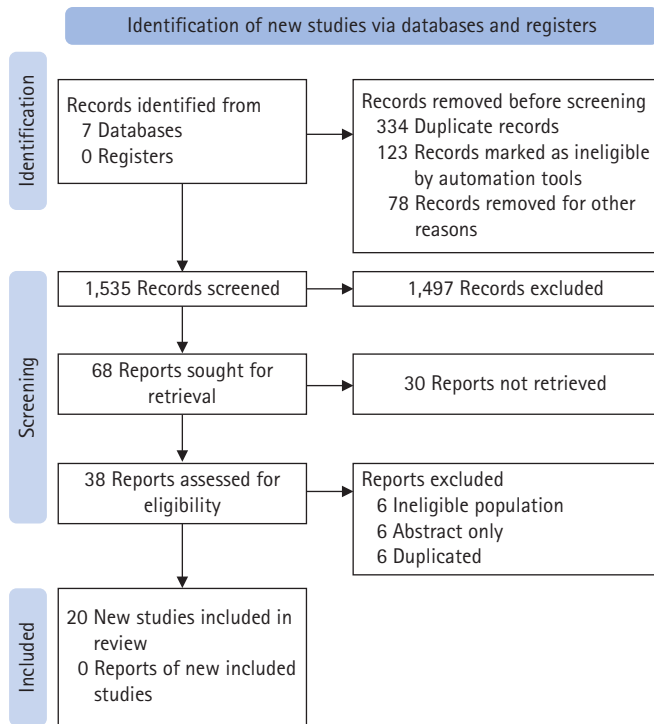


Fig. 2. Systematic review flowchart.

Table 1. Main causes of refractory and super-refractory status epilepticus

Cause of refractory and super-refractory status epilepticus
Head trauma
Cerebrovascular accidents
Central nervous system infections
Intracranial tumors
Cortical dysplasia
Hypoxic-ischemic encephalopathy
Metabolic disorders
Autoimmune disorders
Poisoning (including withdrawal syndrome)

Although the molecular pathophysiology of SE is complex, it complies with some of the body's "laws of homeostasis." For example, seizures are perpetuated by an imbalance between excitatory and inhibitory mechanisms in neuronal tissues [21]. γ -Aminobutyric acid (GABA) is the primary inhibitory and Glutamate is the main excitatory neurotransmitter that mediates excitation by stimulating the NMDA receptor [22,23].

After several minutes of constant seizure activity, "receptor trafficking" appears. This is a phenomenon in which GABA receptors decrease through a process of "internalization," generating a reduction in GABAergic activity. The number of glutamergic receptors on the cell surface increases due to "externalization" from the cytosol to the cell membrane, producing increased neuronal

excitatory activity [24-27]. This is clinically reflected in rapidly progressive resistance to benzodiazepines [28]. In this scenario of impaired GABAergic activity and increased excitotoxicity, NMDA receptor antagonists, such as ketamine, become therapeutically relevant because they have a pathophysiological substrate that favors their effectiveness (Fig 3).

Other events are believed to occur at the tissue and cellular levels and contribute to the development of RSE and SRSE. Among these events, there may be mitochondrial failure or insufficiency [29] and activation of the inflammatory cascade [30,31], which make the blood-brain barrier vulnerable together [32,33]. In treating SE, the primary therapeutic objective is to rapidly control ictal activity to limit neuronal death mediated by excitotoxicity and reduce the systemic complications generated, with benzodiazepines considered the first-line treatment. Other anticonvulsants such as phenytoin, levetiracetam, and valproic acid are the most widely used second-line drugs [34,35].

Having explored the pathophysiological substrate for which a third-line drug with effects on neuronal excitatory activity, specifically on NMDA receptors, could play a leading role, it is time to study the potential role of ketamine. In a retrospective study published in 1996 by Walker et al. [14], a case of SE was reported in which ketamine was used as an anticonvulsant drug, demonstrating a favorable therapeutic response, and no noteworthy adverse effects related to its use were reported. Since then, there have been 20 publications on ketamine and SE: nine case reports, eight retrospective case series two systematic reviews, and one observational (Table 2) [5,14,15,36-52].

Usefulness of ketamine in RSE

In the analysis of the obtained information, two questions arose that motivated this investigation. Is ketamine useful in the treatment of RSE? Although seizures at any given moment may have a certain degree of clinical subjectivity, the two parameters used in the publications to determine the effectiveness of ketamine in RSE were clinical and electroencephalographic cessation of epileptiform activity. Between case reports and case series, there are 265 patients. A systematic review conducted in 2014 [46] grouped 110 patients, and another conducted in 2018 grouped 289 patients [5]. Of the 19 case studies, 12 (63%) achieved complete seizure control, whereas in the remaining case studies, seizure control was partial (31%) or absent (5%).

Table 2 contains some information from the results of studies on using ketamine in RSE. Each publication details, for example, the route of drug administration (intravenous or oral), the administration or not of loading dose, and the response to treatment, which was classified into three categories: good response, refer-

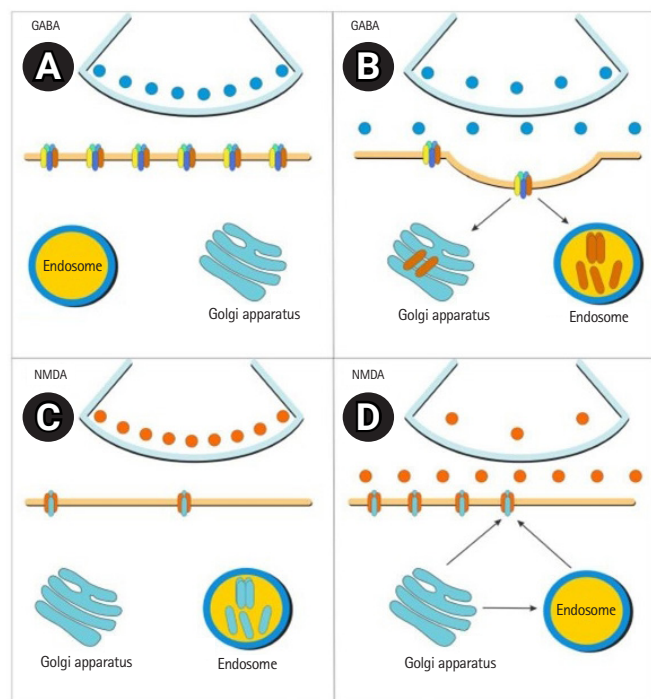


Fig. 3. Receptor trafficking theory. Seizures produce many physiological effects and biochemical changes in the brain; within minutes, the trafficking of receptors causes some key adaptations. (A) Arrangement of γ -aminobutyric acid (GABA) receptors under normal conditions. (B) After recurrent seizures, GABA receptors in the synaptic membrane undergo a process of internalization. These membrane proteins are directed to endosomes in the cytosol or to the Golgi apparatus, where they are recycled to the cellular membrane. (C) Arrangement of N-methyl-D-aspartate (NMDA) receptors under normal conditions. (D) In synapses, unlike GABA receptors, NMDA receptors are mobilized towards the synaptic membrane from amino acids located in the Golgi apparatus and are assembled into receptors that are transported in endosomes to the cell membrane. As a result of this trafficking, the number of functional NMDA receptors per synapse increases while the number of functional GABA receptors decreases [53].

ring to patients in whom the administration of ketamine ceased seizure activity; partial response, referring both to patients in whom seizures recurred after administration of the drug and to groups of patients where seizures were controlled in some patients and not in others; and no response, referring to patients in whom ketamine treatment had no effect on the duration of treatment expressed in hours, days, and months, and adverse drug reactions [5].

In more than 70% of studies regarding seizures controlled with ketamine during the first 48 hours of treatment, it is evident that this drug is effective in treating seizure activity in the RES and that its therapeutic effect is achieved within a few hours [5]. Its effect appears to be related to early onset and is

also likely to have a direct relationship with the administered dose, with reported doses being higher than 0.9 mg/kg/hr [45, 50,51].

A negative aspect that limits the benefit of ketamine in this clinical scenario is recurrence after its cessation. This recurrence appears in 10%–60% of cases in which seizures are successfully suppressed [50,52]. The recurrence of seizures when withdrawing ketamine treatment depends on multiple factors that are difficult to associate with each other, including the etiology of RSE, comorbidities, severity of the convulsive condition, medications used concomitantly or previously, and disorders of the internal environment. This disparity makes it difficult to establish a causal relationship between these two events.

- What is the pharmacodynamic profile of ketamine in RSE? We will analyze the information found on the loading dose, maintenance dose, start time of the drug, duration of treatment, and its therapeutic and adverse effects.

In 70% of the studies, a loading dose of ketamine was administered at a rate of 0.5 to 5 mg/kg. The intravenous infusion doses ranged from 0.05 to 10.5 mg/kg/hr, and for patients who received the drug enterally, the doses ranged from 50 to 250 mg twice a day. Ketamine treatment was administered between the first 24 hours and 140 days after the diagnosis of RES. The duration of ketamine treatment ranged from 2 hours to 29 days. The electroencephalographic response to ketamine treatment, as determined by the burst-suppression phenomenon, was as rapid as 2 hours or as delayed as 28 days.

Adverse effects of ketamine

The reported adverse effects included transient arterial hypertension (one case), supraventricular tachyarrhythmia (two cases), cerebellar syndrome (one case), metabolic acidosis in co-administration with midazolam (one case), and cardiovascular collapse associated with metabolic acidosis (two cases) [5]. However, the heterogeneity in pharmacodynamic information found when using ketamine as a third-line drug in RSE [5] constitutes an unfavorable aspect in determining its therapeutic index and other aspects of its pharmacodynamics. Little information is available regarding the oral administration of the drug. Oral ketamine has been used to control chronic pain in patients with neuropathic pain, cancers of different types, trigeminal neuralgia, and phantom limbs, among other conditions. The analgesic effect is mainly based on NMDA receptor activity. Although the bioavailability of orally administered ketamine is only 16%, its major active metabolite, norketamine, retains its NMDA receptor-antagonistic properties and has less affinity for NMDA receptors.

Until now, it has not been possible to determine the appropriate

Table 2. Studies to the use of ketamine in refractory status epilepticus

Study	Year	Study design	Number	Medication administration way	Previous bolus	Treatment time	Therapeutic response	Side effect
Walker et al. [14]	1996	Case report	1	IV	NI	NI	Not improvement	None
Kofke et al. [36]	1997	Case report	1	IV	Yes	2 hr	Partial improvement	Tachyphylaxis
Ubogu et al. [37]	2003	Case report	1	IV	Yes	5 day	Improvement	Neurotoxicity, cerebellar syndrome
Robakis et al. [38]	2006	Case report	1	IV	NI	7 day	Partial improvement	None
Prüss et al. [39]	2008	Case report	1	IV	Yes	14 day	Improvement	SH transitory
Hsieh et al. [40]	2010	Case report	1	IV	Yes	7 day	Improvement	None
Yeh et al. [41]	2011	Case report	1	IV/PO	Yes	Undefined/PO	Improvement	None
Kramer [42]	2012	Case report	1	IV	Yes	3 day	Improvement	None
Synowiec et al. [43]	2013	Case series	11	IV	Yes	4 hr–28 day	Improvement	None
Zeiler et al. [44]	2013	Case series	2	IV	NI	3 hr–12 day	Improvement	None
Gaspard et al. [45]	2013	Case series	46	IV	Yes	6 hr–27 day	Partial improvement	SVT
Zeiler et al. [46]	2014	Systematic review	110	IV/PO	Yes	2 hr–27 day	Partial improvement	NI
Shrestha et al. [47]	2015	Case series	2	IV	Yes	2 hr–3 day	Improvement	None
Sabharwal et al. [48]	2015	Case series	67	IV	NI	1–29 day	Partial improvement	None
Höfler et al. [15]	2017	Case series	42	IV	Yes	4 day	Partial improvement	None
Pizzi et al. [49]	2017	Case report	1	IV/PO	NI	5 day	Partial improvement	None
Golub et al. [5]	2018	Systematic review	289	IV/PO	Yes	NI	Partial improvement	NI
Alkhachroum et al. [50]	2020	Case series	68	IV	NI	1–4 day	Improvement	NI
Dericioglu et al. [51]	2021	Case series	7	IV	Yes	3–24 day	Improvement	Liver injury
Caranzano et al. [52]	2022	Observational	11	IV	NI	1–16 day	Improvement	NI

IV, Intravenous; NI, non-informed; SH, sudden hypertension; PO, per os; SVT, supraventricular tachycardia.

dosage because the therapeutic range is extensive and ranges between 45 and 1,000 mg/day. However, in patients treated with enteral ketamine, its effectiveness in seizure control appears to be maintained, thus constituting an alternative in cases where the intravenous route cannot be used [13,41]. Regarding adverse effects, it is not easy to establish the association between these and ketamine. Is not a first- or second-line drug, once treatment with this NMDA antagonist is initiated, it is difficult to assign any adverse reactions to ketamine in a critically ill, polymedicated patient with at least two centrally acting drugs. Additionally, the wide range of doses administered and treatment durations complicate the establishment of the causality of a clinical condition with a particular drug. However, several publications have reported sialorrhea, hepatotoxicity, cholestasis, cardiac arrhythmias, and metabolic acidosis related to ketamine use [37,39,45,53-55]. Although this drug is popular because it does not have hemodynamic depressant effects, this is probably due to the release of endogenous catecholamines, which increase peripheral vascular resistance and heart rate [56-58]. Paradoxically, some reports indicated that the effects of endogenous catecholamines on intracellular calcium currents could prolong cardiac action potential and have adverse inotropic effects [59-61]. In patients undergoing multimodal neurological monitoring, ketamine infusion did not gener-

ate harmful changes in intracranial pressure, and it was possible to reduce vasopressor requirements [50].

This particularity of the cardiovascular system may correlate with the cardiovascular collapse observed in two cases where ketamine was used [5]. Metabolic acidosis, which has also been reported in the treatment of RSE, has no clear cause. Some hypotheses suggest that hydrochloric acid, a diluent of midazolam (the first-line drug), can cause hyperchloremia, and thus contribute to acidosis, homeostatic imbalance, and cardiovascular collapse [5].

DISCUSSION

The main goals of RSE and SRSE treatment are to preserve cortical function and reduce morbidity and mortality related to neuronal damage caused by prolonged seizure activity. Cognitive, behavioral, and functional alterations have been reported at rates higher than 75% in patients with RSE and are clearly related to the duration of seizures [62,63]. Given the current knowledge about the biomolecular changes that occur in the neuronal membrane during prolonged seizures and the early onset of drug resistance to GABAergic drugs, there are clear reasons to consider the early initiation of ketamine treatment in RSE protocols [3-26,28-35,

39,41,46].

The scant prominence of ketamine as a rescue treatment for RSE is attributable, in some way, to medical inexperience with the use of the drug in this context, the heterogeneity of the information available regarding its pharmacodynamic profile and side effects, and the lack of studies that include ketamine within their protocols. Although in most studies ketamine was not used in the initial hours of ER and was only used after various anticonvulsants, it was effective in controlling seizures when administered, usually within the first 12 hours [5]. However, there is currently insufficient scientific evidence to support the use of ketamine as a first-line drug or as a monotherapy in the management of RSE and SRSE.

It is reasonable to assume that there is fear and insecurity when using drugs with such disparate pharmacodynamic profiles. It is likely that, as has happened with other drugs, further studies will endorse its use, even more so in extreme clinical scenarios, such as supra-refractory status. For example, only after several years of intravenous lorazepam and diazepam could their toxicity be overcome, finding that it was due to propylene glycol, the excipient used in their pharmacological presentation, rather than this toxicity being inherent to these benzodiazepines. Accordingly, the statistical power of the studies we included was insufficient to relate the infusion of ketamine to a positive or negative impact on the mortality of these patients.

Few studies of report type and case series with small sample sizes and low statistical power, have examined the use of ketamine in RSE and SRSE. Despite the limited available evidence, the rapid efficacy of ketamine in the treatment of RSE and SRSE has been documented. This fact, in addition to the molecular and pathophysiological substrates that support the use of the drug, should encourage further research in this regard. One of the aspects to be clarified is the safety profile of ketamine and its pharmacological interactions with the other anticonvulsants used in RSE and SRSE treatment to elucidate the mechanisms of metabolic acidosis and other homeostatic alterations reported in the studies with ketamine and RSE.

CONCLUSIONS

The treatment of RSE and SRSE represents a therapeutic challenge because of their high mortality rates and poor neurological outcomes. Early initiation of anticonvulsant therapy and its effectiveness are crucial aspects of patient prognosis. Several animal models have shown that, in persistent seizures, the cell membrane experiences a decrease in GABAergic receptors and an increase in

the expression of excitatory receptors, including NMDA glutamatergic receptors.

There are few studies on the use of ketamine in RSE and SRSE, and most of the information comes from case reports, case series, and retrospective studies, mostly with small or unique samples. Although the information is heterogeneous, it suggests that ketamine, used as a third-line drug for RSE and SRSE, is effective in controlling seizures. In this sense, it would be a drug with pathophysiological endorsement for use since the current evidence is favorable, if limited. Despite this, the nature of adverse reactions reported with the use of ketamine varies, and its cardiovascular effects and changes in the internal environment seem to be predominant. Given the methodological limitations of most publications in this regard, information on neurological outcomes measured using the Glasgow Outcome Scale (and modified Rankin scales in patients with SE and SRSE who received ketamine is heterogeneous and inconclusive.

The lack of randomized prospective studies constitutes a significant limitation in recommending and including ketamine in the RSE and SRSE protocols. Additionally, based on the changes in the biochemistry of the neuronal membrane and its receptors that occur in RSE, the question arises as to whether anti-glutaminergic drugs should be started early or as third-line drugs for this pathology. Despite these limitations, ketamine appears to have a promising outlook for RSE and SRSE.

ARTICLE INFORMATION

Ethics statement

This article complies with the requirements of research and publication ethics biomedical and the World Medical Association's Declaration of Helsinki.

Conflict of interest

No potential conflict of interest relevant to this article.

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Conceptualization: LE, DMF. Data curation: LE. Formal analysis: LE, DMF. Investigation: all authors. Methodology: DMF. Project administration: LE, MG. Resources: DMF. Software: DMF. Supervision: MG. Validation: AZ, MG. Visualization: DMF. Writing—original draft: all authors. Writing—review & editing: AZ.

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The etiology and mortality of altered level of consciousness in the emergency room: before and after coronavirus disease

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Background: Coronavirus disease 2019 (COVID-19) has resulted in social, economic, medical, and psychological changes. New-onset altered level of consciousness (ALC) is a classical presentation in real-world medicine. This study investigated changes in ALC in the emergency room (ER) in the periods before (BC) and after (AC) COVID-19.

Methods: This was a retrospective study of patients with ALCs who visited the ER of a tertiary referral center, and their medical records BC and AC were compared. A consortium allocated and analyzed the etiologies of ALC in a case-by-case discussion. The time point for etiological assessment was the time of discharge from the ER.

Results: In total, 1,936 patients with ALCs (731 and 1,205 in BC and AC, respectively) were investigated. The most common etiology was systemic infection (25.9%), followed by metabolic causes (20.8%). Systemic infections (22.9% vs. 30.8%, $P<0.001$) and stroke (14.6% vs. 18.2%, $P=0.037$) were lower in AC than in BC, respectively, whereas rates of toxicity (15.4% vs. 6.0%, $P<0.001$) and traumatic brain injury (TBI; 5.9% vs. 0.8%, $P<0.001$) were higher in AC than in BC. The overall mortality rate of ALC in the ER was 18.5%, which was higher in AC (20.9%) than in BC (14.6%) ($P=0.001$).

Conclusion: This study demonstrated that the major etiologies of ALC in the ER were extra-cranial (58.5%). The mortality of ALC in the ER and the incidence of toxic cause and TBI increased in AC, suggesting a change in medical circumstances after the Pandemic.

Keywords: Consciousness disorders; Neurologic manifestations; Emergency medical services; Emergency room

INTRODUCTION

New-onset altered level of consciousness (ALC) refers to any non-physiological changes or deterioration in attention or arousal from baseline [1]. Since ALC is a potentially life-threatening condition [2], it has been a major consideration in the emergency room (ER). However, ALC has several synonyms, including mental change, altered mental status, and impaired consciousness, im-

plying that ALC has a broad and nonspecific spectrum [2]. Furthermore, identifying or determining its etiology often needs to be clarified.

The prevalence of ALC in the ER has been reported in 0.4% to 5% of all patients visiting the ER; the common etiologies of ALC in the ER include neurologic causes [1,3,4], stroke [5], poisoning [6], pharmacologic and toxicologic etiologies [4], and systemic infection [7]. Recently, a multicenter study demonstrated that the

leading etiology was metabolic causes, accounting for a quarter of the total cases, followed by systemic infection and stroke [8]. However, all studies to date have analyzed the data before the pandemic.

Coronavirus disease 2019 (COVID-19) has significantly impacted medical systems and personal lives. National health policies have changed because of the highly pathogenic severe acute respiratory syndrome coronavirus 2, and people's medical use patterns have also changed [9-11]. ER visits in the period after COVID-19 (AC), compared to those before COVID-19 (BC), decreased from 72% to 22% in the U.S. [12-15], 13% to 5.7% in Europe [16], and 50% to 37% in South Korea [17,18]. There has been a reduction in emergency medical service utilization, which was still under the pre-pandemic levels until the first quarter of 2022 [19].

Given the nature of ALC, which is a representative symptom of a critical condition, patients have no choice but to visit the ER. Medical staff should be aware of the changes in the etiology, and always be aware of the clinical characteristics, of ALC in the ER. This study aimed to evaluate the clinical characteristics, etiologies, and dispositions of patients with ALC in the ER of a university hospital and to compare BC and AC.

METHODS

This retrospective study involved patients who visited the ER of a tertiary referral university hospital. In order to compare before and after the COVID-19 outbreak, we have set BC and AC as follows: BC represents the year before the first case occurred on February 18, from February 2019 to January 2020. After the first case of COVID-19 was found, there were frequent policy changes made by quarantine authorities, frequent ER closures, shortages of medical resources, and insufficient manpower. Perhaps every ER worldwide has suffered from the so-called coronapocalypse. Therefore, we excluded this disruptive period from our analysis. In this study, AC represents a year of new normalcy from July 2020 to June 2021 to represent the period after COVID-19 vaccination began in South Korea.

Patients

This study adopted the methods and inclusion criteria of the previous study [8]. Following suit, every case of ALC in the ER met one of the following conditions: (1) Glasgow Coma Scale (GCS) score ≤ 14 , (2) impaired orientation (to person, time, and place), and (3) the first GCS examiner identified any findings considered ALC (e.g., bizarre or inappropriate behavior, hallucinations, delusions, or confusion). Each patient's GCS score was rated by either

the attending board-certified faculty member or the chief resident in the Department of Emergency Medicine. The exclusion criteria were age < 19 years, revisit within 24 hours of the last discharge from the hospital, cardiac arrest on arrival, death on arrival, and ALC that occurred during hospitalization.

Classification and arrangement of the etiologies

Every patient with ALC in the ER was reviewed based on the medical records and allocated to one category of the 10-etiology classification system of ALC (ALC-10) [8]: (1) metabolic cause, (2) systemic infection, (3) cardiogenic and vascular cause (C&V), (4) stroke, (5) traumatic brain injury (TBI), (6) seizure, (7) central nervous system (CNS) infection, (8) toxic cause, (9) psychiatric disorder, and (10) undetermined. Patients' age, sex, medical history, provisional diagnosis in the ER, destination from the ER, and discharge from hospital were investigated. Medical evaluation included vital signs, physical and neurological examinations, electrocardiography, echocardiography, X-rays, blood tests, computed tomography, magnetic resonance imaging, cerebrospinal fluid analysis, and electroencephalography. The reference time point for determining the etiology of ALC was when the patient left the ER; therefore, the provisional diagnosis may differ from the definitive diagnosis. The medical records of all patients were reviewed based on a multidisciplinary approach. A consortium of board-certified professors affiliated with emergency medicine, internal medicine, and neurology determined the etiology classification through case-by-case discussions.

Statistical analysis

The statistics used were mainly descriptive. We compared BC and AC, using the *t*-test or chi-square test. Statistical analyses were two-tailed, and $P < 0.05$ was considered statistically significant. IBM SPSS ver. 22.0 (IBM Corp.) was used for analysis.

RESULTS

Patient characteristics and the etiologies of ALC in the ER

In BC and AC, 39,273 and 35,968 patients visited the emergency department, respectively. We identified 1,936 eligible patients, including 731 and 1,205 patients with ALCs in BC and AC, respectively (Table 1, Fig. 1). More patients with ALC visited the ER in AC than in BC (3.4% vs. 1.9, $P < 0.001$). There was no statistically significant difference in sex between BC (329, 45.0%) and AC (551, 45.7%) (female, $P = 0.758$) (Table 1). The mean age was 68 ± 17 years for all patients, and was higher in BC (67 ± 17 years) than in AC (67 ± 18 years) ($P = 0.023$). The composition by age group did not differ between BC and AC ($P = 0.108$). The most

Table 1. Demographic data and the etiologies of altered level of consciousness in the emergency room

Variable	Total (n=1,936)	BC (n=731)	AC (n=1,205)	P-value
Female	880 (45.5)	329 (45.0)	551 (45.7)	0.758
Age (yr)	68±17	69±17	67±18	0.023
≤29	82 (4.2)	21 (2.9)	61 (5.1)	0.108
30–39	94 (4.9)	37 (5.1)	57 (4.7)	
40–49	106 (5.5)	35 (4.8)	71 (5.9)	
50–59	234 (12.1)	92 (12.6)	142 (11.8)	
60–69	364 (18.8)	127 (17.4)	237 (19.7)	
70–79	489 (25.3)	193 (26.4)	296 (24.6)	
80–89	510 (26.3)	198 (27.1)	312 (25.9)	
≥90	57 (2.9)	28 (3.8)	29 (2.4)	
Length of stay in the ER (hr)	17.08±21.48	17.89±22.11	16.60±21.09	0.206
Etiology				
Systemic infection	501 (25.9)	225 (30.8)	276 (22.9)	<0.001
Metabolic cause	402 (20.8)	154 (21.1)	248 (20.6)	0.798
Stroke	309 (16.0)	133 (18.2)	176 (14.6)	0.037
Toxic cause	229 (11.8)	44 (6.0)	185 (15.4)	<0.001
C&V	138 (7.1)	51 (7.0)	87 (7.2)	0.840
Seizure	121 (6.3)	51 (7.0)	70 (5.8)	0.304
TBI	77 (4.0)	6 (0.8)	71 (5.9)	<0.001
Psychiatric	35 (1.8)	16 (2.2)	19 (1.6)	0.327
CNS infection	21 (1.1)	6 (0.8)	15 (1.2)	0.383
Undetermined	103 (5.3)	45 (6.2)	58 (4.8)	0.202

Values are presented as number (%) or mean±standard deviation.

BC, before coronavirus disease 2019; AC, after coronavirus disease 2019; ER, emergency room; C&V, cardiogenic and vascular cause; TBI, traumatic brain injury; CNS, central nervous system.

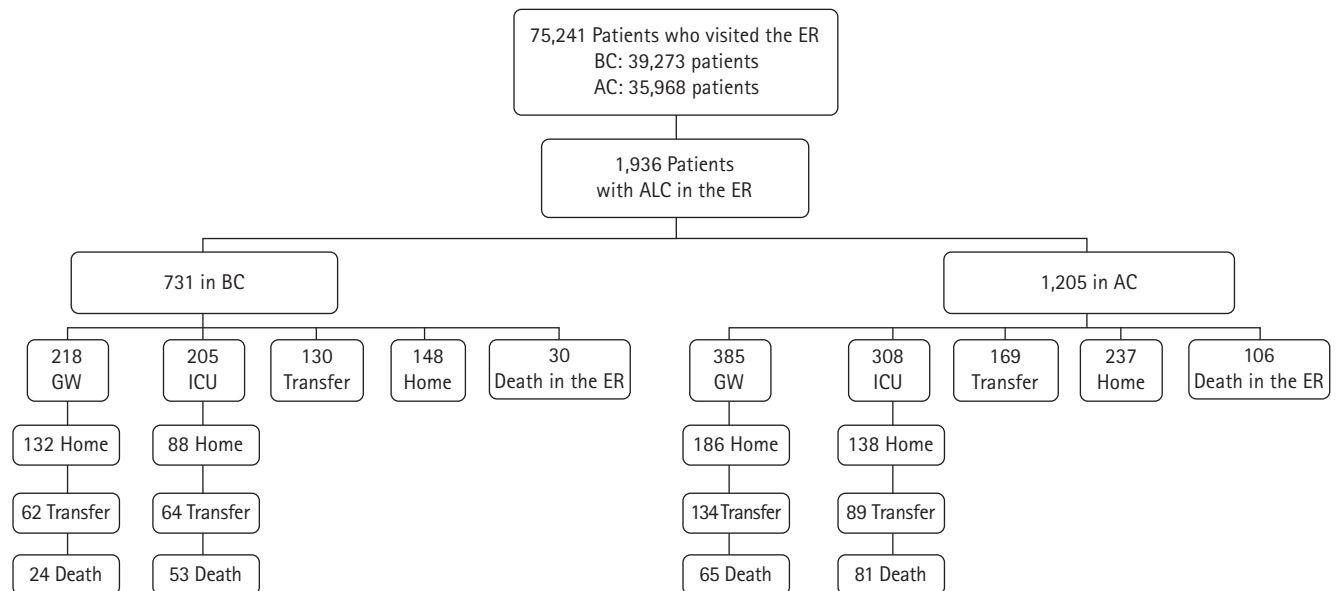


Fig. 1. Flow diagram for disposition of patients with altered level of consciousness before (BC) and after (AC) coronavirus disease 2019. ER, emergency room; ALC, altered level of consciousness; GW, general ward; ICU, intensive care unit.

common age group was the 80s, and more than half of patients (1,056, 54.5%) were aged ≥ 70 years in this study, comprising 419 (57.3%) and 637 (52.9%) patients in BC and AC, respectively. The average stay time in the ER was 17.08 ± 21.48 hours, with no

significant difference between BC (17.89 ± 22.11 hours) and AC (16.60 ± 21.09 hours) (P=0.206).

Table 1 and Fig. 2 show the distribution of etiologies. The causes of ALC that accounted for more than 5% of the total cases in-

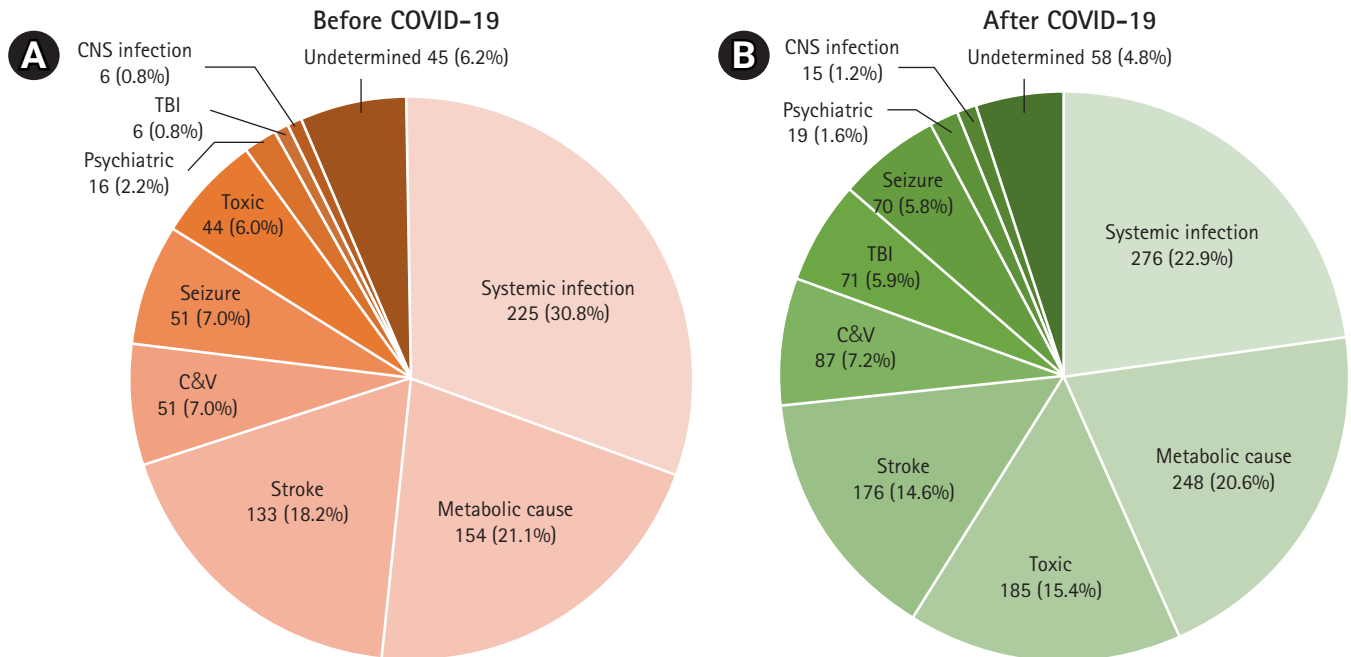


Fig. 2. Pie graph for etiology of altered level of consciousness in patients (A) before and (B) after coronavirus disease 2019 (COVID-19). CNS, central nervous system; TBI, traumatic brain injury; C&V, cardiogenic and vascular cause.

cluded systemic infection (25.9%), metabolic causes (20.8%), stroke (16.0%), toxic causes (11.8%), C&V (7.1%), seizures (6.3%), and undetermined (5.3%). In both BC and AC, the most common etiology was systemic infection, although its proportion in BC (225, 30.8%) was significantly lower than that in AC (276, 22.9%) ($P < 0.001$), followed by metabolic causes (21.1% and 20.6% for BC and AC, respectively). Stroke was the third most common in total cases (309, 16.0%) and in BC (133, 18.2%) but fourth in AC (176, 14.6%) ($P = 0.037$). The rate of toxic causes differed remarkably between BC and AC ($P < 0.001$). Only 44 (6.0%) patients in BC moved to the third position in AC (185, 15.4%). The number of TBIs was six in BC, accounting for 0.8%, and was significantly higher in AC (71, 5.9%) ($P < 0.001$).

The three common extra-cranial etiologies, including systemic infection, metabolic causes, and toxic causes, accounted for 1,132 (58.5%) of the total cases, with 423 (57.9%) and 709 (58.8%) in BC and AC, respectively. The number of intracranial etiologies, including stroke, seizure, TBI, and CNS infection, was 528 (37.3% of the total), consisting of 196 (26.8%) and 332 (27.6%) in BC and AC, respectively.

Disposition from the ER and discharge from the hospital

Fig. 1 and Table 2 show the journey of the patients from disposition from the ER to discharge from the hospital. A total of 1116 (57.6%) of the patients with ALC in the ER were admitted to either the general ward (GW) (603, 54.0%) or the intensive care

unit (ICU) (513, 46.0%). There was no difference between BC and AC in the proportions of patients admitted to the GW ($P = 0.327$) and ICU ($P = 0.230$). Patients discharged home from the ER showed no difference between BC and AC ($P = 0.757$). A total of 299 patients were transferred to another hospital from the ER, which was lower in AC (169, 14.0%) than in BC (130, 17.8%) ($P = 0.027$). Table 2 shows that 136 deaths occurred without admission or transfer, and mortality in the ER before disposition was higher in AC (106, 8.8%) than in BC (30, 4.1%) ($P < 0.001$). After admission, the length of hospitalization of the patients with ALC in the ER was 19.25 ± 25.19 days. It was longer in AC (20.63 ± 27.74 days) than in BC (16.98 ± 20.16 days) ($P = 0.012$); however, there was no statistically significant difference in the destinations on discharge from the hospital.

Table 3 shows the mortality of ALC in the ER. A total of 369 patients died after visiting the ER, with an overall mortality rate of 18.5%. The mortality was higher in AC (252, 20.9%) than in BC (107, 14.6%) ($P = 0.001$). The stroke mortality rates were 13.5% and 23.3% ($P = 0.031$), whereas C&V mortality rates were 25.5% and 63.2% ($P < 0.001$) in BC and AC, respectively.

DISCUSSION

ALC is a significant issue in the ER, and identification of its etiology, investigation of its clinical course, and preparation of a ready-made pathway are needed for real-world practice. This study pro-

Table 2. Dispositions and destinations of patients with altered level of consciousness

Variable	Total	BC	AC	P-value
Disposition from the ER	(n=1,936)	(n=731)	(n=1,205)	
GW	603 (31.1)	218 (29.8)	385 (32.0)	0.327
ICU	513 (26.5)	205 (28.0)	308 (25.6)	0.230
Transfer	299 (15.4)	130 (17.8)	169 (14.0)	0.027
Home	136 (7.0)	148 (20.2)	237 (19.7)	0.757
Death in the ER	136 (7.0)	30 (4.1)	106 (8.8)	<0.001
Destination on discharge	(n=1,116)	(n=423)	(n=693)	
Home	544 (28.1)	220 (52.0)	325 (46.8)	0.088
Transfer	349 (18.0)	126 (29.8)	223 (32.2)	0.403
Death	223 (11.5)	77 (18.2)	146 (21.1)	0.246
Length of hospitalization (day)	19.25±25.19	16.98±20.16	20.63±27.74	0.012

Values are presented as number (%) or mean±standard deviation.

BC, before coronavirus disease 2019; AC, after coronavirus disease 2019; ER, emergency room; GW, general ward; ICU, intensive care unit.

Table 3. Mortality by etiology and overall mortality

Variable	Total (n=1,936)	BC (n=731)	AC (n=1,205)	P-value
Overall mortality	369 (18.5)	107 (14.6)	252 (20.9)	0.001
Systemic infection	138 (27.5)	53 (23.6)	85 (30.8)	0.071
Metabolic cause	56 (13.9)	18 (11.7)	38 (15.3)	0.306
Stroke	59 (19.1)	18 (13.5)	41 (23.3)	0.031
C&V	68 (49.3)	13 (25.5)	55 (63.2)	<0.001
Seizure	4 (3.3)	1 (2.0)	3 (4.3)	0.480
Toxic cause	6 (2.6)	1 (2.3)	5 (2.7)	0.872
Psychiatric	0	0	0	NA
TBI	18 (23.4)	0	18 (25.4)	0.159
CNS infection	3 (14.3)	0	3 (20.0)	0.237
Undetermined	7 (6.8)	3 (6.7)	4 (6.9)	0.963

Values are presented as number (%).

BC, before coronavirus disease 2019; AC, after coronavirus disease 2019; C&V, cardiogenic and vascular cause; NA, not available; TBI, traumatic brain injury; CNS, central nervous system.

vides important information by comparing the etiologies of ALC in BC and AC. ALC has many synonyms such as mental change, altered mental state, and loss of consciousness. It ranges from drowsiness to coma and includes confusion, psychosis, delusions, and abnormal behavior. This inconsistent nomenclature and broad spectrum of symptoms suggest that ALC can be transient and may be derived from diverse medical problems. In addition, the medical environment and medical utilization behaviors have changed owing to the pandemic, resulting in a change in the frequency of the etiologies.

When designing a study comparing BC and AC, we considered that the period of the coronapocalypse should be excluded. The COVID-19 outbreak and surge resulted in changes of national quarantine policy or the related suspension of emergency operations. Since there can be significant bias due to policy or political reasons rather than medical needs, we have stipulated that AC stands for the period after COVID-19 vaccination, to represent the so-called new normal.

There have been studies on changes in medical or ER utilization after the COVID-19 outbreak; however, there needs to be a more coherent definition of AC, discordant inclusion criteria, consistency in the study period, and etiology classification. Several studies have investigated periods of only 2 to 4 months to find a significant reduction in ER visits [15,20,21]. A few studies adopted a contrived definition of AC, with the number 2020 representing the year in the calendar rather than any medical gauge [18]. In addition, many disease- or condition-specific investigations have compared BC and AC, such as pneumonia [22], stroke [23,24], and suicide [25,26]. In contrast, few studies have evaluated ALC in the ER and compared BC and AC. An American study evaluated ALC in the ER in AC [21]; however, the study included only 166 patients over approximately 40 days, and its etiology classification was crude with only three categories: neurologic, metabolic, and indeterminate. Our study showed that the main etiologies of ALC in the ER were extra-cranial in AC and BC, and the leading cause was systemic infection. Intra-cranial etiologies account-

ed for approximately a quarter of the total. This finding is compatible with previous studies on BC [2,8,21]. Although the proportion of systemic infections decreased by approximately 8%, it was still the most common etiology of ALC in the ER, followed by metabolic causes. This implies that systemic infection and metabolic causes remain classic issues in the approach to the ALC in the ER.

The number of patients who visited the ER was higher in BC than in AC; however, the number of patients with ALC in AC was more than 1.5 times higher than that in BC. Between BC and AC, there were differences in the proportions of patients with toxic causes and stroke as ALC etiologies. Toxic causes include ingestion or inhalation of toxic materials such as alcohol, herbicides, caustic soda, and carbon monoxide, as well as medication overdose. According to the etiology classification system used in this study, any overdose was considered toxic. The remarkable increase in toxic cause can be explained by increased depression, suicidal ideation, and resultant suicidal attempts in AC [27,28]. Recent studies suggested that the incidence of stroke had decreased, and the patients were dispersed in AC [24,29,30]. In this study, the rating of the etiologies of ALC in the ER reflects the reality: more depression and suicides but fewer strokes in AC than in BC. In addition, this change resulted in a lower age in AC than in BC. The age of toxic causes was significantly lower than that of stroke (55.38 ± 20.89 vs. 70.22 ± 14.74 years, $P < 0.001$). In previous studies, the mean age of patients with ALC visiting the ER varied from 65 to 69 years [2,5,8], which is consistent with the results of this study. The lower mean age in AC may be due to the remarkable difference in etiologies between BC and AC (more cases of toxic causes and TBIs in AC).

The data from this study alone cannot determine why the number of TBIs in AC was higher than that in BC. Recent studies have also reported an increase in TBIs [31,32]. However, the reason for this remains unclear. Based on our experience, frontline medical institutions lacked the manpower and facilities to handle ALC in TBI patients under the COVID-19 policy. Thus, ALC patients with TBI require a multidisciplinary approach and may need surgery. Therefore, in this university hospital, ALC with TBI was found to be increased in AC. Meanwhile, it is crucial that the etiology was undetermined in approximately 5% of ALC cases, despite 17.08 ± 21.48 hours of stay time in the ER. There were several inevitable situations for which the cause of ALC was undetermined: the diagnosis often remained putative, two or more causes could not be excluded, some clinical situations led to an emergency operation, and some tests required several days to confirm the results (e.g., the aquaporin-4 antibody for neuromyelitis optica and cerebrospinal fluid cytopathology for carcinomatosis cerebri). This

5% rate implies that the clinical approach in the ER may be insufficient for the diagnosis and management of ALC, and additional medical approaches after hospitalization are required.

The average stay time in the ER did not differ between BC and AC in this study. A previous study reported that the ER stay time in AC increased in adult patients and decreased in pediatric patients [18]; however, the polymerase chain reaction test for COVID-19 takes about 6 hours, which was shorter than the average stay time to investigate ALC in the ER and resulted in no difference in stay time. Meanwhile, transfers from the ER to another hospital were reduced because of the quarantine policy in South Korea. Therefore, a negative polymerase chain reaction test for COVID-19 has been an essential prerequisite for all hospital admissions and transfers to another hospital. A previous study also reported an increase in hospitalization periods owing to COVID-19 testing [33]. According to this study, the quarantine policy is thought to have led to a decreased transfer rate from the ER, no change in the transfer rate upon discharge from the hospital, and an increase in the length of hospital stay in the ICU. The higher overall mortality rate and more deaths in the ER in AC were due to stroke and C&V that represent vascular attacks. There have been reports of an increase in the mortality rate of stroke or acute coronary syndrome related to COVID-19 [34,35], and our study supports these findings.

This study had several limitations. First, our study could not exclude selection bias because of the single-center retrospective design. Secondly, only a single ethnic background was considered. Third, the diagnoses in this study were provisional at the time of discharge from the ER, and may differ from the definite diagnosis. Despite these limitations, this is the first study to compare the etiology and mortality of ALC in the ER between AC and BC. The major etiologies of ALC in the ER were extra-cranial in both BC and AC, and the incidences of toxic cause as well as TBI were higher in AC. The mortality rate was higher in AC because of the higher mortality rates of mortality of systemic infection, stroke, and C&V. ALC is a significant issue in the ER because investigations can be time-consuming, multiple causes can coexist, and additional evaluation may be required beyond what the available time allows in the ER. These obstacles make the study of ALC in the ER a challenging but important area for further research.

ARTICLE INFORMATION

Ethics statement

This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments and was approved by the Ethics Committee of

Keimyung University Dongsan Medical Center (No. 2022-09-068). The requirement for written consent was waived because of the retrospective study design.

Conflict of interest

No potential conflict of interest relevant to this article.

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Neuroprotective effects of chloroquine on neurological scores, blood-brain barrier permeability, and brain edema after traumatic brain injury in male rats

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Background: Traumatic brain injury (TBI) is one of the leading causes of death among young people worldwide. Chloroquine, an anti-malarial drug, has been shown to easily cross the blood-brain barrier (BBB) and inhibit autophagy in a variety of disorders, including Alzheimer disease and brain ischemia. We investigated the effects of chloroquine on neuronal protection after induction of brain trauma in male rats.

Methods: A total of 120 male Wistar rats were treated with chloroquine at doses of 1.5, 3, and 6 mg/kg intraperitoneally after induction of diffuse TBIs. The veterinary coma scale was used to assess short-term neurological deficits. BBB disruption was evaluated using the Evans Blue dye method 6-hour post-injury. Vestibulomotor function was evaluated using the beam walk and beam balance methods. Histopathological changes in the brain tissue in different groups were evaluated using light microscopy and hematoxylin-eosin staining. Brain water and cerebrospinal fluid (CSF) contents of matrix metalloproteinase 9 (MMP-9) were assessed using the wet/dry method and enzyme-linked immunosorbent assay, respectively.

Results: The results showed that injecting chloroquine (3 and 6 mg/kg) 30 minutes after TBI significantly reduced brain edema and BBB disruption, and recovered neurological deficits post-TBI ($P < 0.01$). Furthermore, CSF MMP-9 was significantly reduced after administration of 1.5 mg/kg chloroquine ($P < 0.01$).

Conclusion: Chloroquine has neuroprotective effects in the brain, and thus, has the potential to mitigate the effects of brain trauma. It is possible that the anti-inflammatory and neurogenic effects of chloroquine are due to a decrease in MMP secretion in the CSF.

Keywords: Chloroquine; Brain trauma; Neural protection

INTRODUCTION

Traumatic brain injury (TBI) is one of the leading causes of death

among young people worldwide. Furthermore, it is one of the most common causes of hospitalization [1]. TBI is a type of functional brain injury that can affect brain function in somatic, cogni-

tive, and emotional domains. Headache is the most common symptom of TBI, followed by dizziness, balance disorders, loss of awareness of time and place, and sleep disorders [2,3]. TBI can be classified into two stages, with the primary phase as the initial hit that moves the brain inside the skull, and the secondary phase develops over time as a result of cellular events that cause additional damage and can last from a few days to a week or month [4,5]. TBI causes temporary membrane abnormalities that lead to ion and neurotransmitter redistribution, resulting in an increase in levels of calcium and stimulant amino acids, followed by the release of potassium, which inhibits neuronal activity. When sodium-potassium Na^+/K^+ -ATPase pumps regain their balance, the need for energy increases while cerebral blood flow remains low. Disorders in autonomic nervous system regulation can last for several weeks, and the brain may be more vulnerable to damage [5]; however, evidence for drug treatment is limited. The goal of therapy is to maintain symptoms under control. Rest is the most important component of treatment because it can exacerbate concussion symptoms and prevent recovery [6]. Evidence suggests that autophagy increases after a TBI [7,8]. In stroke rats, the administration of a selective autophagy inhibitor (3-methyladenine) has been shown to have neuroprotective effects [9].

Chloroquine (CQ), an antimalarial drug, has been shown to easily cross the blood-brain barrier (BBB) and inhibit autophagy in a variety of disorders, including Alzheimer disease and brain ischemia [10,11]. CQ is also effective in treating cranial oxidative stress, as it reduces the reactive oxygen species in the brain. Therefore, CQ is regarded as neuroprotective in the brain following TBI [12]. CQ, an autophagy inhibitor, can be used to reduce brain tissue destruction and improve neurological function following TBI. Autophagy is activated after brain injury, which can result in neuronal and astrocytic injuries. Matrix metalloproteinases (MMPs) are a group of zinc-dependent endopeptidases that degrade the extracellular matrix (ECM) and other proteins. MMPs are required for ECM remodeling, wound healing, and tissue morphogenesis [13]. Under pathophysiological conditions, MMPs act as proteolytic enzymes that destroy the ECM and the BBB binding proteins. MMPs are secreted by astrocytes, neurons, epithelial cells, fibroblasts, and osteoblasts, and they interfere with natural physiological processes, such as angiogenesis, neurogenesis, inflammatory processes and apoptosis. MMP-2, MMP-3, and MMP-9 levels increase as a result of brain trauma, resulting in neuritis and cell death [14]. We investigated the effects of intraperitoneal (IP) CQ injection on neurological scores, cerebral edema, BBB permeability, and the amount of MMP-9 after inducing severe brain trauma using the Marmarou method [15].

METHODS

Animals and groups

A total of 120 male Wistar rats (250–330 g; Mazandaran University of Medical Science) were housed under standard conditions (air-conditioned room at $22\text{ }^\circ\text{C} \pm 2\text{ }^\circ\text{C}$ temperature with a 12-hour light:12-hour dark cycle) with free access to clean water and food. Animals were injured using Marmarou free-fall TBI technique [16]. Rats were randomly divided into the following groups: (1) TBI group (TBI, $n = 24$): rats were subjected to anesthesia, surgical opening, and TBI induction, (2) Saline group (vehicle, $n = 24$): similar to TBI group, but an equal volume of the 0.9% normal saline (solvent of CQ) was injected intraperitoneally 30 minutes after TBI induction, (3) CQ groups (CQ 1.5, 3, and 6, $n = 24$ in each group): CQ with different doses of 1.5, 3 and 6 mg/kg were injected IP 30 minutes after TBI induction [10,11].

Model of diffuse TBI

The animals were anesthetized using ketamine and xylazine, and the animals were intubated through the mouth (the tracheal cannula was connected to the breathing pump to control breathing and fend off hypoxia). Diffuse TBI was performed using the Marmarou method [17]. To distribute the effect and keep away from the cranium fracture, the scalp was incised to show the cranium, and a metallic disk with a thickness of 3-mm and 10-mm diameter was glued to the bone centrally alongside the coronal among bregma and lambda using polyacrylamide glue with a view to distribute the blow onto a larger area. Subsequently, the animal was positioned in a susceptible function on a 10-mm thick foam bed, and a 400-g blunt steel cylinder was dropped vertically through freefall from a height of 2 m. Following trauma induction, the body temperature was maintained via the methods at $37\text{ }^\circ\text{C}$ by setting the animals on a heating pad. Following trauma induction, the rats were immediately connected to an animal breathing pump (TSE animal respirator, Germany). After recovery, the animals were disconnected from the pump and housed in individual cage [17–21].

BBB permeability assessment

The BBB's permeability to small and massive molecules was assessed qualitatively using intravenous 2% Evans blue dye (molecular weight 6,900, 20 mg/kg). The animals were anesthetized 4 hours after trauma with thiopental (50 mg/kg IP), and 20 mg/kg Evans blue dye (1 mL/kg) was injected through the jugular vein ($n = 8$ per group). One hour after injection, the thorax of the anesthetized animal was opened. The descending aorta was clipped, and isotonic heparinized saline solution (approximately 300 mL) was infused into the circulatory gadget through the left ventricle

to remove the intravascular dye.

Each jugular vein was then cut, and saline infusion was continued until the clean liquid strolled out of the jugular vein. The mind was changed to be eliminated immediately and homogenized after weighting. A 20 mL solution of acetone (14 mL) +1% sodium sulfate (6 mL) was infused into the homogenized mind and placed at the shaker for 24 hours. Then, 1 mL of trichloroacetic acid combined with 1 mL supernatant was placed at a fab place (20 °C) for 3 minutes. After centrifugation of the solution at 2,000 rpm for 10 minutes, Evans blue dye absorption from 1 mL supernatant was measured at 620 nm using a spectrophotometer (Pharmacia Biotech). The following system was used to calculate Evans blue dye content:

Evans blue dye (μg) in brain tissue (g) = $13.24 \times 20 / \text{absorbance tissue weight}$ [19,20].

Determination of brain water content

Brain water content was assessed 24 hours after trauma induction using the dry-wet weight process. Briefly, the brains of anesthetized animals were removed and weighed to obtain the wet weight. The tissue was placed in an incubator at 60 °C–70 °C for 72 hours and reweighed to obtain tissue dry weight. Finally, the percentage of brain water content was calculated using the following equation:

$$100 \times (\text{wet weight} - \text{dry weight}) / (\text{wet weight}) [22].$$

Evaluation of neurological outcomes

Neurological function was evaluated using the veterinary coma

scale (VCS) and expressed as a score from 3 to 15, which was comprised of three parts: motor, eye, and respiratory function. According to VCS criteria, higher scores mean superior neurological outcomes, and lower scores indicate a more severe neurological deficit. The detailed scoring system is shown in Table 1. In the present study, the VCS was measured 1 hours before trauma (Pre), immediately after trauma (D0), and 24 (D1), 48 (D2), and 72 (D3) hours post-trauma (n = 8 per group) [23,24].

Vestibulomotor function evaluation

The beam task was used based on previous training to evaluate vestibulomotor function three times following the damage. Beam training was performed prior to TBI. For the duration of the training, rats were given five trials to traverse a 100 cm long beam with a width of 4 cm, and an additional five trials to travel a 100 cm long beam with a width of 1.5 cm. On the testing days, the mean of the three endeavors for each rat was recorded. The beam walk trial was started with the rat located at the beginning of the beam (2.5 × 100 cm) and ended when the animal effectively traversed a distance of 100 cm. A maximum duration of 60 seconds was permitted for each experiment. The beam balance trial started with the rat being placed on the 2 cm beam and the time spent balancing for 60 seconds was recorded. If an animal stayed on the beam for the entire 60 seconds, a score of 5 was recorded (1 score was given every 12 seconds). A camera was used to record each trial, and traverse time and falls were used to measure vestibulomotor function (n = 8 per group) [20,25].

Table 1. Veterinary coma scale

Variable		score
Motor function	Normal movement	8
	Mildly drowsy with spontaneous purposeful movements	7
	Lethargic, unable to stand, but maintains sternal recumbency	6
	Lethargic, withdraws to pinch, and lifts head with attention to visual stimuli; no sternal recumbency	5
	Withdraws or pedals to pinch	4
	Spontaneous pedaling	3
	Extensor posturing (spontaneous or to stimuli)	2
	Flaccid to stimuli	1
Eye function	Open	4
	Open on stimulation	3
	Normal eyelid reflexes	2
	No eyelid response to stimuli	1
Respiration	Normal	3
	Ataxic	2
	Apneic	1
Total		15

Cerebrospinal fluid collection from cisterna magna and MMP-9 enzyme-linked immunosorbent assay

A single cerebrospinal fluid (CSF) sample was collected from the animals 72 hours after the induction of TBI ($n = 8$ per group). Briefly, animals were mounted on a stereotaxic device (Stoelting), and local anesthesia was applied (0.25 mL of 1% lidocaine). A 25-gauge scalpel related to a 1.0 mL syringe was placed vertically and centrally into the cisterna magna, and CSF was gently aspirated, resulting in a 50–100 μ L sample CSF sample that was centrifuged for 15 minutes at 1,000 $\times g$, and the supernatant was immediately stored at -80°C until analysis. Blood-contaminated CSF samples were discarded. Enzyme-linked immunosorbent assay (ELISA) calculate was performed on the collected CSF samples using a rat MMP-9 ELISA kit (MBS722532) from MyBioSource Inc. [26,27].

Histopathology evaluation

For histopathological evaluation, two rats were randomly selected from each group and sacrificed. Brain samples were obtained, fixed in 10% buffered formaldehyde, sectioned (5 μ m) with an automatic microtome (Leica), and stained with hematoxylin-eosin 24 hours post-TBI. The animals were anesthetized with thiopental (50 mg/kg IP). Pathological changes were evaluated under a light microscope by two pathologists blinded to the animal group and drug used [20,28].

Data analyses

All data are presented as mean \pm standard error of mean (SEM). Normal distribution of the data was squared using Shapiro-Wilk's test. In case of normal data distribution, statistical significance was proven using two-way analysis of variance (ANOVA) monitored by Tukey's post hoc analysis and one-way ANOVA monitored by Newman-Keuls post hoc test. If the data were not normally distributed, a non-parametric Kruskal-Wallis test was used, as surveyed by Dunn's test for post hoc analysis. The area under

the curve (AUC) was calculated using the formula $\Delta X \times [(Y1+Y2)/2] - \text{baseline}$, where Y1 is the value of the point 1 measurement and Y2 is the second measurement, and ΔX is the amount of time that passed. The baseline was considered to be 0 in all measurements. After calculating AUCs, the SEM and sample size were analyzed using one-way ANOVA in order to find statistical differences among groups. Statistical significance was set at $P < 0.05$. GraphPad Prism version 5.00 for Windows (Graph Pad, www.graphpad.com) was used for the data analysis. The subsequent symbols represent significant values.

RESULTS

The effect of CQ on neurological scores

The effects of CQ treatment on the VCS score after experimental TBI are shown in Table 2. Repeated two-way ANOVA measures were followed by Tukey's post hoc test. There was no significant difference between the groups before TBI induction. After TBI, all the groups showed a significant decrease ($P < 0.001$). At 24 hours after TBI, VCS scores in the groups that received CQ 3 and 6 mg/kg exhibited a significant increase compared to the saline and TBI groups ($P < 0.01$). At 48 hours after TBI, both groups that received either CQ 3 or 6 mg/kg showed a significant increase in VCS scores compared to the saline or TBI groups ($P < 0.01$). In addition, the group that received CQ 1.5 mg/kg was not significantly different from the saline group at 48 and 72 hours after TBI. Lastly, 72 hours after TBI induction, both groups that received either CQ 3 mg/kg or 6 mg/kg showed a significant increase compared with saline or TBI groups ($P < 0.05$ and $P < 0.01$). On the day of the measurement, a difference between the treated groups was also observed. At 48 and 72 hours after TBI induction, the CQ 6 mg/kg-treated group had significantly higher VCS scores compared to the group that received CQ 3 mg/kg ($P < 0.01$). The AUC analysis of the VCS score yielded similar results (Table 2). All groups were significantly different

Table 2. Effects of CQ treatment on veterinary coma scale after experimental TBI

Group	Pre-TBI day	Trauma day	1st Day after TBI	2nd Day after TBI	3rd Day after TBI
TBI	15.00 \pm 0.00	4.5 \pm 0.7	5.75 \pm 1.47	5.25 \pm 0.96	6.63 \pm 1.11
Saline	15.00 \pm 0.00	3.5 \pm 0.5	4.62 \pm 0.85	6.12 \pm 1.61	6.00 \pm 1.32
CQ 1.5	15.00 \pm 0.00 ^{a)}	3.6 \pm 0.69 ^{a)}	4.59 \pm 0.83 ^{a)}	6.00 \pm 0.70 ^{a)}	5.38 \pm 0.85 ^{a)}
CQ 3	15.00 \pm 0.00	4.75 \pm 0.96	10.75 \pm 1.39 ^{b)}	9.25 \pm 1.29 ^{c)}	11.00 \pm 1.32 ^{d)}
CQ 6	15.00 \pm 0.00	4.00 \pm 1.00	13.37 \pm 1.75 ^{b)}	14.13 \pm 1.05 ^{c)}	13.63 \pm 0.99 ^{d)}

Values are presented as mean \pm standard error of mean.

CQ, chloroquine; TBI, traumatic brain injury.

^{a)}Not significant compared with the TBI and saline control groups; ^{b)} $P < 0.05$, ^{c)} $P < 0.01$, and ^{d)} $P < 0.001$: significantly different from the TBI and saline control groups.

from the saline group ($P < 0.01$). Groups that were treated with CQ 3 and 6 mg/kg had significantly larger AUC compared to the TBI or saline groups ($P < 0.05$ and $P < 0.01$, respectively).

Effect of CQ on beam balance and beam walk tests

The effects of CQ treatment on beam balance and beam walk tests after experimental TBI indicated a repeated measures two-way ANOVA followed by Tukey's post hoc test. Beam walk and beam balance tasks were used to examine the effect of therapeutic interventions on the vestibulomotor system. Prior to the intervention, all the groups were similar. After TBI, all groups showed sig-

nificantly lower beam walk scores (Fig. 1A) ($P < 0.001$). This result persisted for 24 hours after TBI. Forty-eight hours after TBI injury, groups treated with either CQ 3 or 6 mg/kg had significantly better beam walk scores than the TBI or saline groups ($P < 0.05$, $P < 0.01$, respectively). This improvement was sustained until the last day of measurement. Similar to the VCS score, 72 hours after TBI injury, the group that received CQ 1.5 mg/kg was not significantly different from saline and TBI groups. The AUC analysis of the data produced similar results (Fig. 1B). The beam balance task yielded similar results to those of the beam walk task (Fig. 1C). Groups that were treated with CQ 3 and 6

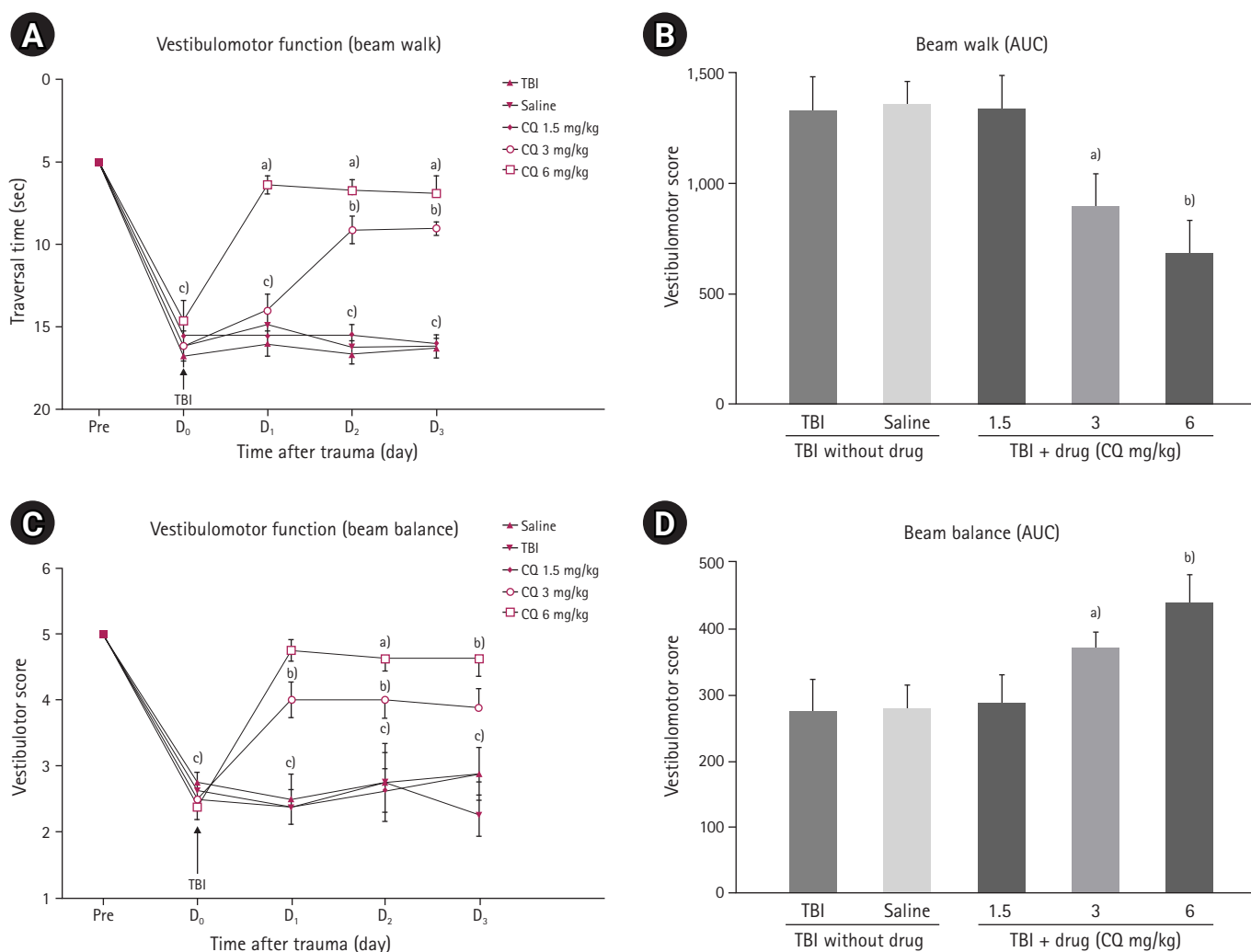


Fig. 1. Beam-walk and beam-balance task scores in three consecutive days after traumatic brain injury (TBI) injury ($n=8$ per group). (A) Beam-walk task transversal time in seconds in three consecutive days after TBI. Data were analyzed using repeated measure two-way analysis of variance (ANOVA) with Greenhouse-Geisser correction. Tukey's HSD test was used as the post-hoc test. (B) Area under the curve (AUC) calculated separately for the beam walk during experimental TBI in male rats in different days (before trauma [pre], on trauma day [D₀], first [D₁], second [D₂] and third [D₃] days). (C) Beam-balance task transversal time in seconds in three consecutive days after TBI. Data are analyzed using repeated measure two-way ANOVA with Greenhouse-Geisser correction. Tukey's HSD test was used as the post-hoc test. (D) AUC calculated separately for the beam balance during experimental TBI in male rats in different days (pre, D₀, D₁, D₂ and D₃ days). CQ, chloroquine. ^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.001$.

mg/kg had significantly better beam balance scores compared to the TBI or saline groups at 48 and 72 hours after TBI injury ($P < 0.01$ and $P < 0.001$, respectively). The observed effect was robust that 48 and 72 hours after TBI injury, the CQ 1.5 mg/kg group was not significantly different from the saline and TBI groups ($P > 0.05$). However, AUC analysis of the data revealed that the CQ 1.5 mg/kg group was not significantly different from the TBI and saline groups (Fig. 1D) ($P > 0.05$).

Effect of CQ on brain water content

The effects of CQ treatment on brain water content were repeated using one-way ANOVA followed by the Newman-Keuls post hoc test. The effect of CQ on brain edema, determined by brain water content 24 hours post-TBI, is shown in Fig. 2. The brain water content in the TBI and saline groups was higher ($P < 0.001$). Remarkably, the group that received CQ 1.5 mg/kg was not significantly different from the saline and TBI groups ($P > 0.05$). CQ 6 mg/kg prevented water accumulation in the brain following TBI in comparison with the TBI or saline groups ($P < 0.01$). Although the CQ 3 mg/kg treated group had significantly lower brain water content than the TBI group, the result was not significant compared to the saline and TBI groups ($P < 0.05$).

Effect of CQ on BBB permeability

The effect of CQ on blood-brain permeability by Evans blue dye content of the brain 24 hours post-TBI analysis by repeated measures one-way ANOVA followed by Newman-Keuls post-hoc test is shown in Fig. 3. The Evans blue dye content of the brains in the

TBI and saline groups was higher ($P < 0.001$). Remarkably, the group that received CQ 1.5 mg/kg was not significantly different from TBI and saline groups ($P > 0.05$). CQ 6 mg/kg prevented Evans blue dye accumulation in the brain following TBI in comparison with the TBI or saline groups ($P < 0.01$).

Effect of CQ on CSF content of MMP-9

The CSF level of MMP-9 24 hours post-TBI in rats indicated by repeated measures one-way ANOVA followed by Newman-Keuls post hoc test is shown in Fig. 4. An increase in MMP-9 level was observed in the TBI and saline groups ($P < 0.001$). CQ 6 mg/kg was not significantly different between the TBI and saline groups ($P > 0.05$). In addition, CQ 1.5 and 3 mg/kg had significantly lower MMP-9 levels than the TBI and saline groups ($P < 0.01$). There was a significant difference between the CQ 1.5 and 3 mg/kg groups and the saline and TBI groups ($P < 0.01$).

Effect of CQ on histopathological changes

The histopathological alterations in the different groups are shown in Fig. 5. The effects of CQ treatment on histopathological changes were repeated using one-way ANOVA followed by the Newman-Keuls post hoc test. Normal histological architecture of the brain cortex was evident in the saline group. Normal neurons with basophilic, euchromatic, and oval-shaped somas are evident. Most of the neurons in the TBI and saline groups were edematous and irregular in shape with dark nuclei in the TBI and saline groups (Fig. 5A and B). Perivascular edema and necrotic neurons were also observed. Endothelial cell expansion and blood vessel

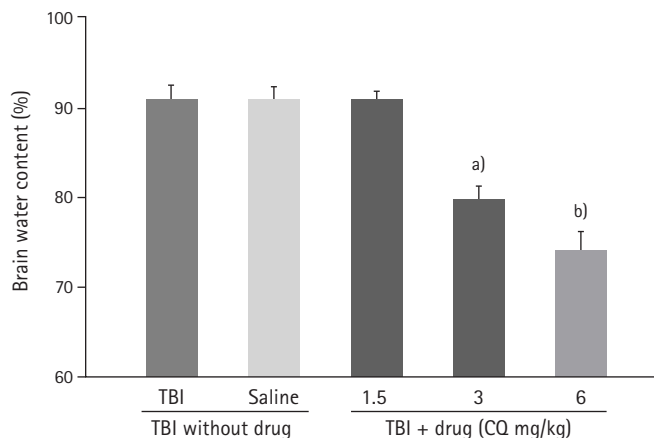


Fig. 2. The effects of chloroquine (CQ) on brain water content (%) 24 hours after traumatic brain injury (TBI). Each bar shows mean \pm standard error of mean for eight rats. Data were analyzed using one-way analysis of variance test. Newman-Keuls test was used as the post-hoc test. Compared with saline and TBI groups: ^{a)} $P < 0.05$; ^{b)} $P < 0.01$.

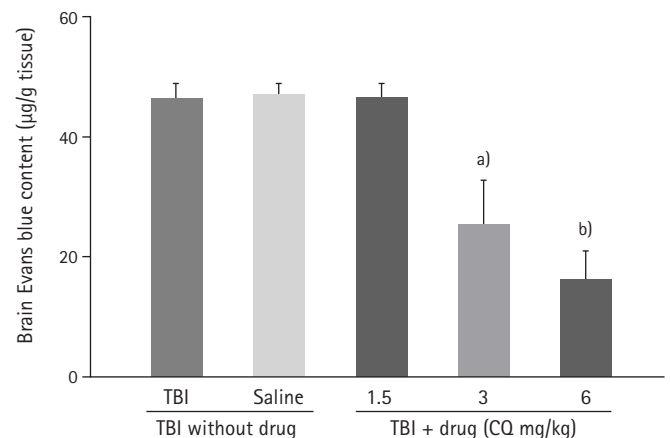


Fig. 3. The effects of chloroquine (CQ) on brain tissue Evans blue dye content 6 hours after traumatic brain injury (TBI). Each bar shows mean \pm standard error of mean for eight rats. Data were analyzed using one-way analysis of variance test. Newman-Keuls test was used as the post-hoc test. Compared with saline and TBI groups: ^{a)} $P < 0.05$; ^{b)} $P < 0.01$.

congestion were also observed. No significant histopathological changes were observed in the saline or TBI groups (Fig. 5A and B). A considerable number of pathological changes were observed in the CQ 3 mg/kg group, with reduced numbers of degenerated and edematous neurons (Fig. 5D). In the CQ 6 mg/kg group,

most neurons were normal in shape, with euchromatic nuclei and clear nucleoli. Endothelial cells, blood vessels, and astrocytes generally had a normal morphology similar to that of the saline group (Fig. 5E). On the other hand, severe pathological alterations similar to the TBI and saline groups were seen in the CQ 1.5 mg/kg group (Fig. 5C).

DISCUSSION

The goal of this study was to determine the effect of CQ on cerebral edema, BBB permeability, and neurological scores in male rats after brain trauma. According to our findings, among rats with concussions, the group that received 6 mg/kg of CQ had the highest VCS score. The level of consciousness score increased on the third day after concussion, with a VCS score comparable to the sham or intact groups. Qin et al. [11] in 2019 discovered that IP injection of 25 mg/kg CQ in male rats following ischemia-induced brain injury improved neurological scores. In 2015, IP injection of 3 mg/kg CQ in male rats reduced cerebral edema, improved cognitive and motor function, inhibited neuronal autophagy, and decreased interleukin-1 and tumor necrosis factor levels in the hippocampus following brain trauma, which is consistent with our findings [10].

Another finding from our study was that 6 mg/kg CQ was more effective than 3 mg/kg CQ in treating brain edema. The lowest effective dose of CQ was 1.5 mg/kg. Lesiak et al. [29] dis-

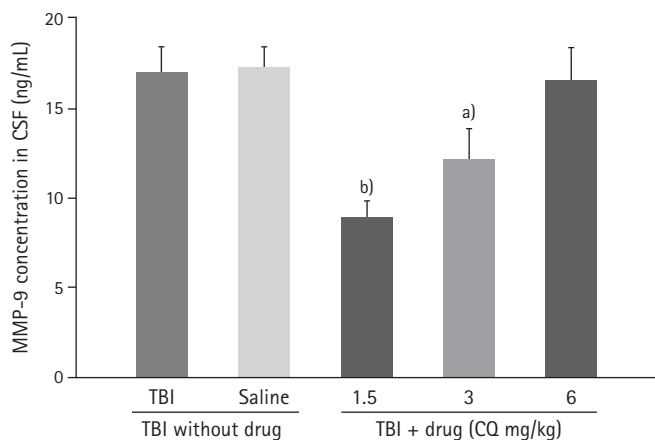


Fig. 4. Cerebrospinal fluid (CSF) content of matrix metalloproteinase 9 (MMP-9) measured by enzyme-linked immunosorbent assay 24 hours after traumatic brain injury (TBI) injury ($n=8$ in each group). Each bar shows mean \pm standard error of mean for eight rats. Data were analyzed using one-way analysis of variance test. Newman-Keuls test was used as the post hoc test. CQ, chloroquine. Compared with saline and TBI groups: ^{a)} $P<0.05$; ^{b)} $P<0.01$.

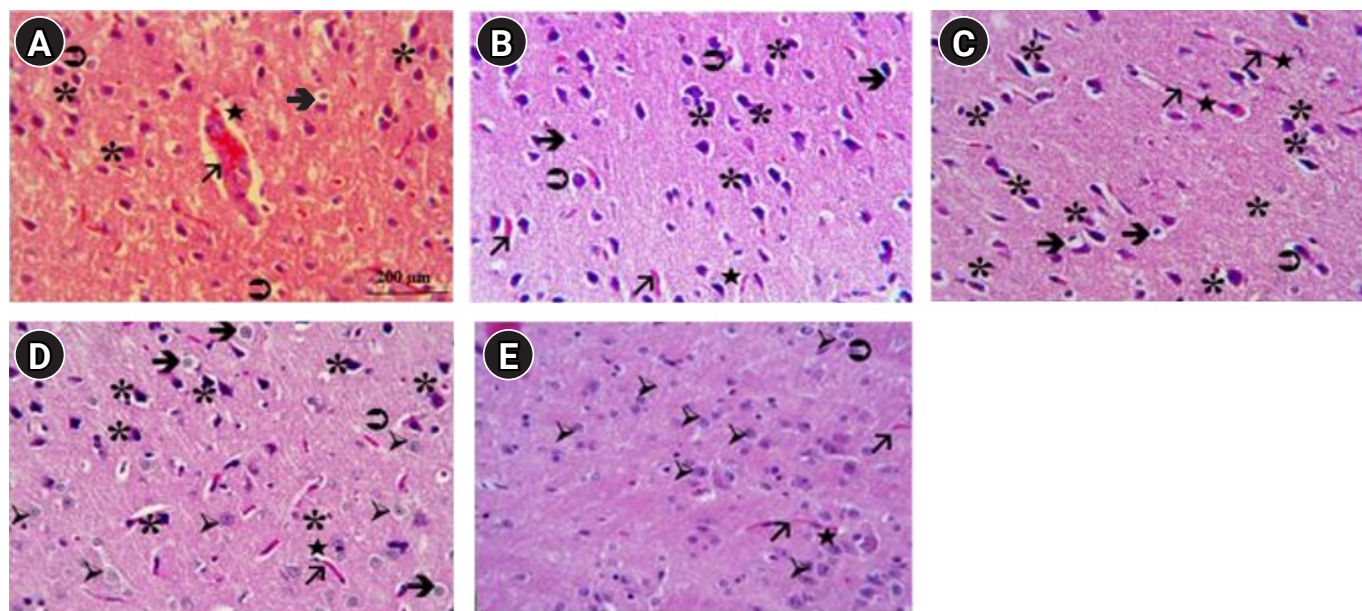


Fig. 5. The effects of chloroquine (CQ) on histopathology changes in 24 hours post-traumatic brain injury (TBI; H&E, $\times 400$). (A) TBI group, (B) saline, (C) CQ 1.5 mg/kg, (D) CQ 3 mg/kg, and (E) CQ 6 mg/kg in male rat's brain. \ominus , swollen astrocyte; \star , blood vessel; $*$, degenerated neuron; \rightarrow , edematous neuron; \swarrow , endothelial cell; \triangleright , Normal neuron.

covered that after treatment with CQ, the median MMP-9 serum level in patients with systemic lupus erythematosus decreased significantly. CQ treatment declines serum MMP-9 level in systemic lupus erythematosus [30]. It has been found that endosomal maturation inhibitors like CQ block expression of MMP-9 thru toll-like receptor-9 inhibition in murine macrophage RAW 264.7 cells [29]. In addition, the activity and expression of MMP-2 and MMP-9 are attenuated by CQ [31]. This finding is consistent with our previous findings on the effect of CQ on MMP-9 expression. In the histopathological study, 5- μ m-thick sections of brains from different experimental groups were prepared and stained with eosin and hematoxylin before being examined under a light microscope. It is likely that the effects of CQ on the MMP may be a major indicator of the loss of BBB integrity. Therefore, we observed behavioral changes with higher doses of CQ. However, for MMP-9, these behavioral changes were observed at lower doses of CQ. The reason may be partly related to the antagonistic and inhibitory effects of this drug on the BBB. Moreover, the dose is toxic and cannot prevent autophagy or apoptosis; thus, the effects of neuroprotection cannot be achieved.

As a result, the histological study found that moderate and high doses of CQ have a positive effect on brain tissue healing, as well as a reduction in cerebral edema, axonal desensitization, and microglial proliferation. Beam balance and beam walk tests were used to assess motor function, and the results showed that 3 days after brain trauma, we gradually observed better results in different groups that received low, medium, and high doses of the drug. The treatment groups had better balance and stayed on the bar for a longer period on the third day of the beam balance test, and the results were similar to those of the sham group.

Dai et al. [32] investigated the effects of CQ on Plasmodium berghei-infected mice in a similar experiment. They used a beam balance test to demonstrate that motor function improved after 10 days of treatment with 20 mg/kg CQ. The amount of Evans blue in the BBB was used to evaluate permeability, which is increased in concussions. The experiments discovered that this index decreased significantly in groups that received CQ doses of 3 and 6 mg/kg, indicating that the CQ had a good neuroprotective effect. The findings of Mielke et al. [33] revealed that for six days, IP administration of CQ (45 mg/kg) had a protective effect on the BBB.

Our findings show that trauma-induced concussion causes cerebral edema and BBB destruction, as well as changes in the animal's neurological and balance scores, and increased MMP-9 levels. On the other hand, CQ at doses of 3 and 6 mg/kg reduced the occurrence of abnormal neurological findings. However, at a dose of 6 mg/kg, these changes were more pronounced, with the exception of a reduction in MMP-9 levels, for which the lowest dose

(1.5 mg/kg) had the greatest effect. Contrary to the other results, the high dose of CQ in this case had no effect on this index. Based on our findings and observations, CQ has neuroprotective effects on the brain, and as a result, may help mitigate the effects of brain trauma. Lastly, we propose that the anti-inflammatory effects and CQ neurogenesis are due to the decreased CSF MMP secretion.

ARTICLE INFORMATION

Ethics statement

All methods involving live animals were carried out in accordance with Institutional Animal Care and Use Committee (IACUC). All experimental protocols were approved by the Ethics Committee of Animal Care and Use Committee of the Mazandaran University of Medical Sciences (IR.MAZUMS.RIB.REC.1400.054).

Conflict of interest

No potential conflict of interest relevant to this article.

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Delayed post-ischemic leukoencephalopathy in emergent large-vessel occlusive stroke after mechanical thrombectomy: case reports

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CASE REPORT

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Background: Delayed post-ischemic leukoencephalopathy (DPIL) is a rare complication after mechanical thrombectomy, with no well-established clinical characteristics and pathomechanism. We explored the characteristics and possible mechanisms in three patients with DPIL.

Case Report: Based on the clinical manifestations and laboratory findings including magnetic resonance imaging, magnetic resonance spectroscopy, electroencephalography, and lumbar puncture, DPIL was diagnosed in three patients. We administered antiplatelet agents and conservative treatment. Cardioembolism, successful recanalization using a balloon guiding catheter, and fluctuating or gradually worsening neurological symptoms in delayed phase between 13 and 70 days were common features of DPIL. Diffusion-weighted imaging and fluid-attenuated inversion recovery showed high-signal intensity in the affected subcortical white matter. Laboratory findings provided no evidence of an epileptic disorder, inflammatory demyelination, or tumorous conditions.

Conclusion: This report shows the characteristics and neuroradiologic images of DPIL. Among the various hypotheses, regional hypoxic-ischemic leukoencephalopathy and delayed reperfusion injury might be the pathomechanism underlying DPIL.

Keywords: Delayed leukoencephalopathy; Thrombectomy; Cerebral infarction; Cardioembolic stroke

INTRODUCTION

Delayed post-ischemic leukoencephalopathy (DPIL) is a rare complication after mechanical thrombectomy (MT) characterized by delayed-onset neurological deterioration, with subcortical white matter hyperintensities, sparing the cortex and basal ganglia [1-3]. The clinical manifestations of DPIL were heterogenous, in-

cluding aphasia, dysarthria, apathy, and executive dysfunction. Despite several hypotheses, the pathomechanism underlying DPIL remains unclear. We encountered four cases of DPIL from May 2021 to February 2022. Herein, we report the cases of three patients who underwent further evaluation, which is expected to contribute to a better understanding of the clinical characteristics and pathomechanism of DPIL for improved diagnosis in future.

CASE REPORTS

Case 1

A 79-year-old woman with a history of hypertension and atrial fibrillation presented with right hemiparesis and global aphasia. Her National Institutes of Health Stroke Scale (NIHSS) score was 21. Diffusion-weighted imaging (DWI) showed no lesions (Fig. 1); however, magnetic resonance angiography (MRA) revealed a left cavernous internal carotid artery (ICA) occlusion. The onset-to-puncture time was 270 minutes. After one aspiration thrombectomy attempt with a balloon guiding catheter (BGC), we achieved modified thrombolysis in cerebral infarction (mTICI) grade 3. The puncture-to-recanalization time was 40 minutes. At discharge on day 6, her NIHSS had decreased to 1. On day 28, she returned with fluctuating motor aphasia, from mild to mute. Additionally, she had a fever (38 °C) with *Escherichia coli* in the blood culture, suggesting a urinary tract infection and uncon-

trolled blood pressure of up to 160/110 mm Hg. DWI and fluid-attenuated inversion recovery (FLAIR) showed high-signal intensities in the entire subcortex of left middle cerebral artery (MCA) territory, without signal changes in the left basal ganglia and gray matter. She was discharged with mild to moderate motor aphasia, urinary tract infection improvement, and controlled blood pressure.

Case 2

A 77-year-old woman with a history of hypertension and atrial fibrillation visited our hospital. Her NIHSS score was 16. DWI showed hyperintense lesions in the left basal ganglia, and severe diffusion-perfusion mismatch was observed (Fig. 2). MRA revealed a left cavernous ICA occlusion. The onset-to-puncture time was 1,125 minutes. After two attempts with a stent retriever and aspiration thrombectomy with a BGC, we obtained mTICI grade 3. The puncture-to-recanalization time was 65 minutes.

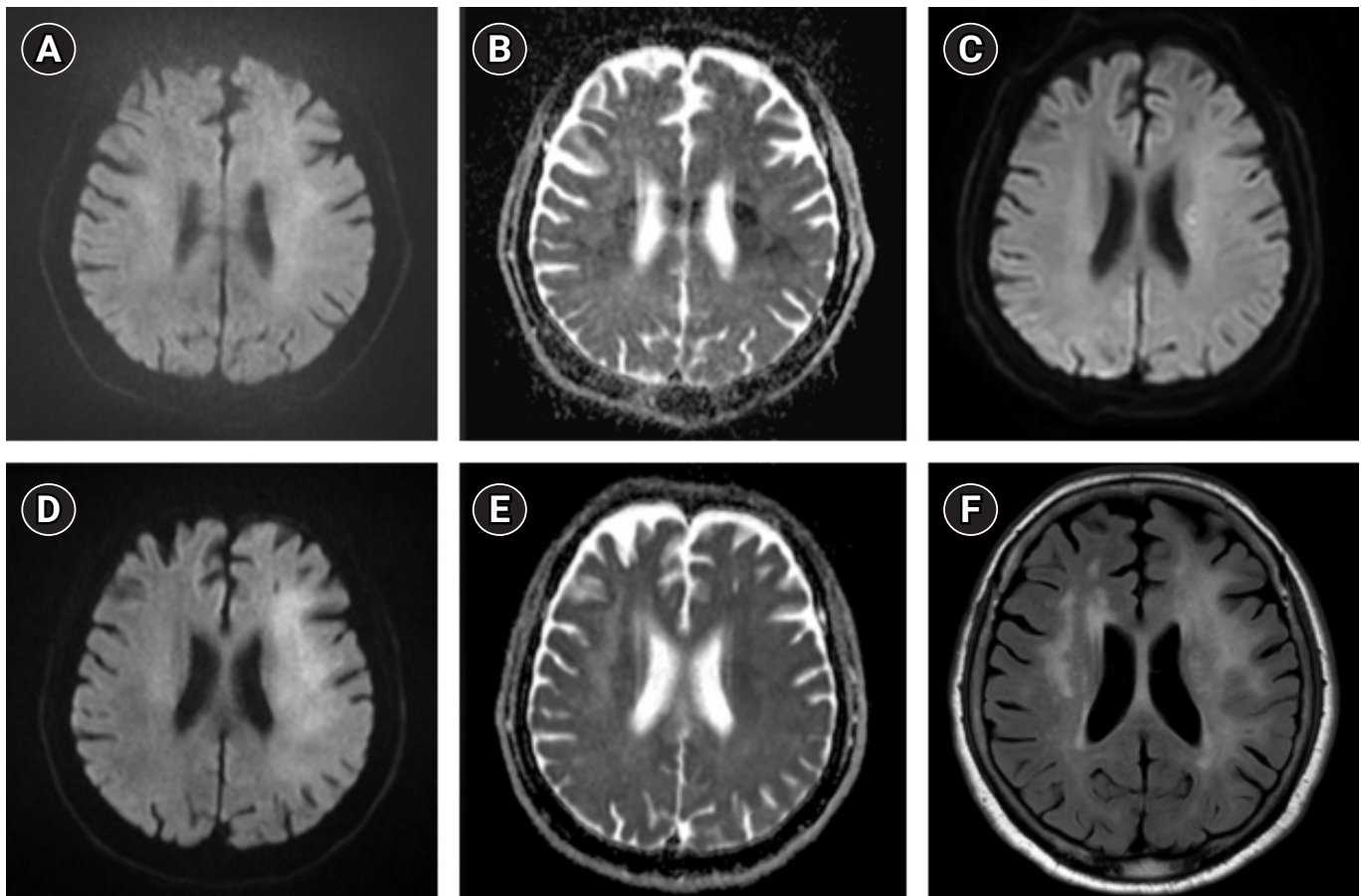


Fig. 1. Magnetic resonance imaging findings in case 1. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (A, B) on admission revealed no definite acute lesions. (C) DWI after mechanical thrombectomy showed some infarcts in the left corona radiata. On day 28, DWI (D) revealed high-signal intensities in the entire subcortex of left middle cerebral artery territory without signal changes on apparent diffusion coefficient (E). Fluid-attenuated inversion recovery (F) showed diffuse subcortical white matter lesions in the same territory.

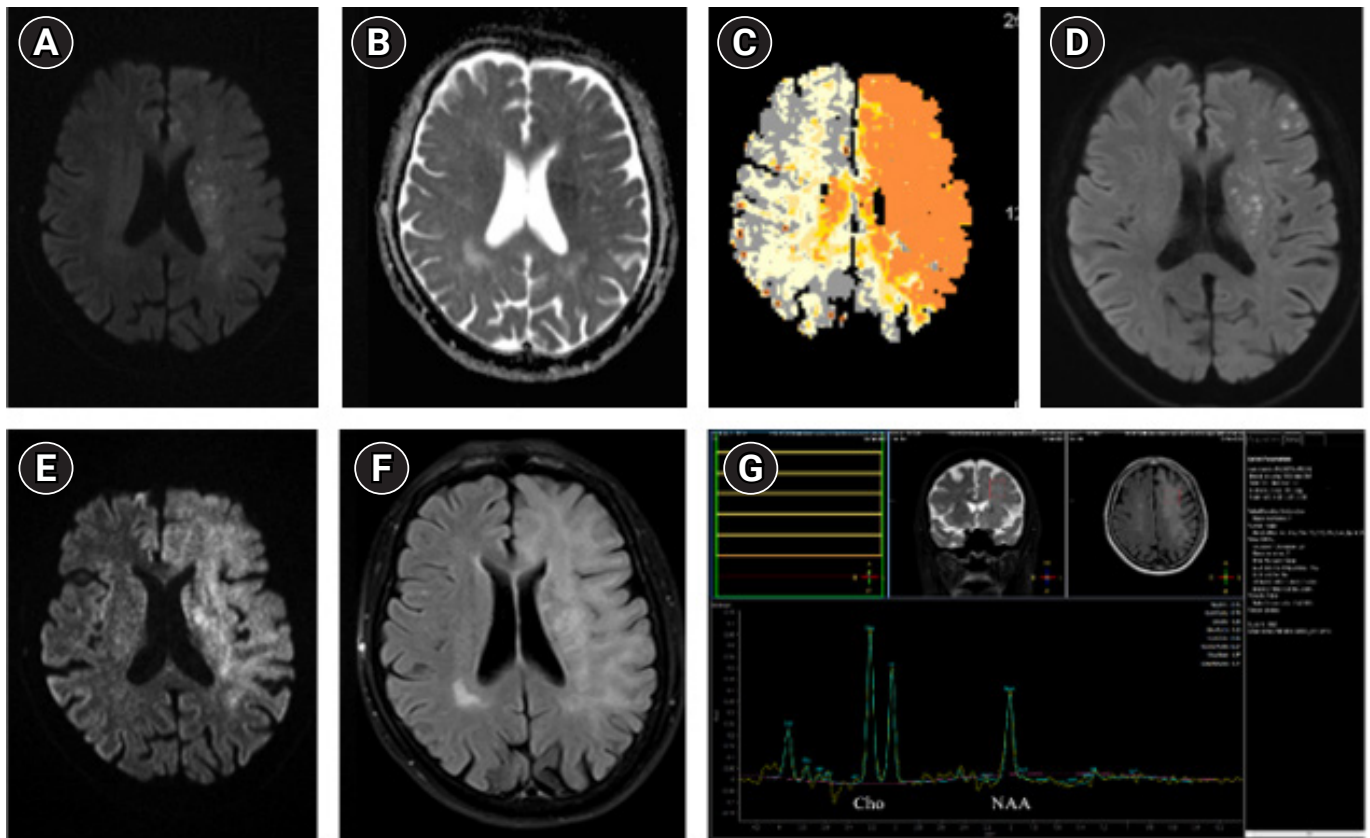


Fig. 2. Magnetic resonance imaging findings in case 2. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (A, B) on admission revealed new infarcts in the left corona radiata and subcortical area. (C) Magnetic resonance perfusion showed severe diffusion-perfusion mismatch. (D) DWI on day 6 showed new infarcts after mechanical thrombectomy. (E, F) On day 30, DWI and fluid-attenuated inversion recovery demonstrated the presence of diffuse subcortical white matter lesions. (G) Magnetic resonance spectroscopy showed a mildly increased choline/N-acetyl aspartate ratio.

The patient was transferred to another hospital on day 6 with an NIHSS score of 5. On day 30, she was readmitted for fluctuating motor aphasia. DWI and FLAIR revealed diffuse hyperintensities in the left MCA territory subcortex, with partial low-signal changes in the apparent diffusion coefficient (ADC). There were no newly developed steno-occlusive lesions in the left ICA or MCA. She was transferred to a rehabilitation hospital on day 38 with improved motor aphasia.

Case 3

A 78-year-old man with a history of hypertension and atrial fibrillation visited a tertiary hospital. His NIHSS score was 16. DWI demonstrated new infarcts in the left basal ganglia and corona radiata (Fig. 3), with severely decreased perfusion in the left MCA territory. MRA revealed occlusion of the left MCA M1 segment. The onset-to-puncture time was 733 minutes. After an attempt with a stent retriever and simultaneous aspiration thrombectomy with BGC, we achieved mTICI grade 2b. The puncture-to-recanalization time was 47 minutes. On day 8, the patient was dis-

charged with an NIHSS score of 1. On day 13, he visited our stroke center because his aphasia had gradually aggravated. He underwent magnetic resonance imaging on day 29. DWI and FLAIR showed diffuse white matter hyperintensities in the left MCA territory, without signal changes in the ADC. He was discharged with moderate motor aphasia.

No patient showed pleocytosis, albuminocytologic dissociation, or oligoclonal bands on cerebrospinal fluid analysis. In the first case, the immunoglobulin G (IgG) index was normal at 0.49. Moreover, magnetic resonance spectroscopy demonstrated mildly increased choline/N-acetyl aspartate ratios of 1.19, 1.57, and 1.38, respectively, which indicate nonspecific findings with no tumorous condition. Electroencephalography showed no epileptiform discharge in the patients.

DISCUSSION

The present case series reported the clinical and neuroradiological feature of three patients with DPIL that developed after MT due

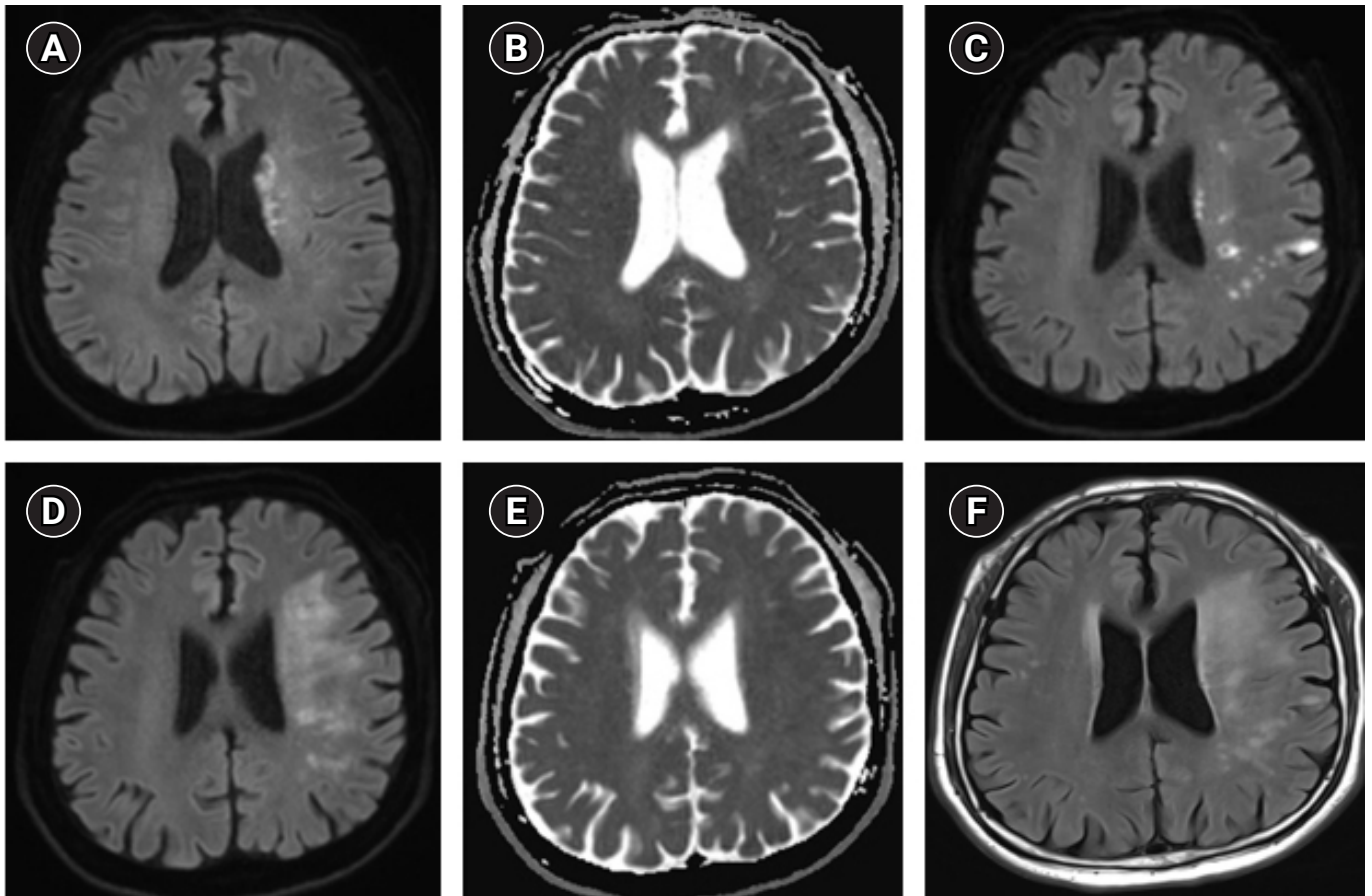


Fig. 3. Magnetic resonance imaging findings in case 3. (A, B) Diffusion-weighted imaging (DWI) and apparent diffusion coefficient on admission showed diffusion-restriction lesions in the left basal ganglia and corona radiata. (C) DWI after mechanical thrombectomy revealed new scattered infarcts in the left middle cerebral artery territory. On day 29, DWI and fluid-attenuated inversion recovery (D, F) demonstrated the presence of diffuse subcortical white matter lesions, without signal changes on apparent diffusion coefficient (E).

to large vessel occlusion. [Table 1](#) summarizes the clinical characteristics of the patients with DPIL that developed after MT due to large vessel occlusion from the current study and previous ones. (1) Cardioembolism, (2) fluctuating or gradually worsening neurologic symptoms in the delayed phase, (3) hyperintensities in the subcortical territory of the occluded vessel, and (4) successful recanalization using BGC during the procedure were common features in all cases. Diffuse subcortical white matter hyperintensities on T2 weighted images of the previously occluded vessel territory were observed in all cases, and impairment of remyelination by oligodendrocytes could be a plausible pathomechanism of DPIL [4]. There was no evidence of neuro-infection, seizures, inflammatory demyelinating disease, or tumorous conditions.

Various hypothetical pathomechanisms have been suggested for DPIL [1-3]. The neuroradiologic features of this condition are similar to those of delayed hypoxic leukoencephalopathy that are reported after carbon monoxide intoxication, cardiac arrest, and opioid or benzodiazepine overdose [5]. Impairment of repair

mechanisms by oligodendrocytes during the subacute to chronic period of ischemic insult might attribute to DPIL. Oligodendrocytes in the white matter may be more vulnerable to ischemic insult than neurons in the cerebral cortex since leptomeningeal collateral circulation is more prominent in the cortex than in the deep white matter [4]. Additionally, oligodendrocytes may be more severely injured in cardioembolic stroke, which is associated with poor collateral circulation [6]. Impairment of myelin regeneration by oligodendrocytes after ischemic insult leads to delayed neurological deterioration with subcortical white matter hyperintensities in the affected vessel territory. Moreover, the use of a BGC to prevent distal embolization during MT, might be one of the hypothetical causes of damage in the subcortical oligodendrocytes and accelerate the impairment of compensatory mechanisms for myelin loss. The absence of albuminocytologic dissociation and normal range of IgG index could rule out active demyelination as a histopathologic process.

Another potential cause of DPIL is reperfusion injury after re-

Table 1. Clinical characteristics of the patients with delayed post-ischemic leukoencephalopathy

Study	Sex/age (yr)	Risk factor	TOAST	Occlusion location	NIHSS (pre → post)	DWI ASPECTS	mTICI grade	HTf	Duration from stroke to delayed symptom (day)	Suspected trigger factor
Current study (case 1)	F/79	HT, AF, previous stroke	CE	Lt cavernous ICA	21 → 6	9	3	No	28	Fever, UTI, high BP
Current study (case 2)	F/77	HT, HL, AF, CHF	CE	Lt cavernous ICA	16 → 5	6	3	HI-1	20	None
Current study (case 3)	M/78	HT, HL, AF, CAD, smoking	CE	Lt MCA M1	16 → 1	7	2b	No	13	None
Current study (case 4 ^{a)})	F/71	HT, HL, AF, renal infarct	CE	Rt proximal CCA	18 → 8	6	3	HI-1	48	High BP
Sasaki et al. (2017) [1]	F/79	AF, CKD	CE	Rt MCA M1	9 → 0	10	3	No	70	None
Singu et al. (2017) [2]	M/66	HT, DM, HL, CAD, HF	CE	Lt MCA M1	NA	NA	2b or 3	No	35	None
Nehme et al. (2019) [3]	F/71	HT, DM, HL, CAD	CE	Lt terminal ICA	18 → 2	10 (CT)	3	No	18	None

TOAST, Trial of Org 10172 in Acute Stroke Treatment; NIHSS, National Institutes of Health Stroke Scale; DWI, diffusion-weighted imaging; ASPECTS, Alberta Stroke Program Early CT score; mTICI, modified thrombolysis in cerebral infarction; HTf, hemorrhagic transformation; HT, hypertension; AF, atrial fibrillation; CE, cardioembolism; Lt, left; ICA, internal carotid artery; UTI, urinary tract infection; BP, blood pressure; HL, hyperlipidemia; CHF, congestive heart failure; HI-1, hemorrhagic infarction type 1; CAD, coronary artery disease; MCA, middle cerebral artery; Rt, right; CCA, common carotid artery; CKD, chronic kidney disease; DM, diabetes mellitus; NA, not available; CT, computed tomography.

^{a)}Not included in the current case reports.

canalization of the large-vessel occlusion. Notably, all patients, including those from previous reports, presented with cardioembolism, which is more likely to cause reperfusion injury [7]. Similar manifestations have been observed in cerebral hyperperfusion syndrome after carotid stenting, caused by disrupted cerebral autoregulation. Moreover, delayed cerebral hyperperfusion syndrome, occurring a few weeks after carotid stenting, has also been reported [8]. Hypertension, chronic kidney disease, poor collateral circulation, and recent stroke are associated with the occurrence of cerebral hyperperfusion syndrome [9]. As the optimal range of blood pressure to maintain cerebral autoregulation varies according to the extent of baseline ischemia or degree of recanalization, delayed reperfusion injury can occur in the absence of high blood pressure [10].

Based on clinical manifestations and neuroradiologic findings, we speculated on the pathomechanism of DPIL. Early recognition of the disease may guide proper management and help avoid unnecessary diagnostic evaluation. Further investigation regarding the histopathologic mechanism, predictors, and long-term prognosis of patients with DPIL is needed.

ARTICLE INFORMATION

Ethics statement

The local Ethics Committee of Asan Medical Center provided approval for this study (No. 2022-0357). The need for written informed consent was waived because this was a retrospective study.

Conflict of interest

Jun Young Chang is an editorial board member of the journal, but he 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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Ticagrelor washout bridged with GPIIb/IIIa inhibitor infusion to facilitate surgical care following placement of pipeline flow diverters: a case report

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CASE REPORT

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Background: Pipeline flow diverters (PFDs) are becoming increasingly common. Antiplatelet medication is required to minimize periprocedural ischemic events. Short-acting GPIIb/IIIa inhibitors are frequently administered intraprocedurally; however, the role of these agents in postprocedural PFD management in the neurocritical care unit (NCCU) has been overlooked.

Case Report: A patient with an unruptured internal carotid artery aneurysm presented for PFD placement. PFD placement was complicated by post-procedure intra-PFD thrombosis and hemispheric ischemia. Aspirin and ticagrelor were restarted, and the surgery department consulted for tracheostomy and percutaneous endoscopic gastrostomy tube placement. Short-half-life GPIIb/IIIa infusions served as bridges to surgery after aspirin and tirofiban washout.

Conclusion: NCCU management of complications of PFD placement remains under-researched. The use of long-acting antiplatelet agents post-PFD limits the safe administration of surgical procedures. Bridging with GPIIb/IIIa infusion may facilitate the safe delivery of intensive care in these cases.

Keywords: Half-life; Platelet aggregation inhibitors; Thrombosis; Aneurysm; Ischemia; Stents

INTRODUCTION

In recent decades, endovascular approaches for treating unruptured intracranial aneurysms (IA) have become increasingly common. Coil embolization has been the mainstay endovascular approach for the treatment of IA for many years; however, pipeline flow diverters (PFD) are an alternative endovascular approach that have been used with increasing frequency. PFDs offer an alternative approach to aneurysm treatment with high rates of com-

plete aneurysmal occlusion. However, PFD placement is associated with several potential complications, including intracranial hemorrhage and ischemic stroke [1]. These complications and routine postprocedural care for IA treated with PFD placement are likely to be managed in a neurocritical care unit (NCCU) and may be encountered in that setting with increasing frequency as PFD placement becomes more common.

In a meta-analysis, Brinjikji et al. [2] found that 6% of patients with IAs experienced ischemic stroke after PFD placement, with

higher rates found in patients with large and giant aneurysms. Intraprocedurally, GPIIb/IIIa inhibitor infusions are often used to prevent thrombosis. Additionally, several PFD design innovations have been tested and implemented in recent years to decrease the likelihood of thromboembolic formation within the device after placement, such as covalently bonded coatings composed of polar molecules [3]. Nevertheless, careful antiplatelet management, preferably in the NCCU setting, in post-PFD IA patients is crucial.

There is no consensus on antiplatelet regimens for post-PFD IA patients, and the approaches differ greatly among institutions. Dual aspirin-clopidogrel therapy is common, with ticagrelor sometimes used instead of clopidogrel [4]. Both clopidogrel and ticagrelor have relatively long half-lives (7–8 and 7–9 hours, respectively) and, when administered without a loading dose at steady-state dosing, can require as many as seven days to reach maximum platelet inhibition [5,6]. At steady-state concentrations, commonly used antiplatelets, such as clopidogrel, require long washout periods to eliminate their antiplatelet effects [7]. Therefore, in patients requiring surgical intervention after PFD placement, especially early after placement, antiplatelet therapy should be temporarily discontinued. Given its relatively long half-life, a washout of typically 7 days is suggested for both clopidogrel and ticagrelor, and neuroaxial procedures should be required [8]. Should emergent neuroaxial intervention be required, in the absence of any acute, direct reversal agents, platelet transfusion in addition to medication cessation is typically employed to minimize the risk of life-threatening hemorrhage [9]. Whether related to an emergent complication or a planned elective procedure, an interdisciplinary intensive care team must conduct patient-specific consideration of the risk of thromboembolic and hemorrhagic complications and administer antiplatelet agents to mitigate the risk. To date, no guidelines have been established for the management of this condition. However, the interim transition to a short half-life and rapidly reversible antiplatelet infusion with rapid washout periods, such as with a GPIIb/IIIa inhibitor, may be useful in post-PFD IA patients requiring elective surgical intervention in an intensive care setting.

CASE REPORT

A 47-year-old female with no prior history of ischemic or hemorrhagic stroke and without any known coagulopathy presented for planned staged treatment of bilateral internal carotid artery aneurysm (right side 6–7 mm in diameter with a depth of 2–3 mm; left side significantly larger) with PFDs (left-sided PFD first, followed by the right side eight weeks later, with comparable preparation

and procedure carried out for each). The left-sided PFD was placed on March 5, 2021, without complications. The patient was discharged after left-sided PFD placement, and ticagrelor and aspirin were initiated and continued through and after right-sided placement 8 weeks later. Three days prior to left-sided placement and antiplatelet initiation, the baseline P2Y12 level was 237. After 48 hours of ticagrelor and aspirin therapy, the P2Y12 value was 48. Three days before right-sided PFD placement, the P2Y12 value was 9, suggesting a therapeutically appropriate response.

The patient continued the 8-week course of preprocedural aspirin/ticagrelor antiplatelet therapy until April 29, 2021, when the patient was admitted for scheduled right-sided PFD placement. Immediately after the placement, the patient was admitted to the NCCU for routine recovery. In the acute post-procedural phase, the patient developed drowsiness and headache (initially attributed to a post-anesthesia effect). Several hours later, the patient became increasingly unresponsive and developed posturing and right gaze deviation. Emergency endovascular intervention revealed in-stent thrombosis causing complete right hemispheric ischemia (Fig. 1). Revascularization was successful and completed within 8 hours of the initial documentation of drowsiness and headaches. Subsequent head computed tomography revealed a resultant complete hemispheric ischemic stroke complicated by subarachnoid hemorrhage and diffuse cerebral edema with subfalcine herniation (Fig. 2). Ticagrelor and aspirin were discontinued to allow decompressive hemicraniectomy. Following the procedure, ticagrelor and aspirin were reinitiated due to concerns regarding repeat in-stent thrombosis. The P2Y12 value immediately before antiplatelet initiation was 403, suggesting normal platelet function.

One week later, the patient was admitted to the NCCU for sup-

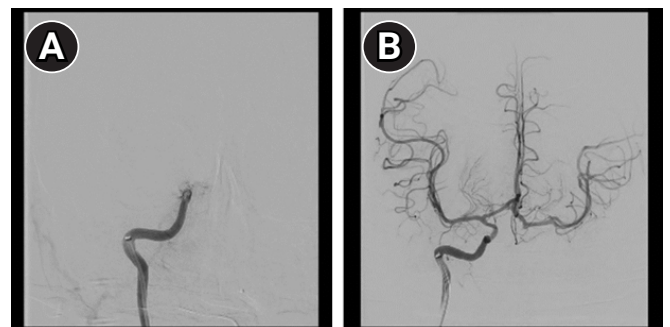


Fig. 1. Digital subtraction angiography performed on the second day of admission. Images were captured by interventional radiologist utilizing digital subtraction angiography. (A) Image demonstrates thrombus present in the internal carotid artery with downstream circulation blocked. (B) Image demonstrates revascularization after successful removal of thrombus via thrombectomy.

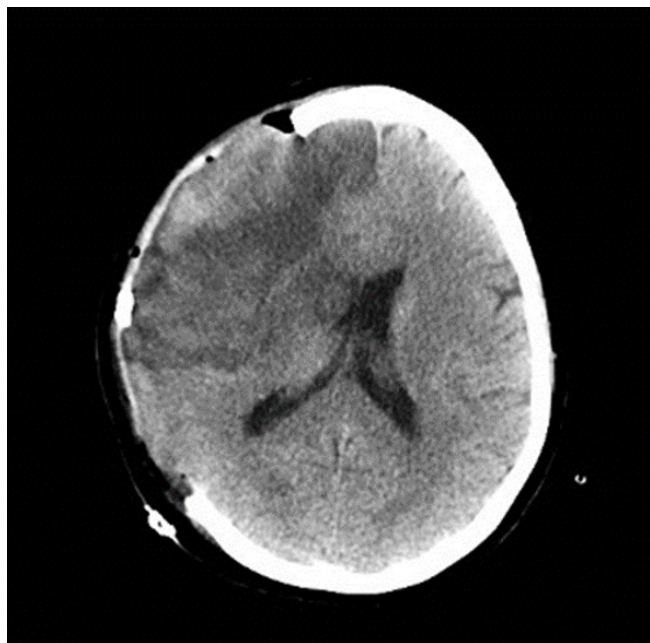


Fig. 2. Head computed tomography imaging captured on the third day of admission. Decompressive right hemicraniectomy evident. Continued subfalcine herniation also demonstrated.

portive care. As per family discussion, and in line with the patient and family wishes, the surgery department was consulted to begin planning for a scheduled tracheostomy and percutaneous endoscopic gastrostomy tube placement. The risk of hemorrhage occurring during these surgeries in patients on ticagrelor and aspirin was weighed against the risk of repeat thrombosis if antiplatelet therapy was discontinued for washout and for the procedure. The surgery and NCCU teams agreed to use a perioperative bridging strategy to mediate these risks and facilitate the planned procedures. To implement this plan, ticagrelor and aspirin were discontinued, and an eptifibatide (GPIIb/IIIa inhibitor; half-life, 2.5 hours) bridge infusion was initiated during the washout period [10]. Due to medication shortages, eptifibatide was replaced by tirofiban (GPIIb/IIIa inhibitor; half-life, 2 hours) [11]. After a planned five-day washout with a GPIIb/IIIa bridge, tirofiban was administered the morning of the scheduled surgery and restarted in the evening. No excessive bleeding was observed during the surgery. The following day, ticagrelor and aspirin were reintiated with the agreement of the general surgery team, and tirofiban infusion was discontinued.

DISCUSSION

Careful management of platelet activity and antiplatelet medication use in patients with unruptured IA undergoing endovascular

treatments is important. As PFD utilization increases, cases similar to the one described above are likely to occur with increasing frequency and are likely to be managed in NCCUs. This case highlights a challenging conundrum: balancing the risk of hemorrhage during urgent surgery with the risk of intra-PFD thrombosis. Although the general conundrum of balancing the risks of hemorrhage and thrombosis is regularly encountered in intensive care settings, there are no established guidelines for antiplatelet management within the specific context of PFD placement for IA.

In this case, we propose a potential approach to balance these risks: a short-half-life antiplatelet bridge via GPIIb/IIIa inhibitor infusion. The GPIIb/IIIa inhibitor clears rapidly, allowing surgery to be performed on the same day as discontinuation. This minimizes the at-risk period for thromboembolic events with antiplatelet discontinuation, thereby reducing the risks of hemorrhage and thrombosis during surgery. In our case, the theoretical platelet activity and risk were estimated and tracked using the P2Y12 values (Fig. 3).

However, one potential concern is that the antiplatelet effects of these agents may persist for a long time despite discontinuation and plasma clearance. Studying the pharmacokinetics of tirofiban, Kereiakes et al. [12] found that *ex vivo* platelet aggregation was restored rapidly after the discontinuation of tirofiban infusion, lagging only slightly behind the tirofiban clearance rate at higher doses. At lower doses of tirofiban, the time taken to restore platelet aggregation was closely in line with its half-life. Kam and Egan [13] stated that platelet aggregation is also restored rapidly after discontinuation of eptifibatide infusion, again closely in line with its half-life. They also noted that along with restored platelet aggregation, hemostasis was clinically normal within a few hours after discontinuation. Evidently, the plasma concentrations of tirofiban and eptifibatide closely align with platelet inhibition; as these agents clear, platelet function and hemostasis rapidly recover.

Cangrelor is a P2Y12 inhibitor that was recently Food and Drug Administration-approved. The drug rapidly reaches a plasma steady state and has a short half-life of 3–5 minutes. Currently, cangrelor is increasingly being used as a “bridge” antiplatelet. A small number of pharmacokinetic studies have found that platelet aggregation is restored rapidly after discontinuation; most patients show baseline aggregation within an hour or less [14]. Van Tuyl et al. [15] compared eptifibatide, tirofiban, and cangrelor as antiplatelet-bridging agents in patients with perioperative cardiac disease. They found that eptifibatide and tirofiban had similar efficacies in this role. However, because of their significant reliance on renal clearing, cangrelor may be a better option for patients with elevated creatinine levels. While not explored, to the best of the

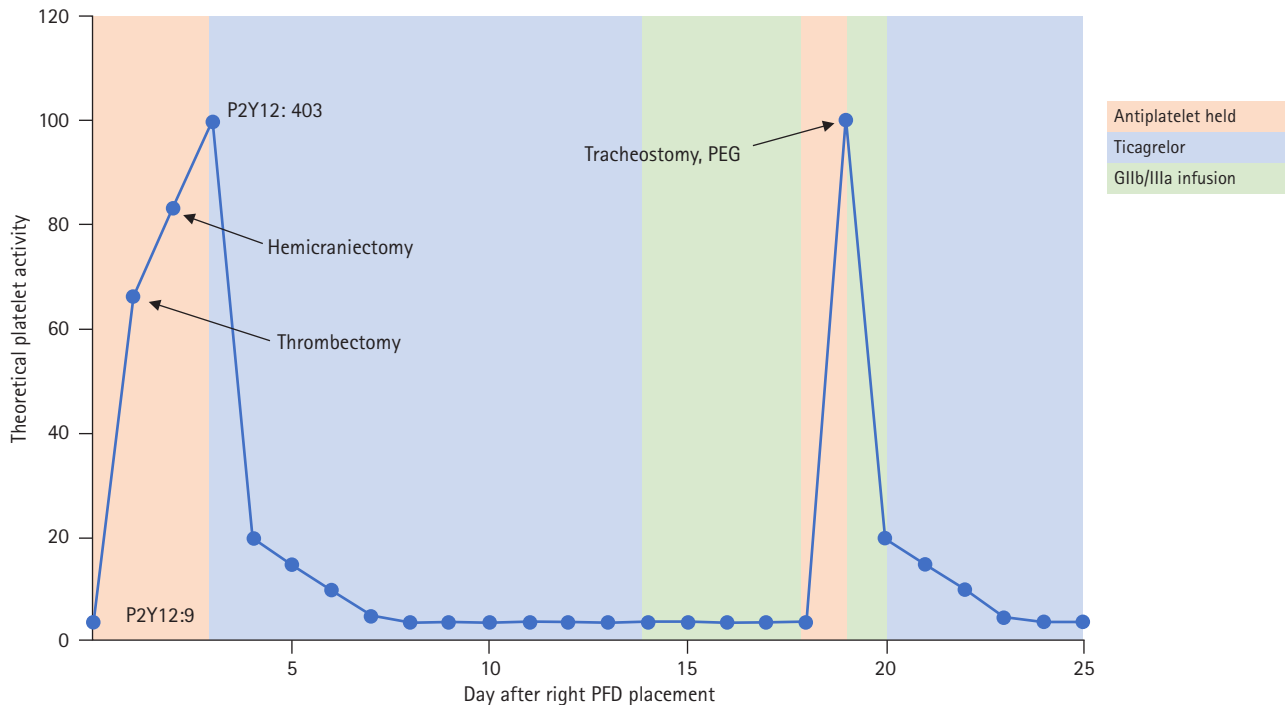


Fig. 3. Day post-pipeline flow diverters (PFD) placement vs. patient's theoretical platelet activity. PEG, percutaneous endoscopic gastrostomy.

authors' knowledge, this approach of using bridging antiplatelets will likely play an increasingly important role in the NCCU, as PFD devices are used with increasing frequency. Most clinical trials on cangrelor have explored its use in a cardiac context. Overall, there is a dearth of literature on the use of GPIIb/IIIa inhibitors or cangrelor as antiplatelet bridges in neurocritical care settings.

This study has several limitations. First, this was a single-patient, single-center study. Additionally, no extensive pharmacokinetic analysis was performed on our patient. Clinically available laboratory studies, such as P2Y12 analysis, have been used to represent real-world clinically applicable experiences. Thromboelastograph platelet mapping, an assay that provides detailed numerical data to better gauge clotting and bleeding risk, could also have been considered; however, at the time of patient management, it was not routinely used in our NCCU.

In light of these limitations, the authors present this report as a real-world, hypothesis-generating case, illustrating the dearth of literature and suggesting further exploration of short-half-life GPIIb/IIIa inhibitors or cangrelor as antiplatelet bridging agents in the neurocritical care context. Antiplatelet management techniques in acute neurology, specifically in the perioperative and intensive care management of patients with PFD for IA, require further research to minimize risk. Irrespective of the specific pharmacological antiplatelet agents used, the efficacy of this regimen and bridging strategies require further study. We present this case to il-

lustrate the clinical framework. However, large-scale clinical data and guidelines are needed to establish an effective approach for antiplatelet management in the NCCU for PFD complications.

ARTICLE INFORMATION

Ethics statement

The retrospective chart review for this report was conducted after receiving Institutional Review Board approval through the Eastern Virginia Medical School (No. 22-03-NH-0036). The institution also provided a "non-research" determination. Informed consent to write this report was obtained from the patient's husband.

Conflict of interest

No potential conflict of interest relevant to this article.

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Concomitant moyamoya syndrome and infratentorial arteriovenous malformation in a neurofibromatosis type 1 patient: a case report

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CASE REPORT

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Background: Neurofibromatosis type 1 (NF1) is a genetic disorder with diverse phenotypic manifestations. Cerebral vasculopathy is one of the multisystem involvements often overlooked unless symptomatic.

Case Report: A 28-year-old male patient with prolonged NF1 complained of right-hand position-specific rhythmic tremor after surviving an ipsilateral cerebellar arteriovenous malformation (AVM) hemorrhagic transformation. Not only did he suffer rupture of the infratentorial vasculopathy but he also endured asymmetric supratentorial occlusive vessel changes in moyamoya syndrome. Due to contralateral limb clumsiness, his right hemispheric vasculature was revascularized by encephaloduroarteriosynangiosis 13 years before the AVM rupture.

Conclusion: This case report describes exceptional NF1 central nervous system involvement where the cerebral vasculature had concomitant moyamoya syndrome and unilateral cerebellar AVM in a single patient. Cerebral vasculopathy should be surveyed and adequately addressed during the follow-up of chronic NF1, as it can cause irreversible sequelae or can be life-threatening.

Keywords: Neurofibromatosis 1; Intracranial arterial diseases; Cerebrovascular disorders

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder involving multiple organs, with variable phenotypes. It develops sporadically without a family history in approximately half of the patients [1]. Central nervous system vasculopathy in patients with NF1 is associated with diverse clinical manifestations. Cerebral arteriopathies, including steno-occlusion, ectasia, and aneurysmal changes, have been reported in the litera-

ture, but their prevalence has not been estimated [1,2].

Not only is it rare to encounter moyamoya-like vessel changes in patients with NF1, but it is also exceptional to observe concomitant arteriovenous malformations (AVMs) in the remaining infratentorial vasculature. Herein, we report a case of contradictory occlusive and excessive intracranial vasculopathy in a single patient with NF1.

CASE REPORT

A 28-year-old man visited our neurological clinic with involuntary movements of his right arm which lasted for 3 months. He described oscillating rhythmic right hand tremors. It started after he survived the rupture of an ipsilateral cerebellar AVM involving the cerebellopontine area. His medical history revealed that he had NF1 since he was 10 years old. His diagnosis was supported by multiple hyperpigmented brownish macules measuring > 15 mm (café-au-lait spots), and axillary/inguinal freckles. He endured one or two episodes of infrequent afebrile epileptic seizures per year until the age of 9, which regressed spontaneously. His intellectual ability lagged slightly behind that of his peers and he manifested an attentional deficit without social incompetence. His motor development was not delayed; however, he appeared to be shorter than his age-average height. At 28 years old, his size reached 164 cm.

At the age of 15, 13 years before the AVM rupture, he reported clumsiness and awkwardness of left limb movements. He was diagnosed with asymmetric moyamoya syndrome (Suzuki grades III and VI in the left and right hemispheres, respectively (Fig. 1A and B) and right cerebellar AVM. The right posterior inferior cerebellar artery (PICA) mainly supplied the vascular tuft, which drained into the sigmoid sinus (Fig. 1C). A Suzuki grade VI in the right hemisphere was presumed to be the cause of the patient's symptoms. Right superficial temporal artery to middle cerebral artery bypass was performed to revascularize the right hemispheric vasculature. The infratentorial AVM was not intervened at the time. After the surgery, the patient stopped experiencing left appendicular symptoms. The bypass conduit was maintained for 13 years (Fig. 1D).

Neither his parents nor brother were diagnosed with any neurological disease. The patient was not taking any medications that might have provoked his unilateral tremor. Right upper and lower limb ataxia were observed on neurological examination. The motor power of the extremities was graded as the Medical Research Council 5. The patient was unstable on foot and required assistance while walking. His right hand tremors had a rhythmic supination-pronation nature within 2–4 Hz when his hand rested in the mid-position between supination and pronation. The Mini-Mental Status Examination score was 23/30, revealing global cognitive impairment. However, he had the total capacity to engage in conversations and respond to commands. Serological assessment, including copper metabolism, revealed no metabolic derangement relevant to the tremor. Ophthalmological evaluation did not reveal any copper deposits.

Six months before the tremors, the right cerebellar AVM had

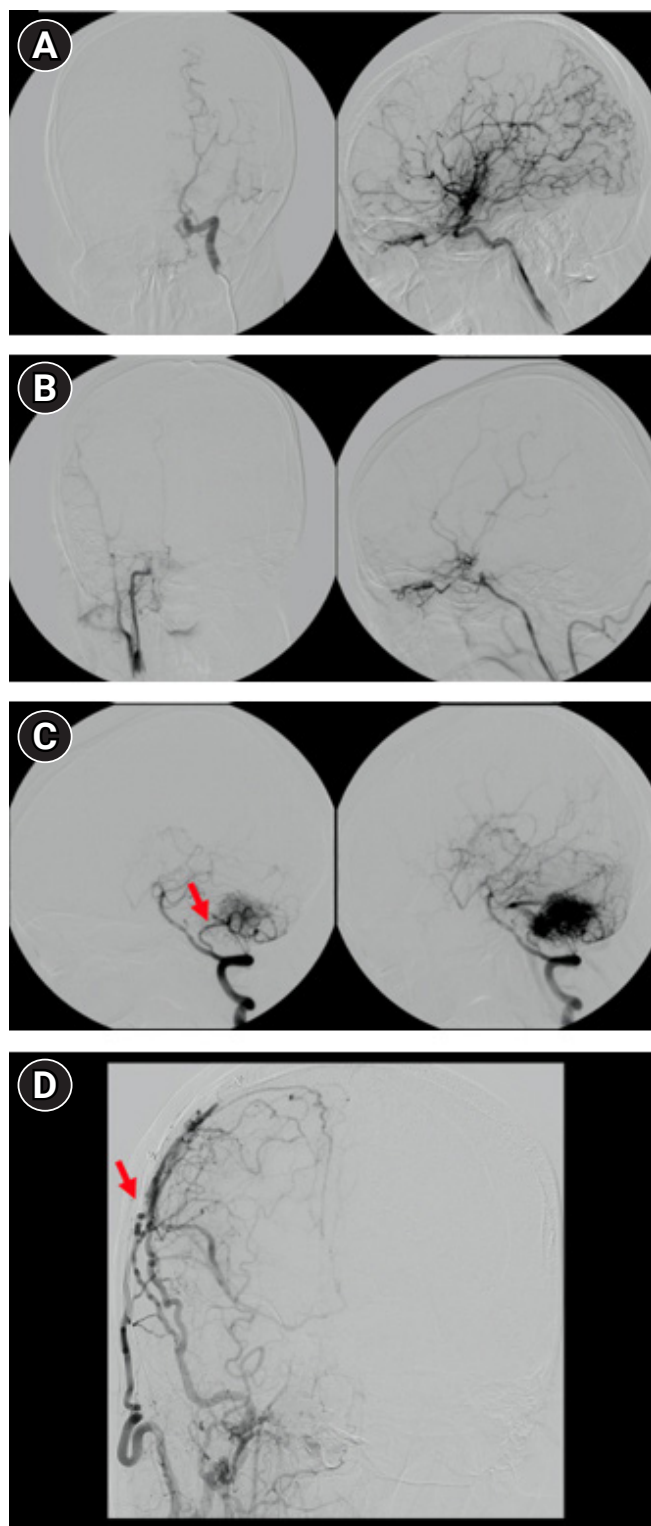


Fig. 1. Transfemoral cerebral angiography (TFCA) at age 15 years revealed asymmetric moyamoya vessels of (A) Suzuki grading III of the left and (B) VI of the right hemisphere, and (C) right cerebellar arteriovenous malformation (main feeder: right posterior inferior cerebellar artery; red arrow). (D) Postoperative TFCA; the superficial temporal artery–middle cerebral artery bypass flow (bypass conduit; red arrow) was well-preserved after 13 years.

ruptured. The right anterior and posterior inferior cerebellar arteries (AICA and PICA) and superior cerebellar artery supplied the AVM. The AICA and superior cerebellar artery feeders were successfully embolized, whereas the PICA was partially blocked with remaining residual flow (Fig. 2A and B). The extant PICA was not intervened further because its flow velocity significantly decreased and other feeders were blocked. Regular follow-ups were planned to monitor for any changes. Brain magnetic resonance imaging at rupture and at follow-up (Fig. 2C and D) revealed edematous hemorrhage in the cerebellum/cerebellar peduncles and incomplete regression, respectively.

After 6 months of follow-up, his position-specific tremors persisted despite improvement in his limb ataxia. The patient could walk independently with his feet wide. Although his tremors did not disappear, they did not interfere with his daily activities of living, and ataxia rehabilitation was maintained without any medication.

DISCUSSION

NF1 is a multisystem disease with diverse progression and severity throughout life [3]. Phenotypic variants occur across multiple organs and represent structural and/or functional deficits [3-6]. Its diagnosis can be postponed when an affected individual without a known family history presents only with skin hyperpigmentation and later develops other signs that fulfill the diagnostic criteria [1,3]. The patient's diagnosis of NF1 was delayed at 10 years of age because other non-skin manifestations, such as intellectual/attentional deficits and below-average stature, became apparent later and indicated its suspicion.

Five years after his diagnosis, asymmetric moyamoya syndrome was identified, and the symptomatic hemispheric vasculature was

rescued by bypass surgery. Although cerebral arteriopathy is rarely reported, NF1 is associated with cerebrovascular abnormalities in the adult and pediatric populations [1]. Moyamoya syndrome is one of its subtypes with higher risk of ischemic or hemorrhagic stroke than in the general population [2,7]. Right hemispheric ischemia caused by asymmetric steno-occlusive intracranial cerebral vessels (more severe on the right) was interpreted as evoking left appendicular awkwardness when demanding execution was required. The patient's infrequent epileptic seizures, which resolved spontaneously, could also be explained by cerebral vasculopathy. Hemodynamic insufficiency could have occasionally kindled epileptogenic firing above the threshold, which disappeared after rescue surgery.

Ecstatic or aneurysmal vasculopathy associated with NF1 has been investigated in a systemic review, but infratentorial AVM has seldom been reported, let alone concomitant cerebrovascular abnormalities in a single NF1 individual [2-4,8,9]. The pathomechanism underlying cerebrovascular disease is poorly understood [1]. The coexistence of opposing vasculopathies (occlusive vs. hyperplastic) may be a coincidence. However, simultaneous observations of advanced moyamoya syndrome and a large infratentorial AVM in childhood, which affected approximately three-quarters of all intracranial vessels, suggested that the chronic pathobiology of NF1 took place for a prolonged time and played a role in its vasculopathy.

The position-specific tremor associated with limb ataxia was ipsilateral to the AVM rupture. The exact pathomechanism remains elusive, but its time-locked appearance after hemorrhage implies that the destruction of a central oscillator network, such as the Guillain-Mollaret triangle, may have caused its hyperkinetic movements [10]. Cerebral vasculopathy is a consistent and relevant manifestation of NF1 and can take variable forms with exten-

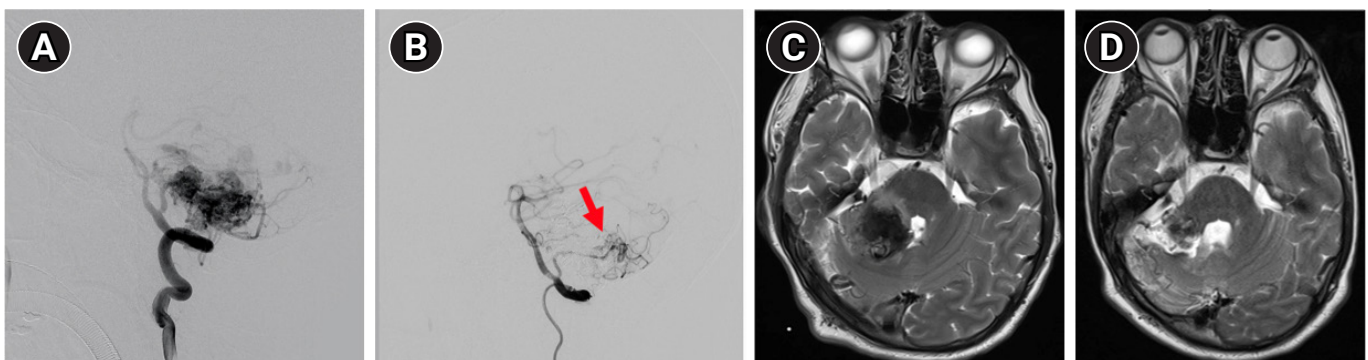


Fig. 2. Transfemoral cerebral angiography at the time of rupture unveiled (A) three right anterior and posterior inferior cerebellar arteries and superior cerebellar artery supplying the vascular tuft, and (B) two were successfully embolized except posterior inferior cerebellar artery with residual flows (red arrow). Brain T2 weighted resonance imaging of the right infratentorial arteriovenous malformation displayed (C) the ruptured hemorrhage within its nidus at the initial and (D) partial resolution after 6 months.

sive involvement, even in early childhood, as seen in this case report. Its prevalence and natural history are unknown because active screening for cerebrovascular diseases is not routinely performed [2]. Approximately 44.5% of NF1 patients who demonstrated vascular abnormalities were asymptomatic, emphasizing the need for early screening and not waiting for symptoms to emerge [2].

In summary, we report a case of chronic NF1 with extensive concomitant opposing cerebral vasculopathy. Investigations and interventions for cerebrovascular disease were only performed when the patient became symptomatic. The overall annual rate of AVM rupture is estimated to be 2.3% (1.3% for unruptured vs. 4.8% for ruptured AVM), and specific genes increase the risk of rupture [11,12]. Therefore, as in this case report, AVMs with genetic predispositions require active surveillance with a tailored prediction of rupture and preemptive intervention. Extensive cerebral vasculopathy can occur even in childhood and is life-threatening if not adequately addressed.

ARTICLE INFORMATION

Ethics statement

This study was approved by the Institutional Review Board of St. Mary's Hospital (No. KC23ZASI0322). The requirement of informed consent was waived.

Conflict of interest

No potential conflict of interest relevant to this article.

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Myelin oligodendrocyte glycoprotein antibody-associated disease manifesting as intractable fever managed by bromocriptine: a case report

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CASE REPORT

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Background: Demyelinating events expressed as abnormal thermoregulatory responses are rare, but intractable fever in myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is very rarely reported.

Case Report: A 56-year-old woman presented with quadriplegia with acroparesthesia. During the admission, fever developed and persisted for 2 days despite the administration of high-dose antipyretics. Brain magnetic resonance imaging (MRI) showed hyperintense lesions involving the upper brainstem. A diagnosis of MOGAD was made according to the clinical characteristics and presence of seropositive MOG antibody. After administration of oral bromocriptine (2.5 mg/day), fever was slowly controlled for a few days.

Conclusion: The present case explained that persistent fever in MOGAD could manifest as an uncommon manifestation. The lesion in the upper brainstem within the brain MRI could be thought of as a lesion anterior to the periaqueductal gray and the lesion at that site could be the cause of the patient's persistent fever with unknown origin.

Keywords: Myelin oligodendrocyte glycoprotein antibody-associated disease; Fever; Encephalomyelitis

INTRODUCTION

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are classified into separate disease entities from multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD) [1,2]. MOGAD manifests as diverse demyelinating syndromes, and unusual manifestations have been reported [1,3]. Although demyelinating events expressed as abnormal thermoregulatory responses in NMOSD or MS are rare, manifestation as central fever in MOGAD is very rare [4,5]. In this study, we report a case of a patient with MOGAD manifesting as central fever.

CASE REPORT

A 56-year-old woman presented with an acute quadriplegia with limb paresthesia 2 days prior to examination. The patient had complained of nausea and vomiting 3 days before. On a neurological examination, the patient was mildly drowsy and complained of dysarthria and dysphagia, and then a nasogastric tube was inserted. A neurological examination revealed a weakness of Medical Research Council grade 4 in the upper extremities and grade 0 to 1 in the lower extremities, with hypesthesia below the L2-L3 sensory dermatome. The patient had been treated for hyperten-

sion and diabetes mellitus for several years.

Brain magnetic resonance imaging (MRI) performed on the first day revealed several non-specific small signal changes in the T2-weighted images. Spinal cord MRI showed long segmental signal intensity changes in the spinal cord, from T1 to T11 on the T2-weight images without swelling or abnormal enhancement (Fig. 1A and B). Cerebrospinal fluid revealed a mild pleocytosis (34 cells/ μ L) and hyperproteinorrachia (0.65 mg/dL; reference range, 8–43 mg/dL), and negative cultures and polymerase chain reaction for viruses. Intravenous (IV) methylprednisolone (MPDS) treatment was started the day before the onset of fever. On the second day, a fever developed, and alertness was decreased. Then, the fever persisted for 2 days despite the administration of propacetamol (1 g every 6 hours) and ibuprofen (400 mg every 6 hours).

A septic screen, including white blood cell count, C-reactive protein (CRP), erythrocyte sedimentation rate, urinary analysis, had no significant findings. CRP levels were mildly elevated (0.99 on day 1, 0.60 on day 2; reference range, ≤ 0.3 mg/dL), but the white blood cell count was normal. Endocrinologic assays showed unremarkable results. After the administration of oral bromocriptine (2.5 mg/day), the fever was slowly controlled for a few days.

Brain MRI performed on day 3 demonstrated T2-weighted MRI hyperintense lesions involving the midbrain and pons in front of the cerebral aqueduct (Fig. 1C and D). The patient was treated with IV MPDS at 1 g daily for 5 days, but drowsiness and weakness in whole extremities aggravated. We decided to initiate plasma exchange (PLEX) in addition to IV MPDS under the consideration of severe encephalomyelitis due to brain and spinal cord MRI, and decreased consciousness, and the first PLEX was started on the day of fever. Since the fever did not improve well

even after high-dose antipyretics, IV MPDS, and 1st PLEX, bromocriptine was administered on the second day of the fever, and the fever gradually recovered. In a cell-based assay, the serum was positive for anti-MOG immunoglobulin G (IgG) antibodies and negative for anti-aquaporin-4 (AQP4) IgG antibodies. Thus, a diagnosis of MOGAD was made according to the core clinical and neuroimaging characteristics and seropositivity for MOG antibody [1,6]. The patient finally underwent ten courses of PLEX.

DISCUSSION

The present case showed that persistent fever in MOGAD could be an uncommon manifestation. AQP4-NMOSD can also be expressed through endocrinopathy, autonomic dysfunction, and dysregulated thermoregulation as a diencephalic syndrome or hypothalamic involvement and has rarely been reported [4,7].

MOGAD has a phenotype similar to AQP4-NMOSD, but a rare and diverse phenotype has been revealed recently [1-3]. The poorly controlled persistent fever, in this case, can also be thought of as a form of diencephalic syndrome in AQP4-NMOSD. At the beginning of hospitalization, the fever did not develop, and no diencephalic lesions were observed on brain MRI. In addition, despite the use of antipyretics, the fever was not fully controlled, and no obvious cause was found in other septic screens or endocrinologic assays. The lesion in the upper brainstem within the follow-up brain MRI was anterior to the periaqueductal gray, a component of the central thermoregulatory pathways from the hypothalamus to the spinal cord, and could be the cause of the patient's persistent fever with unknown origin. However, pleocytosis in the cerebrospinal fluid, increased mild CRP, and possible aspiration due to decreased consciousness can be difficult to completely rule

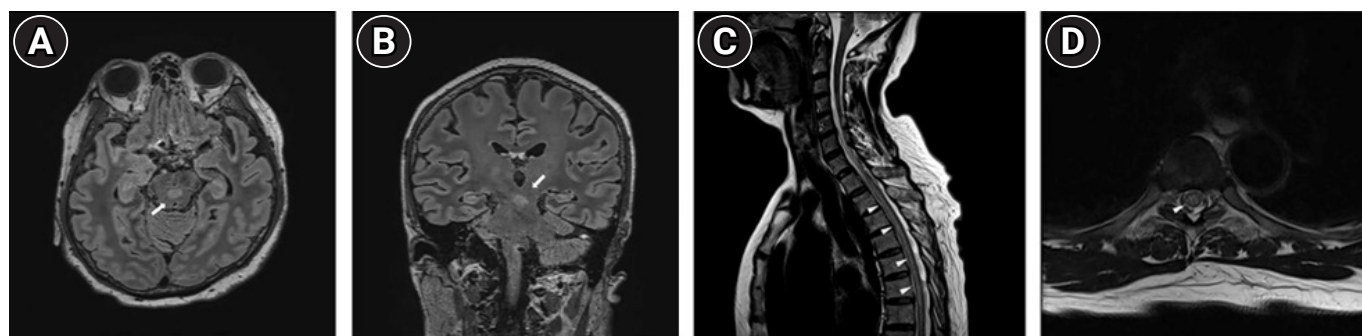


Fig. 1. (A, B) Brain magnetic resonance imaging (MRI) and (C, D) spinal cord MRI. (A) Axial and (B) coronal T2 fluid-attenuated inversion recovery images demonstrated hyperintense lesions (arrows) at both sides of the medulla, dorsal pons, and midbrain. Fluid-attenuated inversion recovery images demonstrated hyperintense lesions (arrows) at both sides of the medulla, dorsal pons, and midbrain. (C) Sagittal and (D) axial T2-weighted images show long segmental signal intensity changes (arrowheads) in the spinal cord, from T1 to T11 levels without swelling or abnormal enhancement.

out as causes of fever. Nevertheless, since there were no specific findings on the patient's septic screen, and the fever was relatively well-controlled with bromocriptine, it could be assumed that it is a central fever caused by damage to the thermoregulatory pathway.

In conclusion, we report a rare case of MOGAD presenting with bromocriptine-responsive fever. MOGAD can present as a fever of unknown origin with or without other demyelinating symptoms, and hence, a workup for MOGAD is needed to treat it appropriately.

ARTICLE INFORMATION

Ethics statement

This case was reviewed and approved by the Ethics Committees of the Inje University Busan Paik Hospital (No. 2022-11-053). The need for informed consent was waived by the Board.

Conflict of interest

No potential conflict of interest relevant to this article.

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Unexpected epileptogenic effect of lethal doses of pentobarbital: a case report

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CASE REPORT

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Background: Barbiturate poisoning is rare but potentially fatal.

Case Report: We reported a case of barbiturate poisoning in a 28-year-old woman who recovered from lethal pentobarbital deliberate self-poisoning. The initial blood pentobarbital concentration was 61 mg/L, corresponding to a potentially lethal dose. Despite the ingestion of a high dose of pentobarbital, the electroencephalogram revealed an unattended pattern compatible with possible nonconvulsive status epilepticus. Following resuscitation maneuvers, appropriate care, and antiseizure medication, the patient awakened after 7 days. The evolution was excellent without neurological deficits at 2 months.

Conclusion: Despite the expected and known effects of high-dose pentobarbital in reducing and suppressing cortical activity in the brain, the present case demonstrates that lethal dose of pentobarbital may have an epileptogenic effect. Our hypothesis was that the mechanism of the origin of such a picture is a relatively abrupt decrease in toxic doses of pentobarbital, resulting in a withdrawal phenomenon.

Keywords: Pentobarbital; Status epilepticus; Nonconvulsive status epilepticus; Ictal-interictal continuum; Forensic science

INTRODUCTION

Barbiturates, derivatives of barbituric acid, are chemically synthesized substances used as drugs. Owing to their mechanisms of action, they perform hypnotic, sedative, antiseizure, and anesthetic activities. Barbiturates act on gamma aminobutyric acid (GABA-A) receptors in a dose-dependent manner by increasing the open time of the chloride ion channel, which involves postsynaptic hyperpolarization and central nervous system (CNS) depression. GABA is the main inhibitory neurotransmitter in the CNS and reduces neuronal activity [1]. Owing to severe side-effects,

the use of barbiturates has decreased over time. Their therapeutic indications are circumscribed, particularly in cases of refractory and super-refractory status epilepticus (SE) [2] or refractory intracranial hypertension after head trauma.

Currently, pentobarbital is mainly used by veterinarians (anesthesia and euthanasia) or for end-of-life procedures (lethal injection in the United States or assisted suicide in Belgium and Switzerland [3]). Currently, its use in suicide attempts is rare, although recent cases have shown an increase in the popularity of pentobarbital poisoning as a peaceful suicide method [4]. Here, we report a case of phenobarbital self-poisoning complicated by cardiac ar-

rest (CA) and unexpected acute nonconvulsive SE (NCSE) in a 28-year-old woman who recovered.

CASE REPORT

A 28-year-old woman with a history of depression ingested potentially lethal doses of pentobarbital with suicidal intent and sent a goodbye message to her family. She was found by her family members unconscious, pulseless, and cardiopulmonary resuscitation (CPR) was started.

The rescue team arrived 10 minutes after the alarm (20–30 minutes post-ingestion) and found the patient with pulseless electrical activity, CA, and bilateral mydriasis. CPR was resumed using manual compression and endotracheal intubation. She received 1 mg of epinephrine every 3–5 minutes, as recommended by advanced cardiac life support guidelines, 0.5 mg of naloxone, and 0.4 mg of flumazenil with a return of spontaneous circulation after 20 minutes (40–50 minutes after intake). During transportation to the hospital, supplementary doses of epinephrine were administered.

On arrival at the emergency department, the patient remained deeply comatose (Glasgow Coma Scale [GCS] score, 3/15) with bilateral nonreactive mydriasis without sedatives. She was hypothermic (33 °C). Her heart rate was 84 bpm, and blood pressure was 84/52 mm Hg on norepinephrine infusion. The electrocardiogram revealed no conduction or re-polarization abnormalities. The initial laboratory test showed lactic acidosis (arterial blood gas analysis: pH, 7.32; partial pressure of carbon dioxide, 4.56 kPa; partial pressure of oxygen, 30.2 kPa; HCO₃, 17 mmol/L; lactate, 4.417 mmol/L; and hypokalemia, 2.6 mmol/L), without organ failure. Toxicology tests were positive only for barbiturates, and an advanced analysis performed at the forensic laboratory using gas chromatography-mass spectrometry was positive for pentobarbital. The initial concentration was 61 mg/L, well above the therapeutic target value (approximately 1–3 mg/L) and within the range of values observed in deaths following massive pentobarbital use (approximately 10–169 mg/L) [5].

Cerebral computed tomography angiography performed as an initial workup revealed mild brain edema and normal perfusion. Charcoal treatment via a nasogastric tube was initiated immediately to limit barbiturate absorption, and the patient was transferred to the intensive care unit (ICU). On day 1, she developed diabetes insipidus, which was treated with desmopressin.

From days 1 to 3, she developed a vasoplegic shock requiring vasopressor support with norepinephrine (maximum dose, 0.32 µg/kg/min), hydrocortisone (200 µg/24 hr), and fluid resuscitation (approximately 11 L). As kidney function was normal, renal

replacement therapy (RRT) was not initiated. Supportive care consisted of charcoal treatment (three times in total) and urine alkalization. The patient received 100 mL of sodium bicarbonate (8.4%) twice to maintain a urinary pH > 7.5. On day 3, because of persistent coma, the patient underwent continuous electroencephalogram (cEEG) monitoring, which showed a pattern in the ictal-interictal continuum compatible with possible NCSE [6,7] (Fig. 1A). Antiseizure medications (clonazepam 1 mg, levetiracetam 40 mg/kg, and lacosamide 8 mg/kg) were started, with EEG improvement after 36 hours (Fig. 1B); however, no clinical improvement was observed before day 7. The pentobarbital level was 28 mg/L during NCSE (> 50% reduction from day 1). Fig. 2 shows the kinetics of pentobarbital blood concentrations during the ICU stay.

To exclude hypoxic–ischemic encephalopathy as a potential cause of NCSE, a complete neuroprognostic assessment was performed. Brain magnetic resonance imaging performed on day 4 from intoxication revealed no abnormalities (Fig. 3). Somatosensory evoked potentials were bilaterally preserved with normal voltage (left, 2.02 µV; right, 2.82 µV) and neuron-specific enolase was at 5.5 µg/L. Therefore, we excluded the contribution of hypoxic ischemia. Favorable evolution on EEG (only mild encephalopathy on day 5) allowed the reduction in clonazepam; because of an allergic reaction to levetiracetam, the latter was stopped, and lacosamide was increased.

On day 7, the patient showed the first signs of awakening. On day 8, the GCS score was 15/15, and she was extubated. On day 9, the patient was transferred to a mixed medical and psychiatric unit. The EEG activity returned to normal on day 10 without signs of encephalopathy. The patient's neurological evolution was excellent, and she was discharged from the hospital after 1 month. Antiseizure treatment was gradually tapered and fully stopped after a normal follow-up (clinical examination and routine EEG) 2 months after intoxication.

DISCUSSION

Voluntary poisoning with pentobarbital is rare because this molecule is no longer used in human medicine, except for assisted suicide. However, it is still used by veterinarians to euthanize animals. It is a short-acting weak-acid barbiturate used as an anticonvulsant, hypnotic, induction and sedative agent. It has a rapid onset of action, between 10 and 60 minutes after oral absorption. Its plasma half-life is 15–50 hours and is dose-dependent. It has high lipid solubility and is metabolized by the liver and excreted in the urine as an inactive metabolite, with negligible renal excretion (< 1%). Blood levels range between 1 and 4 mg/L within 30 min-

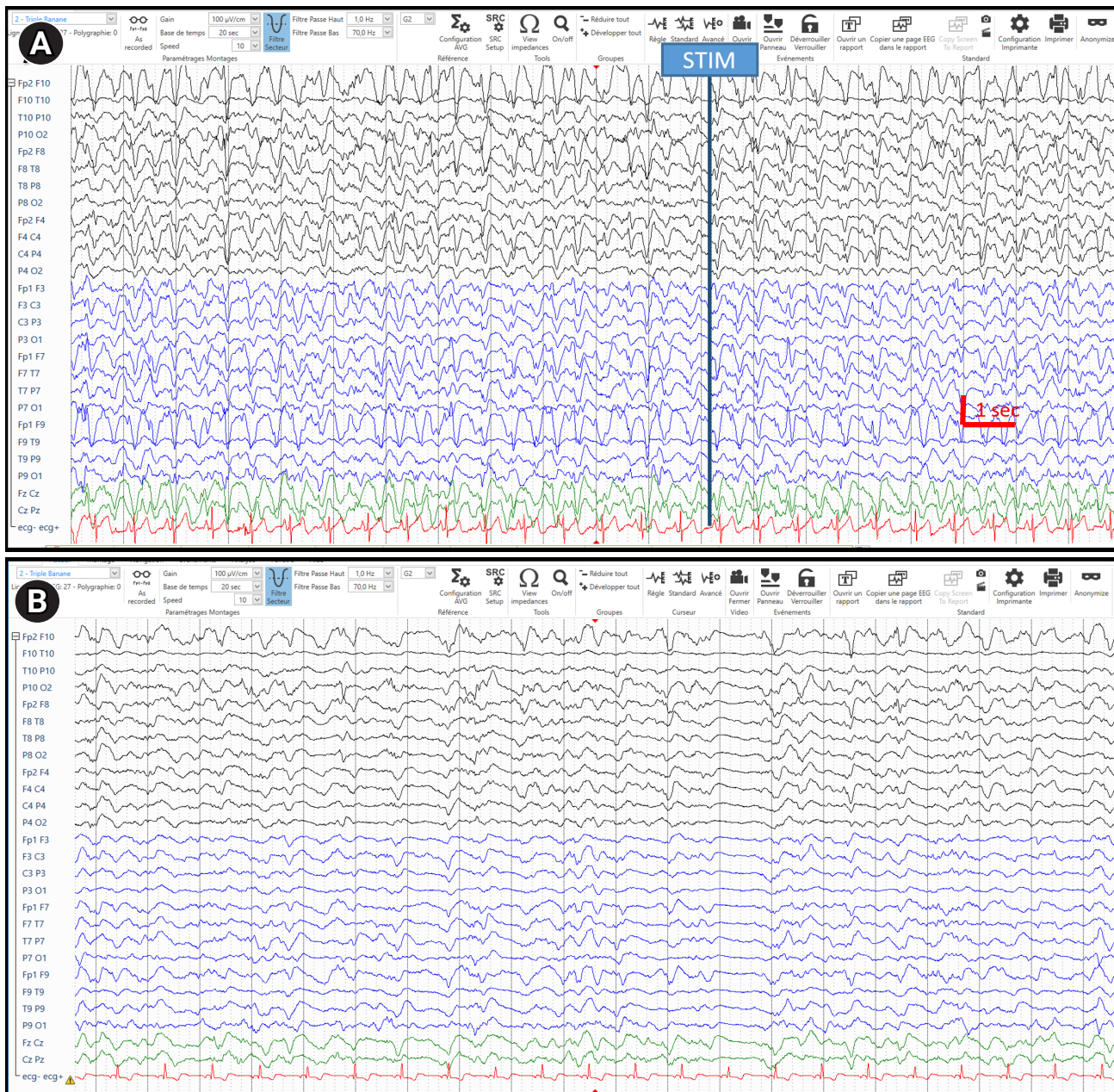


Fig. 1. The image shows 20 seconds of 25-channel electroencephalogram (EEG) in bipolar longitudinal montage. Distance between bold vertical grey bars: 1 seconds electrocardiogram. (A) Rhythmic and periodic patterns with morphology of 2 Hz spike-wave and/or 2–3 Hz generalized rhythmic delta activity+sharp frontally predominant, unreactive to pain stimulus, compatible with possible nonconvulsive status epilepticus in coma, day 3 from intoxication. (B) Generalized slow activity on a sub-continuous background (delta band predominant). EEG improved after parenteral anti-seizure medication, 36 hours after status epilepticus onset. STIM, stimulus.

utes to 2 hours after oral absorption of 100–600 mg of pentobarbital [5]; blood levels are considered toxic at 5 mg/L or more and lethal from 10 to 169 mg/L. Barbiturates act on GABA-A receptors and reduce neuronal activity. Pentobarbital overdose classically leads to impaired consciousness and coma, mimicking the features of brain death. It can also lead to airway compromise, cardiovascular collapse, respiratory depression, CA, or even death

[5,8]. The patient described here presented with pentobarbital levels in the lethal range on day 1, which persisted at toxic and potentially fatal values until day 6 (Fig 2).

Pentobarbital poisoning is mainly managed by supportive care, including invasive mechanical ventilation, fluid loading, vasopressors, and CPR in most severe cases. Currently, no specific antidotes for barbiturates exist. The therapeutic procedures that may

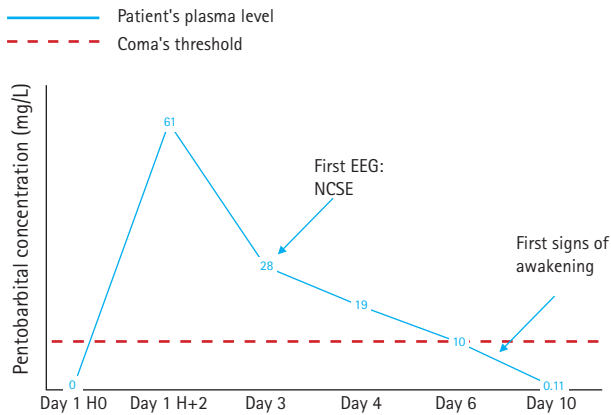


Fig. 2. Pentobarbital's plasma level (mg/L) during intensive care unit stay. EEG, electroencephalogram; NCSE, nonconvulsive status epilepticus. HO, zero hours (time of injection); H+2, 2 hours after injection.

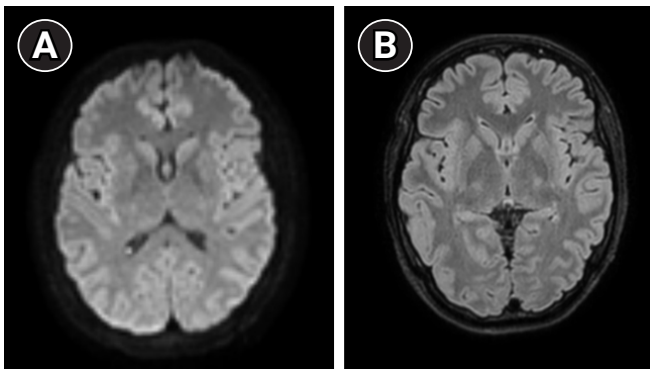


Fig. 3. Brain magnetic resonance imaging on day 4 from intoxication revealing no abnormalities. (A) Horizontal section of diffusion-weighted imaging. (B) Fluid-attenuated inversion recovery.

enhance barbiturate elimination are debatable. Although multiple dose activated charcoal may be useful for most phenobarbital poisonings to reduce the duration of intubation and mechanical ventilation, it plays no role in urine alkalinization. RRT appears to enhance elimination; however, clinical benefits relative to potential complications and costs are poorly defined. Activated charcoal was administered in accordance with the recommendations of American and European toxicological societies. RRT was not an option, because pentobarbital is a short-acting barbiturate [9].

On day 3, the patient presented an EEG pattern in the ictal-interictal continuum compatible with possible NCSE in coma and was treated successfully with escalation of antiseizure medications, as recommended by the guidelines of SE [2]. Such EEG pattern was unexpected, as these molecules usually shut down synaptic and metabolic activities in the brain, producing a suppressed or suppression-burst pattern on the EEG [10]. Barbiturates are well-established treatments for refractory and super-re-

fractory SE [2]. Our patient did not present with a suppressed, suppression-burst, or discontinuous background. However, no EEG was performed during the first 2 days after intoxication; therefore, it cannot be excluded that this pattern occurred earlier and was overlooked. Different hypotheses have been proposed to explain the development of NCSE following pentobarbital intoxication. NCSE may have occurred as a sign of drug-induced encephalopathy; however, this is unlikely because the usual effect of barbiturates on EEG is to suppress the background and epileptiform activity instead of activating it. NCSE may have occurred secondary to a hypoxic-ischemic insult. However, this could be excluded in the absence of structural or functional cortical brain abnormalities; moreover, SE following CA is often super-refractory and has a poor prognosis [11].

Epileptic seizures and SE may occur in severe forms of withdrawal [12], and when barbiturates are used regularly as a treatment for epilepsy or as sedatives, their cessation should not be abrupt to avoid withdrawal seizures. Cases of withdrawal acute symptomatic seizures have been reported in chronic nonepileptic users and newborns of mothers treated with barbiturates [13]. In animal models, GABA withdrawal syndrome is a common model of local SE following the interruption of chronic GABA infusion [14]. In humans, the appearance of generalized periodic discharges related to anesthetic withdrawal (GAWs; pentobarbital or propofol) resolves spontaneously within hours without additional treatment [15]. From days 1 to 3, the blood level of pentobarbital decreased by > 50%. A "relative" abrupt withdrawal of toxic doses of barbiturate may, therefore, be proposed as the mechanism underlying the development of such SE resolving under treatment in 36 hours. We cannot exclude the possibility that urine alkalinization with an increased elimination rate worsens withdrawal. The rapidity of the change is more important than the absolute blood level as a provoking factor for acute symptomatic seizures in electrolyte disturbance, medication (i.e., benzodiazepines), and alcohol withdrawal. If we apply the same principle, withdrawal can occur when toxic levels of pentobarbital decrease rapidly and persist in toxic and potentially lethal ranges. At the time of the development of NCSE, the origin of such EEG activity was undetermined. The critical clinical context, unknown blood pentobarbital level, uncertainty of other possible molecules used for self-poisoning, and possible post-CA encephalopathy led us to treat such EEG patterns using antiseizure medication. Nevertheless, spontaneous resolution of this epileptiform EEG pattern without treatment, similar to GAWs, cannot be excluded. Although much less frequent than before, barbiturate poisoning remains amongst the most severe forms of intoxication. Withdrawal symptoms, such as seizures, occur in cases of chronic intake.

Here, we highlighted, in a 28-year-old patient, the development of acute NCSE after pentobarbital lethal intoxication due to an abrupt reduction in the blood level of barbiturate, persisting in toxic and potentially lethal ranges. A specific titration protocol based on concentration rates is difficult to propose because local laboratories (such as our hospital) often cannot offer daily dosages of specific toxic molecules, such as pentobarbital. Based on our experience, we recommend cEEG monitoring of patients from the time of ICU admission to detect and eventually treat electrographic seizures and SE. This prevents the effect of ongoing epileptic activity due to its increased metabolic demand and deleterious consequences on neuronal networks and tissues. cEEG monitoring is a relatively inexpensive and noninvasive tool for the dynamic assessment of the brain pathophysiology, allowing a continuous analysis of brain activity and helping and guiding management.

ARTICLE INFORMATION

Ethics statement

No institutional or ethics committee approval was required for this case report. Written informed consent was obtained from the patient, and the CARE guidelines were followed to enhance the quality and standardization of the reported cases.

Conflict of interest

No potential conflict of interest relevant to this article.

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Posterior reversible encephalopathy syndrome superimposed on neuronal intranuclear inclusion disease

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A 54-year-old female patient presented to the emergency room with vomiting and convulsions, which subsided after the administration of 4 mg of intravenous (IV) lorazepam. The patient was previously diagnosed with neuronal intranuclear inclusion disease (NIID) at another tertiary hospital. The patient was stuporous and had a fever (39.2 °C) and elevated blood pressure (180/90 mm Hg).

Brain magnetic resonance imaging (MRI) showed high signal intensity in the bilateral parietooccipital lobe and cerebellum on fluid-attenuated inversion recovery (FLAIR), which was suggestive of posterior reversible encephalopathy syndrome (PRES) (Fig. 1A and B) [1,2]. Additionally, MRI revealed bilateral diffusion restriction in the corticomedullary junction on diffusion-weighted imaging (DWI), in accordance with NIID (Fig. 1C and D) [3,4].

Her blood pressure was meticulously adjusted using IV nicardipine [2]. The patient slowly improved and experienced drowsiness. Follow-up brain MRI revealed less prominent FLAIR high signal intensity, which implied improved PRES (Fig. 1E and F). However, the MRI findings of NIID were aggravated, and lesions were more prominent in the bilateral frontotemporal lobes (Fig. 1G and H). At discharge, the patient was alert, and her cognitive impairment and apraxia persisted [4].

Neurologists should always consider the possibility of other conditions, such as PRES, when managing patients with NIID with drowsy mental status and excessively high blood pressure. The highly variable symptoms of NIID might confuse physicians [3].

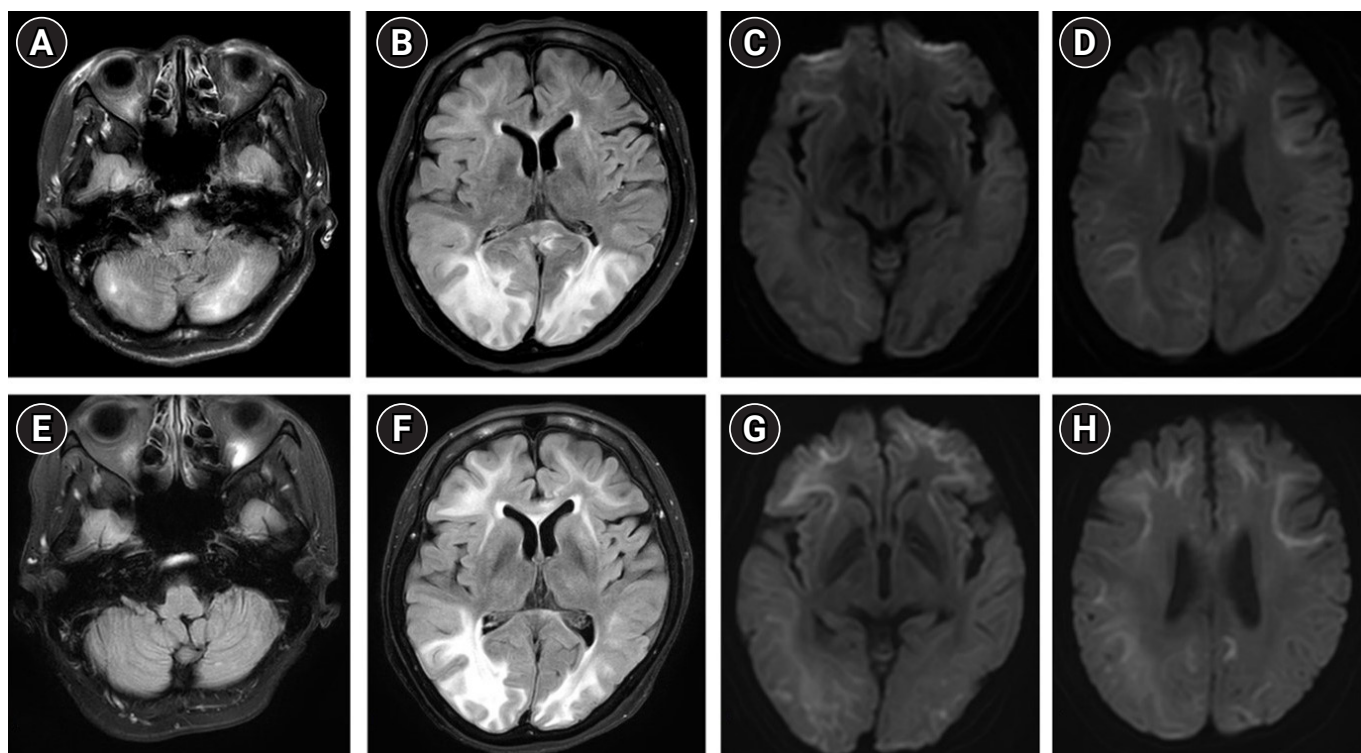


Fig. 1. Brain magnetic resonance imaging scans performed 12 hours after the seizure (A–D) and after 3 weeks of treatment (E, F). (A, B) Fluid-attenuated inversion recovery (FLAIR) revealed high signal intensity lesion at the bilateral parietooccipital lobe, right temporal lobe, and cerebellum. (E, F) The follow-up image showed less prominent high FLAIR signal intensity at the cerebellum and parietooccipital lobes. (C, D) Diffusion-weighted imaging (DWI) showed bilateral symmetric diffusion restriction lesions in the corticomedullary junction, at the frontal, parietal, and temporal lobes. (G, H) The follow-up DWI showed slightly worsened diffusion restriction at the bilateral frontotemporal lobes.

ARTICLE INFORMATION

Ethics statement

This study was reviewed and approved by the Institutional Review Board of Hanyang University Hospital (No. 2022-10-013). The need for informed consent from the patient was waived by the board.

Conflict of interest

No potential conflict of interest relevant to this article.

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Anti-N-methyl-D-aspartate receptor encephalitis after resection of cerebral astrocytoma

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Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common type of autoimmune encephalitis associated with underlying neoplasms, mainly ovarian tumors [1]. The association between NMDAR encephalitis and brain neoplasm is very rarely reported. We report a case of NMDAR encephalitis which manifested as seizures after surgery for cerebral astrocytoma.

A 34-year-old man presented with generalized tonic seizures. Brain magnetic resonance imaging (MRI) showed a mass lesion with enhancement in the right insula (Fig. 1A and B) and a mass lesion in the temporal lobe. MR spectroscopy showed increased choline to creatine ratio and decreased N-acetylaspartate peak at right basal ganglia, suggesting a neoplastic lesion (Fig. 1C). A biopsy revealed a diffuse astrocytoma. Three months later, seizures and aphasia suddenly occurred, and a brain MRI showed that, compared to postoperative images (Fig. 1D), a new parietotemporal lesion had appeared in the left hemisphere (Fig. 1E and F). Anti-NMDAR antibodies were found in the blood and cerebrospinal fluid using the cell-based immunocytochemistry method and indirect fluorescence assay. High-dose intravenous steroids and anti-epileptic drugs were administered, and the patient is slowly recovering from the symptoms.

Paraneoplastic NMDAR encephalitis occurring after tumor re-

moval is very rare, and it can be difficult to distinguish between NMDAR encephalitis and tumor infiltration or metastatic lesions [2,3]. It becomes even more difficult in cases with scattered cortical lesions, which was an unusual finding of our case. This case diagnosed NMDAR encephalitis through identification of anti-NMDAR antibodies in a patient with epileptic seizures and encephalitis after surgery.

ARTICLE INFORMATION

Ethics statement

This work was approved by the Ethics Committees of the Inje University Busan Paik Hospital (No. 2020-01-068), and written informed consent was obtained from the patient.

Conflict of interest

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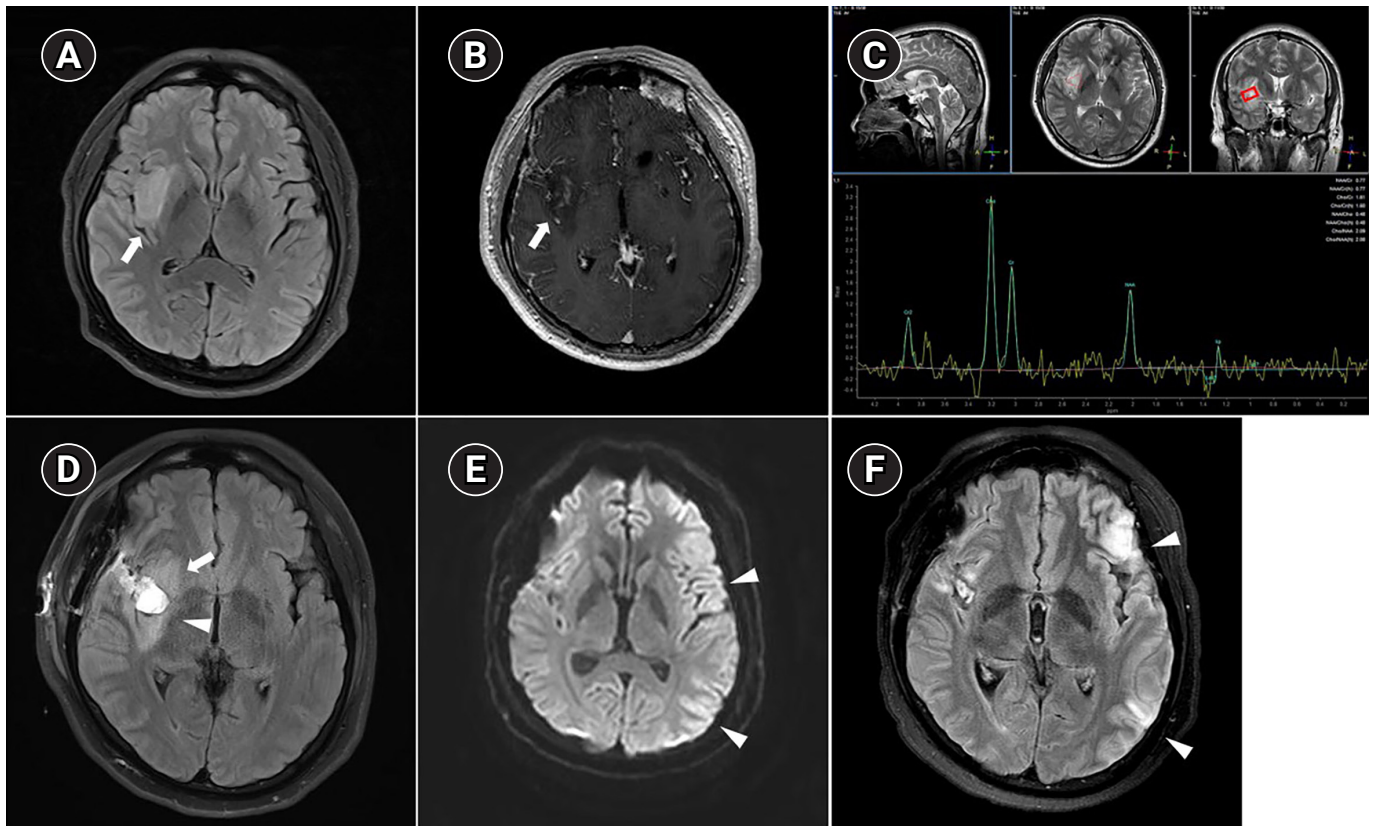


Fig. 1. Brain magnetic resonance imaging (MRI). Brain MRI showed an ill-defined, mass-like lesion (arrow) with high signal intensities at right basal ganglia, insula, external capsule, the temporal lobe on fluid-attenuated inversion recovery (FLAIR) image (A) and irregular enhancement (arrow) on axial contrast-enhanced T1-weighted image (B). (C) MR spectroscopy showed the slightly increased value of choline to creatine ratio and decreased value of N-acetylaspartate peak at the mass-like lesion involving right basal ganglia, insula, external capsule, and temporal lobe, suggesting tumorous condition (red square: volume of interest). (D) In the postoperative follow-up MRI, FLAIR showed remained tumor (arrow) and postoperative hemorrhage (arrowhead) on the right temporal lobe. After 3 months with seizure presentation, diffusion-weighted image (E) and FLAIR (F) showed newly occurred, multifocal hyperintense lesions (arrowheads) at left temporo-parietal lobes.

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Progressive cerebral large-vessel vasculitis in a patient with Sjögren's syndrome

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Extraglandular involvement in Sjögren's syndrome (SS) can manifest in the central or peripheral nervous system. Changes in major cerebral vessels in SS are rarely reported [1,2]. Pathomechanisms in SS are known to be mainly associated with small- or medium-sized vasculopathy [1,3]. A 59-year-old woman who presented with left transient hemiparesis a few days prior was diagnosed with SS with dry mouth. Anti-SS-related antigen A (SSA/Ro) and B (SSB/La) had shown strong positivity on previous evaluations. Brain magnetic resonance imaging (MRI) showed multiple diffusion-restricted lesions in the right middle cerebral artery border zone area, suggesting acute infarctions (Fig. 1). Magnetic resonance angiography (MRA) upon admission showed moderate-to-severe stenosis of the right distal internal carotid artery (ICA) (Fig. 2). The patient reported transient right hemi hypesthesia following admission. On MR carotid plaque imaging performed 4 days later, there was focal concentric wall thickening with enhancement in the right distal ICA stenosis at the location of the lesion shown on the previous MRA. Additionally, concentric wall thickening with enhancement was observed in the left distal ICA (Fig. 2). Bilateral distal ICA stenosis with wall thickening and enhancement occurred consecutively. Therefore, it was likely caused by vasculitic stenosis associated with SS.

This report showed that a patient with high disease activity de-

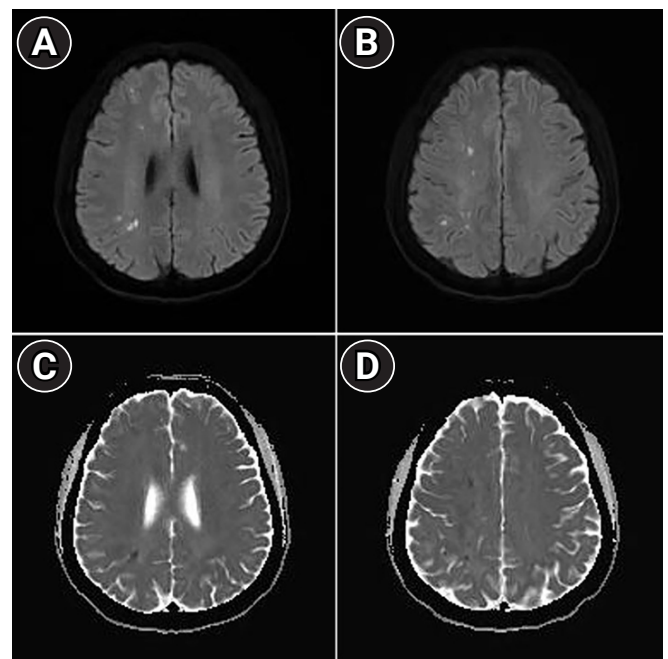


Fig. 1. Brain magnetic resonance imaging scans upon admission. (A, B) There were high signal-intensity lesions on diffusion-weighted images in the right middle cerebral artery borderzone area at the right frontal and parietal lobes, and (C, D) relevant lesions were noted on the apparent diffusion coefficient map.

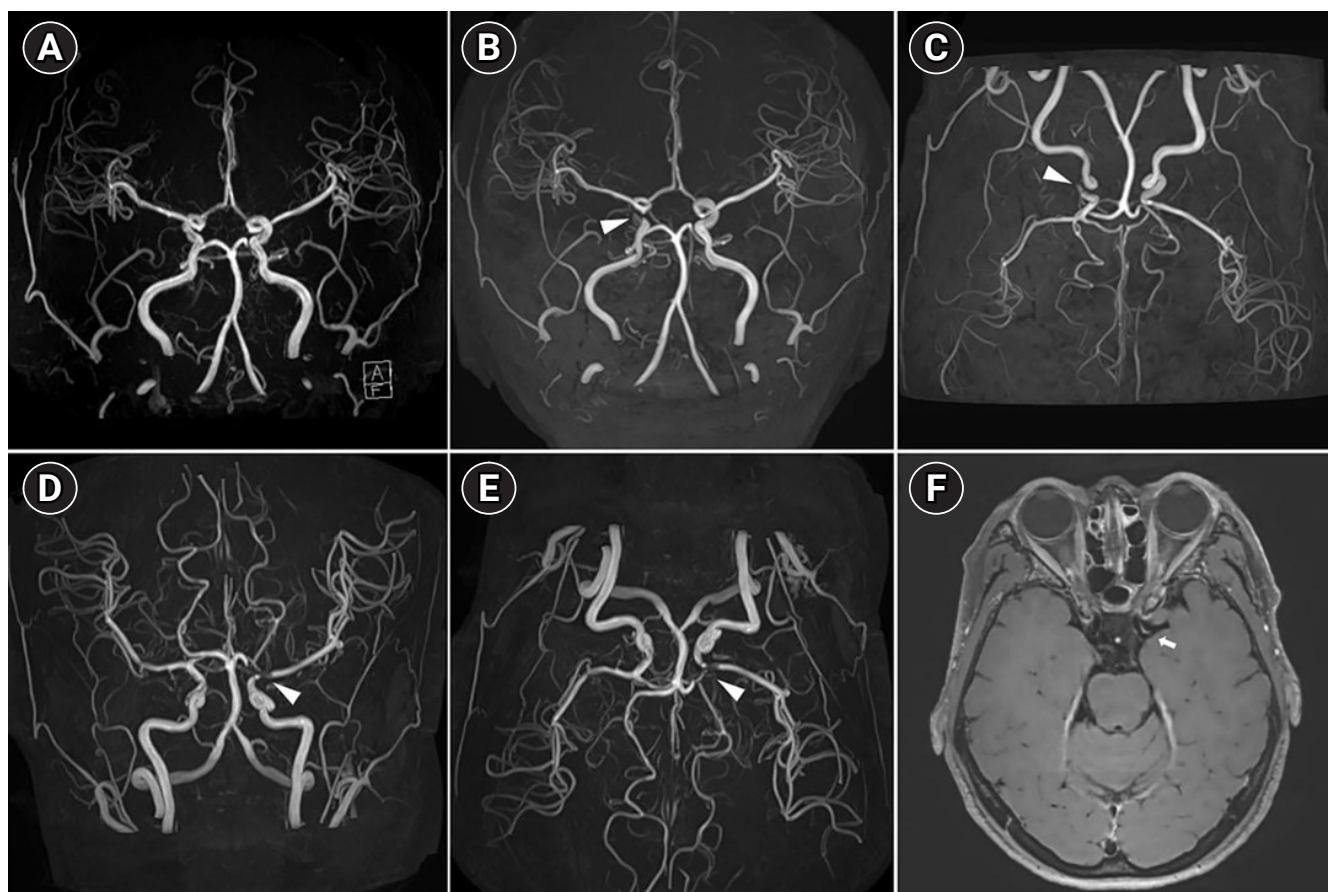


Fig. 2. Brain magnetic resonance angiography (MRA) and high-resolution magnetic resonance imaging (MRI) of the carotid plaque. (A) MRA taken 1 year before admission showed no stenosis in both distal internal carotid arteries (ICAs). (B, C) MRA taken upon admission showed moderate to severe stenosis in the right distal ICA (arrowhead). (D, E) On MRA taken 4 days later, severe stenosis was newly discovered in the left distal ICA, proximal M1, and proximal A1 (arrowhead), and (F) focal concentric wall thickening with enhancement at the left distal ICA was confirmed on high-resolution MRI (arrow).

veloped severe vasculitic stenosis that occurred consecutively within a few days. A high-resolution MRI of the carotid plaque indicated the presence of vasculitis with large-artery involvement, which could be helpful when considering the pathology.

ARTICLE INFORMATION

Ethics statement

This work was approved by the Ethics Committees of the Inje University Busan Paik Hospital (No. 2015-01-271), and written informed consent was obtained from the patient.

Conflict of interest

No potential conflict of interest relevant to this article.

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Instructions to Authors

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2. van den Bent MJ, Keime-Guibert F, Brandes AA, Taphoorn MJ, Eskens FA, Delattre JY. Temozolomide chemotherapy in recurrent oligodendroglioma [abstract]. *Neurology* 2000;54(suppl 3):12.
3. Di Luca DG, Mohny NJ, Kottapally M. Paroxysmal sympathetic hyperactivity with dystonia following non-traumatic bilateral thalamic and cerebellar hemorrhage. *Neurocrit Care* 2019 Feb 6 [Epub]. <https://doi.org/10.1007/s12028-019-00677-9>

- Book & book chapter

4. Layon A. Textbook of neurointensive care. 1st ed. Elsevier; 2003. p. 10-7.
5. Rincon F, Mayer SA. Intracerebral hemorrhage. In: Lee K, editor. *NeuroICU book*. 2nd ed. McGraw-Hill; 2018. p. 36-51.

- Online source

6. Weinhouse GL, Young GB. Hypoxic-ischemic brain injury in adults: evaluation and prognosis [Internet]. UpToDate; c2019 [cited 2019 Feb 10]. Available from: <https://www.uptodate.com/contents/hypoxic-ischemic-brain-injury-in-adults-evaluation-and-prognosis>

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NOTICE

The revised instructions for authors will be applicable from September 2021.

Revision History

- Aug 2020
 - Included a statement regarding IRB approval for case reports.
- Sep 2021
 - Enhanced the description regarding institutional or ethical approval and informed consent.
 - Added details regarding requirement of the manuscripts to adhere to recognized reporting guidelines relevant to the research design used and to submit a checklist as part of the initial submission.
- Mar 2023
 - Updated the requirement of the manuscripts in accordance with the latest version (ver. 11) of the AMA Style Manual.
 - Added regarding Article sharing policy to Editorial policy.

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As the corresponding author, I declare the following information regarding the specific conflicts of interest of authors of our aforementioned manuscript.

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