Journal of Neurocritical Care

pISSN 2005-0348
eISSN 2508-1349

Journal of Neurocritical Care Vol. 16 No. 2 December 2023

pages 59-126

www.e-jnc.org

THE KOREAN NEUROCRITICAL CARE SOCIETY

pISSN 2005-0348
eISSN 2508-1349

Journal of Neurocritical Care

Vol. 16
No. 2
December 2023

www.e-jnc.org

THE KOREAN NEUROCRITICAL CARE SOCIETY

www.e-jnc.org

pISSN 2005-0348
eISSN 2508-1349

Journal of Neurocritical Care

Vol. 16, No. 2, December 31, 2023

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, epilepsy 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.

Open Access

Publisher
The Korean Neurocritical Care Society

Editor-in-Chief
Tae Jung Kim
Department of Neurology and Critical Care Medicine, Seoul National University Hospital,
101, Daehak-ro, Jongno-gu, Seoul, 03080 Korea
Tel: +82-2-2072-1810, E-mail: editor@e-jnc.org

Correspondence
The Korean Neurocritical Care Society
1412, 359 Gangnam-daero, Seocho-gu, Seoul 06621, Korea
Tel: +82-2-521-1412, Fax: +82-2-598-1413, E-mail: office@neurocriticalcare.or.kr
Website: http://www.neurocriticalcare.or.kr

Printing Office
M2PI
#805, 26 Sangwon 1-gil, Seongdong-gu, Seoul 04779, Korea
Tel: +82-2-6966-4930, Fax: +82-2-6966-4945, E-mail: support@m2-pi.com

Published on December 31, 2023

Editorial Board

Journal of Neurocritical Care

Contents

Journal of Neurocritical Care

Vol. 16, No. 2, December 2023

REVIEW ARTICLE

ORIGINAL ARTICLE

CASE REPORT

Contents

Journal of Neurocritical Care

Vol. 16, No. 2, December 2023

IMAGES IN NEUROCRITICAL CARE

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):59-68
https://doi.org/10.18700/jnc.230037

Journal of Neurocritical Care

Management strategies for refractory status epilepticus

Jung-Won Shin, MD, PhD

Department of Neurology, CHA Bundang Medical Center, CHA University, Seongnam, Korea

REVIEW ARTICLE

Received: November 3, 2023
Revised: November 21, 2023
Accepted: November 21, 2023

Corresponding Author:
Jung-Won Shin, MD, PhD
Department of Neurology, CHA Bundang Medical Center, CHA University, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea
Tel: +82-31-780-5058
Email: limitsum@cha.ac.kr

Refractory status epilepticus (RSE) is defined as the persistence of either clinical or electrographic seizures despite the administration of appropriate doses of an initial benzodiazepine and suitable second-line antiepileptic drugs (AEDs). The Neurocritical Care Society and the American Epilepsy Society have proposed a treatment paradigm for the management of convulsive status epilepticus (CSE). The third-line therapy in refractory CSE may involve general anesthesia using intravenous midazolam, propofol, or other agents, while recent evidence supports the use of ketamine to manage RSE in both adults and children. However, although these treatment strategies are frequently employed in nonconvulsive status epilepticus (NCSE), the efficacy of AEDs and anesthetics in NCSE has not been thoroughly investigated. Recent evidence has demonstrated the safety and efficacy of newer AEDs, including levetiracetam and lacosamide, in the treatment of status epilepticus (SE) and RSE, which also encompasses NCSE. Use of multiple combinations of various intravenous AEDs can also be considered in NCSE before the administration of general anesthesia. In addition, AEDs alone exhibit limited effectiveness in managing SE for new-onset RSE (NORSE) and its subset, febrile infection-related epilepsy syndrome. Therefore, in cases of refractory status, it is imperative to explore treatment options beyond AEDs, including immunotherapy and the incorporation of a ketogenic diet. The present review suggests treatment approaches for RSE based on subgroups, including CSE, NCSE, and NORSE. A discussion of recent clinical studies on AEDs and anesthetics in the management of RSE, as well as proposed treatment methods for NORSE, is also provided.

Keywords: Anesthetics; Antiepileptic drug; Convulsive status epilepticus; Non-convulsive status epilepticus

INTRODUCTION

Refractory status epilepticus (RSE) is characterized by seizures that persist despite administration of first-line treatment with benzodiazepines and second-line options, including "classic" anticonvulsant therapy, such as phenytoin (PHT)/fosphenytoin, valproate (VPA), or levetiracetam (LEV). Typically, managing RSE necessitates the use of anesthetics and continuous electroencephalogram (EEG) monitoring [1,2]. The prevailing guidelines suggest an immediate stepwise intervention, starting with benzodiazepines as the initial monotherapy, and if status epilepticus (SE) persists, second-line drugs should be incorporated sequentially [3]. In experimental models, extended seizures result in the internalization of gamma-aminobutyric acid A (GABAA) receptors,

while the concentration of glutamate receptors, particularly an N-methyl-D-aspartate (NMDA) receptor, increases at the synapse [4]. Further, following internalization, GABA receptors undergo reconfiguration, rendering them insensitive to benzodiazepines. Additionally, these receptors are preferentially relocated to extrasynaptic sites. These changes involve alterations in GABAA receptor function and the transmembrane gradient for chloride, both of which diminish the capacity of benzodiazepines to enhance inhibitory synaptic signaling [5]. Hence, resistance to benzodiazepines may also be alleviated by alternative mechanisms, including modifications in other ion channels, including sodium or cholinergic mechanisms [4]. Furthermore, promising candidates among clinically available agents that target NMDA receptors include ketamine and those targeting α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (also known as AMPA) receptors, such as perampanel. These receptors appear to be upregulated in SE, and also play a role in the degradation of GABAA receptor-mediated inhibition. Investigations of the early administration of ketamine for treating RSE, often in combination with other drugs, in animal models have yielded promising results [3]. Further, recent research has demonstrated the remarkable neuroprotective effects of ketamine, achieved through the blockade of NMDA receptors, even when administered following the onset of SE [6].

The American Epilepsy Society has proposed practical conclusions and an integrated treatment algorithm for the management of convulsive status epilepticus (CSE) across the age spectrum, from infants through adults [7]. The Neurocritical Care Society has recommended guidelines for CSE based on the literature, utilizing standardized assessment methods from the American Heart Association and the Grading of Recommendations Assessment, Development, and Evaluation system [8]. Nevertheless, no consensus exists on how aggressively to approach nonconvulsive SE (NCSE) during RSE treatment. We have previously attempted intravenous polytherapy with antiepileptic drugs (AEDs); however, this strategy is marred by the controversy regarding when and how to administer anesthetics for refractory NCSE. New-onset RSE (NORSE) and its subset, febrile infection-related epilepsy syndrome (FIRES), is an uncommon and severe condition characterized by the sudden onset of RSE without any identifiable acute or active structural, toxic, or metabolic cause. Thus far, no randomized controlled trials have investigated the management of NORSE, and consensus guidelines are currently lacking. Recently, the International NORSE Consensus Group issued recommendations for managing NORSE, backed by supporting evidence. Therefore, when addressing the management of RSE, distinct treatment algorithms tailored to specific subgroups including CSE, NCSE, and NORSE of RSE must be considered.

This review explored the recent findings related to the administration of anesthetics, including the use of ketamine, which has garnered significant attention in both pediatric and adult cases of RSE. Within specific subgroups of RSE, I emphasized the crucial considerations of when and how to initiate anesthesia in the treatment of NCSE. Additionally, I discussed recent recommendations regarding the implementation of ketogenic diets and immunotherapy in cases of NORSE.

MANAGEMENT STRATEGIES FOR SUBGROUPS OF RSE

In guidelines established by the American Epilepsy Society and International League Against Epilepsy, SE is defined using two time points, denoted as t1 and t2; t1 represents the duration beyond which seizures are likely to be prolonged, while t2 represents the time beyond which seizures can result in long-term consequences. For tonic-clonic seizures, t1 is set at 5 minutes, and t2 is set at 30 minutes. However, for focal SE or absence status, these specific time points either differ or remain unknown [7,9].

Diagnosing NCSE poses a significant challenge in the medical field. The Salzburg consensus criteria achieves high sensitivity (97.7%) and specificity (90%) by relying on electrographic/electroclinical features. These criteria include EEG evidence of rhythmic epileptiform discharges at a frequency >2.5 Hz, or rhythmic EEG discharges at a frequency ≤ 2.5 Hz accompanied by spatiotemporal evolution, subtle clinical changes correlating with EEG alterations, or EEG and clinical improvement after intravenous AEDs therapy [10]. The latest standardization of critical care EEG terminology by the American Clinical Neurophysiology Society has integrated the Salzburg criteria, while also mandating the continuous presence of EEG changes indicative of NCSE for a minimum duration of 10 min or 20% of any 60-minute EEG recording [11]. Currently, in the management of NCSE, no consensus exists on how aggressively to pursue treatment. Considering the principle of "Time is brain," the treatment paradigm for NCSE is similar to that of CSE. Experiments in animal models have yielded substantial evidence to indicate the infliction of neuronal damage during prolonged episodes of NCSE [12,13]. Further, investigations in rat models have shown neuronal loss, sustained immune response, and changes in synaptic proteins crucial for maintaining the excitatory/inhibitory balance [14]. In a clinical study, Cheng confirmed the prior finding that a 30-minute delay in therapy initiation in NCSE was linked to elevated morbidity and mortality [15], Another prospective study indicated that early initiation of treatment leads to good control of NCSE [16].

https://doi.org/10.18700/jnc.230037

Nevertheless, in patients with NCSE, the underlying etiology is a critical prognostic factor, and evaluating the sole impact of NCSE on neuronal damage in patients is often challenging [17]. Currently, there is little high-quality evidence to guide the best management practices. Hence, when making decisions regarding the management of RSE, it is imperative to assess the potential risks associated with general anesthesia. Therefore, factors such as the severity of the underlying brain injury, patient's age, comorbidities, and the overall goals of care must be considered, especially in cases of NCSE.

NORSE is a rare but profoundly devastating condition encompassing a range of diseases and disorders. It is characterized by the sudden onset of uncontrollable seizures, referred to as RSE, without any identifiable acute or active structural, toxic, or metabolic cause [18]. FIRES is regarded as a subset of NORSE rather than a distinct entity, and is characterized by the presence of a preceding febrile infection occurring between 2 weeks and 24 hours before the onset of RSE [19]. Currently, the evidence to guide the treatment of NORSE is primarily sourced from case reports, case series, and limited observational studies, and there are currently no available randomized controlled trials or consensus guidelines for the management of this condition. Recently, Wickstrom et al. [20] developed recommendations for diagnostic approaches, evaluation, and treatment utilizing the Delphi consensus approach, endorsed by the International League Against Epilepsy. According to the recommendations, the disease characteristics for NORSE/FIRES allow for diagnoses at any age, although the patterns of immune activation may vary between different age groups. Differentiating cases that are secondary to identifiable autoimmune encephalitis from cryptogenic NORSE is crucial, as it is likely to assist in determining the appropriate treatment and establishing the prognosis. In terms of acute phase management, the consensus is that treatment of seizures with AEDs and anesthetics during the initial 48 hours should follow a similar approach to the acute treatment of RSE in other conditions.

Current guidelines recommend that the management of NORSE/FIRES patients should be conducted in a tertiary center equipped with the necessary resources and the input of a multidisciplinary team of experts in epileptology, rheumatology, immunology, and intensive care. Additionally, a crucial distinction from the majority of treatment algorithms for RSE involves the incorporation of immunotherapy. The summary of the treatment strategy for SE specific to each subgroup within RSE is presented in Fig. 1.

Intensive care management in RSE

When treating patients with SE, it is critical to assess airway, breathing, and circulation as a fundamental aspect of care. Respiratory failure or the presence of markers indicating cardiac injury occurs in approximately one-third of SE episodes, and is significantly associated with poor outcomes [21]. Further, the administration of a high dose of AEDs or anesthetics may contribute to respiratory depression, and it is important to note that up to one-third of patients with SE develop neurocardiogenic pulmonary edema, adding to the complexity of managing their condition [22]. Infections can occur as complications in up to 50% of SE cases [23]. Infections in SE cases are linked to a prolonged duration of SE, the requirement for mechanical ventilation, unfavorable discharge outcomes from the hospital, and overall poor recovery [24]. Prolonged seizures can lead to complications such as rhabdomyolysis. Patients experiencing rhabdomyolysis often exhibit additional abnormalities, including hyperkalemia, hyperphosphatemia, and hypocalcemia, particularly in cases involving severe acute kidney injury [25]. As such, intensive medical care management is essential. When treating patients with RSE, it is imperative to take into account the aforementioned systemic complications. In addition, continuous intravenous neuromuscular blocking drugs could mask ongoing seizure activity, making it challenging for clinicians to detect seizures without EEG monitoring. As such, it is prudent to avoid these drugs in such cases. Continuous EEG monitoring is essential when using anesthetics in the intensive care unit (ICU). The justification for tracheal intubation in suspected or confirmed NCSE has not yet been firmly established and requires meticulous evaluation. This assessment must weigh the evident risks associated with prolonged tracheal intubation and ICU stay against the uncertain benefits of therapeutic coma. It is also recommended to explore trials of non-sedative intravenous second-line AEDs before resorting to anesthetic induction in NCSE.

Anesthetics

Current continuous intravenous anesthetics' options include midazolam, propofol, and pentobarbital in the management of RSE or super RSE. Additionally, recent reports have explored the use of ketamine as an alternative agent. However, there are currently no randomized controlled trials to provide guidance on the selection of anesthetic drugs for the treatment of RSE. As such, which anesthetic third-line treatment for RSE offers superior outcomes, minimizes adverse effects, and is most effective in halting seizures in the ICU currently remains unclear. Most of the existing studies lack uniform data collection instruments, making it exceptionally challenging to draw meaningful comparisons between patients [26]. However, one recent retrospective, multicenter, observational cohort study was conducted to compare the efficacy of

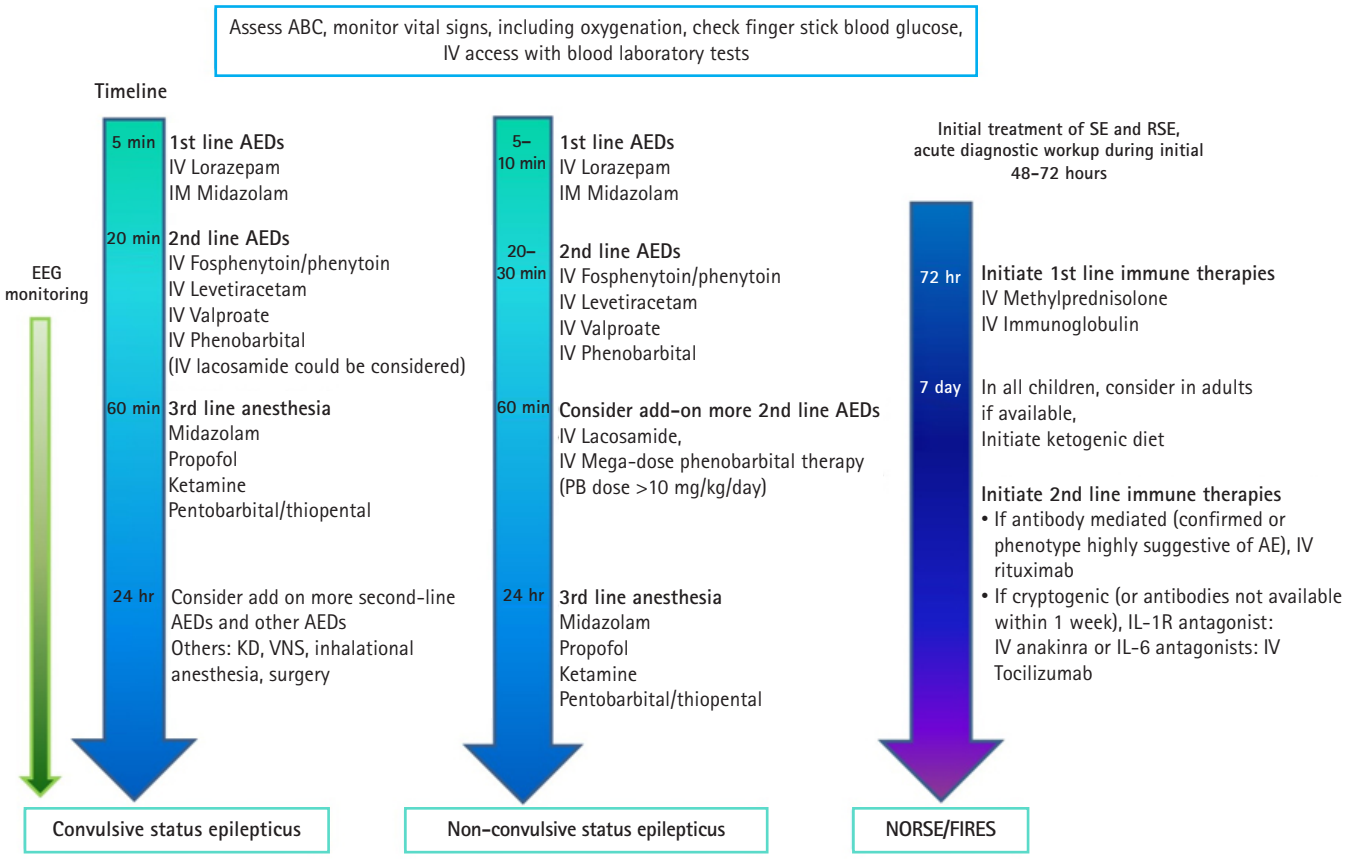

Fig. 1. Treatment approaches for refractory status epilepticus based on subgroups including convulsive status epilepticus, non-convulsive status epilepticus, and new-onset refractory status epilepticus (NORSE)/febrile infection-related epilepsy syndrome (FIRES). ABC, airway, breathing, circulation; IV, intravenous; EEG, electroencephalogram; AED, antiepileptic drug; IM, intramuscular; KD, ketogenic diet; VNS, vagus nerve stimulation; PB, phenobarbital; SE, status epilepticus; RSE, refractory status epilepticus; AE, autoimmune encephalitis; IL, interleukin.

propofol (median maximum dose: 37 μg/kg/min [interquartile range, IQR: 23–56 μg/kg/min]) and midazolam (median maximum dose: 0.5 mg/kg/hr [IQR: 0.2–2.0 mg/kg/hr]) in the treatment of RSE in the ICU [27]. A favorable outcome was observed in 25 and 21% of patients treated with propofol and midazolam, respectively. The need for vasopressors, and occurrence of lactic acidosis, hyperkalemia, rhabdomyolysis, and hypertriglyceridemia was reported with comparable frequencies in patients treated with both propofol and midazolam.

Ketamine, functioning as an NMDA receptor antagonist, is currently gaining prominence as the most encouraging alternative among anesthetics in the management of RSE. The primary and highly appealing theoretical benefit of ketamine lies in its distinct mechanism of action. Unlike standard anesthetics that act on GABA receptors, ketamine targets an alternative pathway via action on the NMDA receptor. This unique characteristic opens new avenues for the management of RSE [28,29]. Additionally, research on the neuroprotective effects of ketamine has accumulated substantial scientific data, showcasing the potential advantages of this drug [6]. Furthermore, ketamine demonstrates fewer cardiovascular and respiratory side effects compared to those associated with other anesthetics [1]. Conversely, ketamine is associated with numerous drawbacks, including hallucinations and sympathetic adrenergic effects, leading to elevated intracranial pressure [30]. One systematic review, included 244 cases of SE treated with ketamine (starting dose: 0.2 mg/kg/hr [IQR: 0.1–0.5 mg/kg/hr] and continued for 1.6 days [IQR: 0.6–2.9 days]), encompassing 13 case reports and five case series in adults, along with four case reports and three case series in children that were extracted from the PubMed database. The overall rate of success was 74% (153 out of 207 cases) in adults and 73% (27 out of 37 cases) in children [31]. Further, two recent studies have highlighted the use of ketamine for RSE and super RSE. One was a single-center retrospective study of 69 children who received ketamine for RSE [32]. Ketamine infusions were initiated at 1 mg/kg/hr in 66 of 69 patients (96%) and continuous infusion doses

https://doi.org/10.18700/jnc.230037

were 1–7 mg/kg/hr. The median total duration of ketamine infusion was 85.7 hours (IQR: 49.7–128.0 hours). Seizure termination was notably more successful when ketamine was administered as the initial anesthesia, compared to its success in cases where it was used after midazolam had been attempted first and proved ineffective. Furthermore, the in-hospital adverse effects were considered limited and manageable. This study contributed significant data from neonates and younger children to the global literature, with strong results indicating that ketamine can be utilized effectively and safely in the treatment of RSE in both adults and children. The second study involved a consecutive series of 68 adult patients diagnosed with super RSE, all of whom received ketamine treatment between 2009 and 2018 [33]. The average dose of ketamine infusion was 2.2 ± 1.8 mg/kg/hr, with median duration of 2 days (IQR: 1–4 days). Within the first 24 hours of initiating ketamine treatment, the seizure burden decreased by 50%, and complete cessation was observed in 63% of cases. In this particular study, 11 patients underwent multimodal monitoring in the ICU, and ketamine administration was linked to a stable mean arterial pressure, leading to reduced vasopressor requirements over time. Moreover, there were no discernible effects on intracranial pressure, cerebral blood flow, or cerebral perfusion pressure in cases involving both traumatic and nontraumatic brain injuries. These results indicate that ketamine treatment is advantageous for RSE, with high doses demonstrating improved hemodynamics without an increase in intracranial pressure. This study corroborates the results of previous case reports and series suggesting that ketamine is a favorable option for the management of patients with hemodynamically unstable RSE [34,35].

Considering the pathomechanism of SE, where GABAA receptors are internalized and glutamate receptors increase their concentration at the synapse, initiating c with a combination of a benzodiazepine and a second-line drug, such as LEV that modulates glutamate receptors, or other multi-action drugs, such as VPA, appears to be a practical approach. In third-line therapy, several studies have indicated favorable outcomes with early anesthetic combination therapies for RSE or super RSE, such as propofol-ketamine or midazolam-ketamine [35,36]. Early initiation of combined anesthetics may be beneficial, considering the underlying pathomechanism, and the need to mitigate side effects resulting from the high accumulation of propofol or barbiturates, by including propylene glycol.

Different anesthetics have similar efficacy for RSE, but are accompanied by a unique set of side effects. Side effects can impose limitations on the duration of infusion that can be administered. Consequently, the decision to continue should involve monitoring specific laboratory values (such as creatinine kinase, acid/base balance, serum lactate, and lipid profile) and conducting electrocardiograms and echocardiograms. Neurointensivists must assess whether or not each patient's symptoms are related to the anesthetic drugs before proceeding further. Anesthetics management could be personalized, considering the individual characteristics of each patient.

The advantages and disadvantages, and initial and maintenance dose of each anesthetic which are summarized in Table 1, play a crucial role in their selection. When treating RSE with anesthesia, the primary goal is seizure suppression. However, the optimal extent of seizure suppression, including the need for burst suppression, remains unclear in the management of SE. In addition, while a continuous infusion is typically maintained for 24–48 hours before weaning [37], the duration of therapeutic coma is a subject of controversy. A recent observational study suggested that a deeper and shorter duration of therapeutic coma may be associated with a decreased risk of withdrawal seizures and complications related to prolonged hospitalization [38]. Therefore, considering the patient's medical condition, we should aim to wean anesthetics as soon as possible after 24–48 hours with sufficient seizure suppression. Additionally, other nonanesthetic AEDs should be added to prevent the re-emergence of seizures during the anesthesia weaning process.

Volatile inhalational anesthetics have been explored as an alternative salvage therapy in cases of super RSE. These anesthetics are believed to suppress seizure activity by inhibiting NMDA excitotoxicity and activating GABA receptors [39]. Inhalational anesthetics offer advantages such as easy titration to EEG at the bedside and an ultrafast onset of action. Nevertheless, existing studies on inhalational anesthetics show disparity in outcomes, lack comparative groups, and exhibit variations in the treatment regimens. Furthermore, the utilization of these anesthetics is curtailed by the potential for serious adverse events, particularly following prolonged usage [39].

Intravenous AEDs

Table 2 summarizes the pharmacological characteristics of intravenous AEDs used in the management of SE. Traditionally, guidelines recommend the administration of intravenous fosphenytoin/PHT (20 mg/kg PHT equivalent), VPA (20–40 mg/kg), phenobarbital (PB; 15–20 mg/kg), and LEV (60 mg/kg or 3,000–4,500 mg) for the treatment of established SE resistant to benzodiazepines [7].

In the recent literature, the majority of studies pertaining to LEV have focused on its application in established SE. Three significant randomized trials published in 2019 examined larger loading doses of LEV specifically for established CSE. Notably,

Table 1. Anesthetics used for the treatment of refractory status epilepticus

	Main mechanism	Onset of action/ half-life (elimination)	Loading dose/ maintenance dose	Clinical consideration
Midazolam	Potentiation of the inhibitory action of GABA receptors by increasing the frequency of chloride channel opening	1.5 min/1.8–6.4 hr	0.2 mg/kg followed by 0.05–2 mg/kg/hr	Respiratory depression, hypotension, tachyphylaxis after long use Does not contain propylene glycol
Propofol	GABA receptor modulation and NMDA receptor blockade	15–30 sec/4–7 hr	1–2 mg/kg followed by 30–200 μg/kg/min	Respiratory depression, hypotension, metabolic acidosis, pancreatitis Due to its high lipid solubility, prolonged infusions cause propofol to accumulate in peripheral tissue.
Barbiturates (Thiopental/Pentobarbital)	Potentiation of GABA receptors by increasing the duration, not frequency, of chloride channel opening Deep coma with profound reduction in cerebral metabolism	Thiopental: 10–40 sec/ 3–22 hr Pentobarbital: <60 sec/ 15–50 hr	2–7 mg/kg (thiopental) or 5–15 mg/kg (pentobarbital) followed by 0.5–5 mg/kg/hr	Respiratory depression, hypotension, decreased cardiac output, ileus, immune suppression Contains propylene glycol, which accumulates with continuous infusions, and can result in metabolic acidemia, cardiac toxicity and severe hypotension Due to its high lipid solubility, prolonged infusions cause barbiturate to accumulate in peripheral tissue.
Ketamine	Non-competitive NMDA receptor antagonist Reduction in glutaminergic neuronal transmission and excitotoxicity	<30 sec/2.5 hr	0.5–3 mg/kg followed by 0.1–5 mg/kg/hr	Cardiac arrhythmias (rare), hypertension, pulmonary edema, anaphylaxis
Isoflurane	Inhibition of seizure activity via inhibition of NMDA excitotoxicity and activation of GABA receptors	Ultrashort acting	Not established/end-tidal concentrations 0.8%–2% titrated to EEG	Cardiac and respiratory depression, infections

GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; EEG, electroencephalogram.

Table 2. Intravenous antiepileptic drugs used for the treatment of status epilepticus

	Initial dose	Maintenance dose	Clinical consideration
Fosphenytoin/ phenytoin	20 mg phenytoin equivalents/kg IV, maximum rate up to 150 mg phenytoin equivalents/min	100 mg IV every 8 hr	Arrhythmia, hypotension Contains propylene glycol which can cause metabolic acidosis Inducer of several cytochrome P450 enzyme, which can cause strong interactions with other drugs
Levetiracetam	1,000–3,000 mg IV, up to a maximum dose of 4,500 mg	500–1,500 mg IV every 12 hr	Requires dose adjustment in renal impairment Avoided in patients with history of agitation or psychiatric disease
Valproate	20–40 mg/kg IV	500–750 mg IV every 8 hr	Risk of hepatotoxicity (particularly in patients with mitochondrial diseases), pancreatitis, thrombocytopenia, platelet dysfunction and severe encephalopathy (monitoring of ammonia is necessary) Phenytoin and valproic acid interact by increasing their free levels
Phenobarbital	20 mg/kg IV Megadose-phenobarbital therapy: enteral or parenteral phenobarbital >10 mg/kg/day	50–100 mg IV every 12 hr	Inducer of several cytochrome P450 enzymes (strong interactions with other drugs) Serum level above 70 μg/mL can cause severe sedation. Contains propylene glycol which causes metabolic acidosis, and cardiac arrhythmias in higher cumulative doses. When administering mega-dose phenobarbital therapy, serum level and cardiac arrhythmia should be monitored.
Lacosamide	200–400 mg IV	100–200 mg IV every 12 hr	PR prolongation, atrial arrhythmia; first, second, and third degree heart block

IV, intravenous.

https://doi.org/10.18700/jnc.230037

the Class I ESETT study involved 384 patients (ranging in age from 1 to 95 years old) with benzodiazepine-resistant established CSE. These patients were randomized using a Bayesian adaptive design to receive fosphenytoin at 20 mg PE/kg, LEV at 60 mg/kg, or VPA at 40 mg/kg [40]. Termination of SE was observed in comparable percentages with LEV (47%), fosphenytoin (45%), and VPA (46%). No significant disparities were noted in terms of enhanced consciousness levels or major safety incidents. However, there were numerically more instances of hypotension and intubation associated with fosphenytoin, while LEV was found to be linked to a higher number of fatalities. In the Class III EcLiPSE open-label randomized controlled trial conducted in the United Kingdom, 286 children experiencing CSE following initial treatment with a benzodiazepine were compared in terms of second-line therapy. This study evaluated the efficacy of intravenous LEV at a loading dose of 40 mg/kg and intravenous PHT at 20 mg/kg [41]. CSE was terminated more frequently with LEV compared to its frequency of termination with PHT ($P=0.20$). Furthermore, serious adverse events were reported with PHT, including life-threatening hypotension, exacerbated focal seizures, and a decreased level of consciousness. In the Class III open-label randomized controlled Convulsive Status Epilepticus Paediatric Trial (ConSEPT) conducted in Australia and New Zealand, 352 children experiencing CSE following initial benzodiazepine treatment were evaluated for second-line therapy. This study compared the effectiveness of intravenous LEV at a loading dose of 40 mg/kg, and intravenous PHT at 20 mg/kg [42]. Seizure activity ceased clinically within 5 minutes following the completion of the loading dose in 60% of children in the PHT group and 50% in the LEV group ($P=0.16$), and no significant adverse events were reported.

Lacosamide (LCS) is available as an IV solution. Between 2009 and 2019, a total of 32 clinical trials exploring the use of intravenous LCS for SE treatment were conducted. These trials employed varied definitions of RSE, with some encompassing a significant portion of focal SE or electrographic NCSE cases. The efficacy of LCS in managing recurrent electrographic nonconvulsive seizures was evaluated through a comparison with fosphenytoin (intravenous LCS 400 mg vs. fosphenytoin 20 mg; PHT equivalent per kilogram). In a prospective, multicenter, randomized controlled trial designed to assess noninferiority, LCS demonstrated superiority over fosphenytoin in preventing seizure recurrence, with rates of 63.3% vs. 50% ($P=0.02$) [43]. A recent comparative review involving 115 cases of LCS and 166 cases of PHT demonstrated comparable rates of seizure control and adverse events. However, patients with PHT exhibited a higher incidence of serious side effects compared to those associated with LCS (5.1 vs. 0.8%, $P=0.049$) [44]. In a recent review conducted by the American Epilepsy Society Treatment Committee, there is a suggestion that LCS might be effective at halting RSE for both children and adults [45].

PB, one of the first antiepileptic medications to be developed, can be employed as a second-line therapy for managing controlled SE. Nevertheless, the utilization of PB was restricted due to its increased incidence of sedation, respiratory depression, and hypotension, as well as a higher number of drug interactions than those associated with LEV or LCS. Recently, the use of PB is being reconsidered. During the eighth London-Innsbruck Colloquium on Status Epilepticus in 2022, Eugen Trinka emphasized the high efficacy of PB use due to its GABAergic and anti-glutamatergic properties. Consequently, considering its mechanisms of action, the application of PB in both early and established cases of SE, including RSE, appears to be justified [46]. In 2019, one study aimed to assess the relative effectiveness and safety of AEDs in adults experiencing CSE resistant to benzodiazepines. Five randomized controlled trials were analyzed, encompassing 349 patients. PB exhibited the highest likelihood of achieving optimal control of SE and seizure freedom, while VPA and LCS were found to have the best safety outcomes. No differences in the incidence of respiratory depression and hypotension were observed among the medications [47]. One prior study further investigated the effectiveness and safety of mega-dose PB (mega-dose [MDPB]; enteral or parenteral PB > 10 mg/kg/day) for managing super refractory status epilepticus. Half of the patients achieved successful control of super RSE with a median duration of 45.5 days for MDPB treatment. The median maximum serum PB level reached 151.5 μg/mL [48]. Taking these findings into account, and considering the reduced risk of respiratory depression compared to those associated with other anesthetics, MDPB could be a viable and advantageous treatment choice for refractory NCSE.

NCSE, even if prolonged, may not require intensive care or anesthetic management, as the clinical variables are related to prognosis [39]. As yet, no extended prospective studies have yet been conducted to delineate the natural progression of NCSE or identify which patients would benefit from aggressive treatment. Therefore, when contemplating the use of anesthetic drugs for third-line therapy in refractory NCSE, it is crucial to assess whether this approach is more beneficial than it is detrimental to the patients involved. Considering the recent more favorable evidence data for intravenous AEDs, the initial consideration for third-line therapy in refractory NCSE could lean towards adding more second-line AEDs rather than opting for anesthetics.

NORSE: EXPLORING TREATMENT STRATEGIES FOR SUBGROUPS

In 2022, the International NORSE Consensus Group presented recommendations for managing NORSE, including FIRES [20]. In the acute phase of NORSE, an expert consensus supports the management of seizures with AEDs and anesthetics in the initial 48 hours should align with the acute treatment protocols followed for RSE in other conditions. Experts recommend initiating first-line immunotherapy, which may include corticosteroids, intravenous immunoglobulins, or therapeutic plasma exchange (TPE), within the initial 72 hours following the onset of SE in NORSE/FIRES cases. However, panel members exhibited significant disparities in their perspectives on the utilization of TPE. Consequently, this consensus document refrained from providing a specific recommendation regarding TPE, except for emphasizing that its use should not impede the initiation of subsequent treatments. Due to the probable engagement of immune mechanisms in perpetuating seizures, the consensus group also advocates for the initiation of a ketogenic diet and second-line immunotherapies within one week for noninfectious NORSE/FIRES patients exhibiting an insufficient response to first-line immune treatment. As existing evidence is insufficient to clearly endorse any particular second-line immunological treatment, the decision should be guided by the suspected underlying cause. For example, rituximab should be the first choice in the majority of cases where a pathogenic antibody is identified, or there is a strong suspicion of an autoimmune process. For cryptogenic NORSE/FIRES without evident clinical features of a specific autoimmune encephalitis syndrome, the administration of anakinra (interleukin 1 [IL]-1 receptor antagonists) or tocilizumab (IL-6 blockers) should be seriously contemplated.

CONCLUSION

In SE, early treatment and cessation of SE is crucial. However, when implementing aggressive treatment with general anesthesia and coma therapy, it is crucial to rely on evidence-based treatment modalities to prevent mortality and complications arising from RSE. Therefore, in the management of SE, status epilepticus could be classified into subgroups, such as CSE, NCSE and NORSE including FIRES. In refractory NCSE, the patient's medical condition and weighing the benefits and risks of using anesthetics must be considered. Alternate options, such as add-on multiple non-sedative intravenous AEDs therapy, can be considered. Intravenous MDPB therapy could also be considered an effective treatment for super RSE when tapering out prolonged use of anesthetics. When choosing anesthetics, the choice should be individualized and it is important to consider the pros and cons of each drug before determining their use. Ketamine is favorable for children with RSE and adults with a hemodynamic unstable condition, and ketamine could be used as an add-on with other anesthetics with a GABAergic mechanism. In cases of NORSE, including FIRES, clinicians should consider administering immunotherapy and implementing a ketogenic diet. Management in each subgroup necessitates a multidisciplinary approach involving neurologists, intensivists, and other specialists. Individualized care based on each patient's specific characteristics and underlying condition is paramount in improving outcomes in RSE.

ARTICLE INFORMATION

Ethics statement
Not applicable.

Conflict of interest
Jung-Won Shin is an editorial board member of the journal, but she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

ORCID
Jung-Won Shin https://orcid.org/0000-0003-2155-9068

REFERENCES

1. Legriel S, Oddo M, Brophy GM. What's new in refractory status epilepticus? Intensive Care Med 2017;43:543-6.
2. Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain 2011;134:2802-18.
3. Amengual-Gual M, Sánchez Fernández I, Wainwright MS. Novel drugs and early polypharmacotherapy in status epilepticus. Seizure 2019;68:79-88.
4. Joshi S, Rajasekaran K, Hawk KM, Chester SJ, Goodkin HP. Status epilepticus: role for etiology in determining response to benzodiazepines. Ann Neurol 2018;83:830-41.
5. Burman RJ, Rosch RE, Wilmshurst JM, Sen A, Ramantani G, Akerman CJ, et al. Why won't it stop? The dynamics of benzodiazepine resistance in status epilepticus. Nat Rev Neurol 2022;18:428-41.
6. Fujikawa DG. Starting ketamine for neuroprotection earlier than its current use as an anesthetic/antiepileptic drug late in refractory status epilepticus. Epilepsia 2019;60:373-80.

https://doi.org/10.18700/jnc.230037

7. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016;16:48-61.
8. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care 2012;17:3-23.
9. Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, et al. A definition and classification of status epilepticus: report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56:1515-23.
10. Trinka E, Leitinger M. Which EEG patterns in coma are nonconvulsive status epilepticus? Epilepsy Behav 2015;49:203-22.
11. Hirsch LJ, Fong MW, Leitinger M, LaRoche SM, Beniczky S, Abend NS, et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2021 version. J Clin Neurophysiol 2021;38:1-29.
12. Olney JW, Collins RC, Sloviter RS. Excitotoxic mechanisms of epileptic brain damage. Adv Neurol 1986;44:857-77.
13. Meldrum BS. Excitotoxicity and selective neuronal loss in epilepsy. Brain Pathol 1993;3:405-12.
14. Avdic U, Ahl M, Chugh D, Ali I, Chary K, Sierra A, et al. Nonconvulsive status epilepticus in rats leads to brain pathology. Epilepsia 2018;59:945-58.
15. Cheng JY. Latency to treatment of status epilepticus is associated with mortality and functional status. J Neurol Sci 2016;370:290-5.
16. Gutiérrez-Viedma Á, Parejo-Carbonell B, Cuadrado ML, Serrano-García I, Abarrategui B, García-Morales I. The relevance of timing in nonconvulsive status epilepticus: a series of 38 cases. Epilepsy Behav 2018;82:11-6.
17. Power KN, Gramstad A, Gilhus NE, Engelsen BA. Adult nonconvulsive status epilepticus in a clinical setting: semiology, aetiology, treatment and outcome. Seizure 2015;24:102-6.
18. Hirsch LJ, Gaspard N, van Baalen A, Nabbout R, Demeret S, Loddenkemper T, et al. Proposed consensus definitions for new-onset refractory status epilepticus (NORSE), febrile infection-related epilepsy syndrome (FIRES), and related conditions. Epilepsia 2018;59:739-44.
19. Gaspard N, Hirsch LJ, Sculier C, Loddenkemper T, van Baalen A, Lancrenon J, et al. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES): state of the art and perspectives. Epilepsia 2018;59:745-52.
20. Wickstrom R, Taraschenko O, Dilena R, Payne ET, Specchio N, Nabbout R, et al. International consensus recommendations for management of New Onset Refractory Status Epilepticus (NORSE) incl. Febrile Infection-Related Epilepsy Syndrome (FIRES): statements and supporting evidence. Epilepsia 2022;63:2840-64.
21. Hawkes MA, Hocker SE. Systemic complications following status epilepticus. Curr Neurol Neurosci Rep 2018;18:7.
22. Busl KM, Bleck TP. Neurogenic pulmonary edema. Crit Care Med 2015;43:1710-5.
23. Sutter R, Tschudin-Sutter S, Grize L, Fuhr P, Bonten MJ, Widmer AF, et al. Associations between infections and clinical outcome parameters in status epilepticus: a retrospective 5-year cohort study. Epilepsia 2012;53:1489-97.
24. Sutter R, Marsch S, Fuhr P, Rüegg S. Mortality and recovery from refractory status epilepticus in the intensive care unit: a 7-year observational study. Epilepsia 2013;54:502-11.
25. Huerta-Alardín AL, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis. An overview for clinicians. Crit Care 2005;9:158-69.
26. Minicucci F, Ferlisi M, Brigo F, Mecarelli O, Meletti S, Aguglia U, et al. Management of status epilepticus in adults: position paper of the Italian League against Epilepsy. Epilepsy Behav 2020;102:106675.
27. Chiu WT, Campozano V, Schiefecker A, Rodriguez DR, Ferreira D, Headlee A, et al. Management of refractory status epilepticus: an international cohort study (MORSE CODe) analysis of patients managed in the ICU. Neurology 2022;99:e1191-201.
28. Gaspard N, Foreman B, Judd LM, Brenton JN, Nathan BR, McCoy BM, et al. Intravenous ketamine for the treatment of refractory status epilepticus: a retrospective multicenter study. Epilepsia 2013;54:1498-503.
29. Espinosa L, Gomez M, Zamora A, Molano-Franco D. Refractory and super-refractory status epilepticus and evidence for the use of ketamine: a scope review. J Neurocrit Care 2023;16:1-9.
30. Groth CM, Droege CA, Connor KA, Kaukeinen K, Acquisto NM, Chui SH, et al. Multicenter retrospective review of ketamine use in the ICU. Crit Care Explor 2022;4:e0633.
31. Byun JI. Management of convulsive status epilepticus: recent updates. Encephalitis 2023;3:39-43.
32. Jacobwitz M, Mulvihill C, Kaufman MC, Gonzalez AK, Resendiz K, MacDonald JM, et al. Ketamine for management of neonatal and pediatric refractory status epilepticus. Neurology 2022;99:e1227-38.
33. Alkhachroum A, Der-Nigoghossian CA, Mathews E, Massad N, Letchinger R, Doyle K, et al. Ketamine to treat super-refractory status epilepticus. Neurology 2020;95:e2286-94.
34. Hurth KP, Jaworski A, Thomas KB, Kirsch WB, Rudoni MA, Wohlfarth KM. The reemergence of ketamine for treatment in

critically ill adults. Crit Care Med 2020;48:899-911.
35. Choi JW, Shin JW. Early combination therapy of ketamine and midazolam in patients with refractory status epilepticus in hemodynamic unstable state. J Epilepsy Res 2021;11:150-3.
36. Sabharwal V, Ramsay E, Martinez R, Shumate R, Khan F, Dave H, et al. Propofol-ketamine combination therapy for effective control of super-refractory status epilepticus. Epilepsy Behav 2015;52:264-6.
37. Trinka E, Leitinger M. Management of status epilepticus, refractory status epilepticus, and super-refractory status epilepticus. Continuum (Minneap Minn) 2022;28:559-602.
38. Muhlhofer WG, Layfield S, Lowenstein D, Lin CP, Johnson RD, Saini S, et al. Duration of therapeutic coma and outcome of refractory status epilepticus. Epilepsia 2019;60:921-34.
39. Migdady I, Rosenthal ES, Cock HR. Management of status epilepticus: a narrative review. Anaesthesia 2022;77 Suppl 1:78-91.
40. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med 2019;381:2103-13.
41. Lyttle MD, Rainford NE, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019;393:2125-34.
42. Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. Lancet 2019;393:2135-45.
43. Husain AM, Lee JW, Kolls BJ, Hirsch LJ, Halford JJ, Gupta PK, et al. Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures. Ann Neurol 2018;83:1174-85.
44. Panda PK, Panda P, Dawman L, Sharawat IK. Efficacy of lacosamide and phenytoin in status epilepticus: a systematic review. Acta Neurol Scand 2021;144:366-74.
45. Vossler DG, Bainbridge JL, Boggs JG, Novotny EJ, Loddenkemper T, Faught E, et al. Treatment of refractory convulsive status epilepticus: a comprehensive review by the American Epilepsy Society Treatments Committee. Epilepsy Curr 2020;20:245-64.
46. Trinka E. Phenobarbital in status epilepticus: rediscovery of an effective drug. Epilepsy Behav 2023;141:109104.
47. Brigo F, Del Giovane C, Nardone R, Trinka E, Lattanzi S. Intravenous antiepileptic drugs in adults with benzodiazepine-resistant convulsive status epilepticus: a systematic review and network meta-analysis. Epilepsy Behav 2019;101:106466.
48. Byun JI, Chu K, Sunwoo JS, Moon J, Kim TJ, Lim JA, et al. Mega-dose phenobarbital therapy for super-refractory status epilepticus. Epileptic Disord 2015;17:444-52.

https://doi.org/10.18700/jnc.230037

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):69-76
https://doi.org/10.18700/jnc.230030

Journal of Neurocritical Care

Diurnal variation in quantitative pupillary reactivity in large hemispheric stroke

Tae Jung Kim, MD, PhD[1,2]; Ji Sung Lee, PhD[3]; Soo-Hyun Park, MD, PhD[4]; Sang-Bae Ko, MD, PhD[1,2]

[1]Department of Neurology, Seoul National University College of Medicine, Seoul, Korea
[2]Department of Critical Care Medicine, Seoul National University Hospital, Seoul, Korea
[3]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[4]Department of Neurology, Kangdong Sacred Heart Hospital, Seoul, Korea

ORIGINAL ARTICLE

Received: September 7, 2023
Revised: September 27, 2023
Accepted: October 10, 2023

Corresponding Author:
Sang-Bae Ko, MD, PhD
Departments of Neurology and Critical Care Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-2278
Fax: +82-2-3672-7553
Email: sangbai1378@gmail.com

Background: Pupillary light reflex (PLR) assessment is an important neurological examination reflecting neurological deterioration in severe stroke cases. This study investigated the impact of diurnal variation in the PLR using quantitative pupillometry in stable patients with large hemispheric stroke.

Methods: We included 35 patients with large hemispheric stroke without neurological worsening, who were admitted to the neurological intensive care unit between April 2017 and November 2021. Quantitative pupillometry was performed every 4 hours. Pupillometer parameters of maximum pupil size, percentage of constriction (%CH), latency (LAT), constriction velocity (CV), dilation velocity (DV), maximum constriction velocity (MCV), and neurological pupil index (NPi) score were recorded. We evaluated changes in the pupillometer parameters over time using linear mixed model analysis.

Results: The diurnal variations revealed that the following parameters were significantly higher at 04:00 than at 20:00: maximum pupil size (right [Rt]: 3.59 vs. 3.21 mm, $P<0.001$; left [Lt]: 3.51 vs. 3.18 mm, $P<0.001$), %CH (Rt: 31.48 vs. 25.72, $P<0.001$; Lt: 31.42 vs. 24.98, $P<0.001$), CV (Rt: 1.97 vs. 1.68 mm/sec, $P<0.001$; Lt: 1.98 vs. 1.65 mm/sec, $P<0.001$), and DV (Rt: 0.97 vs. 0.84 mm/sec, $P<0.001$; Lt: 0.94 vs. 0.82 mm/sec, $P=0.001$). However, no significant diurnal variations were observed in the NPi values.

Conclusion: Pupillary dynamics based on quantitative pupillometer parameters, including the NPi, demonstrated diurnal variations over 24 hours in large hemispheric stroke patients without neurological worsening. However, all changes in the pupillometer parameters were within normal ranges.

Keywords: Pupil disorder; Circadian rhythm; Stroke

INTRODUCTION

Pupillary light reflex (PLR) assessment is a crucial neurological examination in neurologically critical patients. A quantitative pupillometer allows quantitative and objective assessment of the PLR. Therefore, it is widely accepted as a reliable and standard tool for assessing the PLR during neurological examination in the neurological intensive care unit (neuroICU) [1-4]. An acute change in the PLR based on the pupillometer is an early indicator of increased intracranial pressure (ICP) or worsening intracranial

pathology. Additionally, significant deterioration in the pupillometer parameters, including the neurological pupil index (NPi), has been linked to worsening ICP or midline shift [5-7].

Pupillary reactivity, including pupil size, is influenced by the sleep cycle, circadian rhythm, changes in autonomic nervous system status, and ambient light levels, which could show diurnal variations [8-13]. Therefore, changes in the PLR or pupil size could be due to the time-of-day effect. However, the extent of the effects of the diurnal factors on the interpretation of PLR remains unclear in patients with large stroke in the neuroICU. The time-of-day effect has rarely been considered on the PLR based on the pupillometer parameters assessed over 24 hours in patients with large hemispheric stroke and stable neurological symptoms. Therefore, this study aimed to investigate the variations in pupillometer parameters at different time points over 24 hours in large hemispheric stroke patients without neurological deterioration.

METHODS

Study population

This retrospective study initially screened 65 patients, who were admitted to the neuroICU between April 2017 and November 2021 for large hemispheric stroke (ischemic or hemorrhagic) and were evaluated using a pupillometer. The exclusion criteria were as follows: (1) neurological worsening during monitoring (n = 18), (2) posterior circulation stroke (n = 5), and (3) missing values in the serial PLR data (n = 7), depending on the neurological condition and time interval of neurological assessment. Finally, 35 patients with anterior circulation stroke were included in the analyses and evaluated using an automated pupillometer during monitoring.

Baseline characteristics and clinical information

We analyzed the clinical information and demographic variables, including age, sex, and vascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, atrial fibrillation, history of stroke, and pre-stroke functional status. The patients' diagnoses and lesion sites were assessed during admission. Neurological severity was evaluated using the Glasgow Coma Scale (GCS) at admission and every 4 hours during monitoring. Moreover, information regarding sedation therapy was collected during the monitoring period.

Measurement of quantitative pupillary reactivity

When the neurological symptoms were stable, quantitative pupil assessment was performed using NPi-100 Pupillometer (NeurOptics Inc.) every 4 hours by neurointensivists or neuroICU nurses in charge of the standard care of patients. The pupillometer parameters of maximum pupil size, percentage of constriction (%CH), constriction velocity (CV), maximum constriction velocity (MCV), dilation velocity (DV), latency (LAT), and NPi in the right and left eyes were recorded at 0:00, 4:00, 8:00, 12:00, 16:00, and 20:00 [1,2,4]. The values recorded at 20:00 were considered as the baseline, as the lights were turned off at 00:30 in the neuroICU. The pupillometer parameters were then paired with the GCS scores at each time point.

Statistical analysis

Baseline characteristics and clinical information were used for descriptive analysis. Nominal data are presented as frequencies (%), normally distributed continuous variables as means ± standard deviations, and non-normally distributed continuous variables as medians and interquartile ranges (IQRs). We compared the pupillometer parameters according to the lesion side of the stroke (ipsilateral side or contralateral side). Additionally, the change in the pupillometer parameters at different times during monitoring was analyzed using a linear mixed model with a random intercept model for repeated measures analysis, adjusting the GCS score at each time point of pupillary reactivity measurement as the fixed factor. Statistical significance was set at P-value < 0.05. All statistical analyses were conducted using IBM SPSS ver. 25.0 (IBM Corp.), Statistical Analysis Software 9.4 (SAS Institute Inc.), and GraphPad Prism (version 9, GraphPad Software).

RESULTS

Among the 35 included patients (mean age, 69.5 years; 62.9% men), 951 measurements of quantitative bilateral pupillary assessment were performed and analyzed. The baseline characteristics and clinical information are described in Table 1. Regarding diagnosis, 62.9% (n = 22) of the patients had ischemic stroke, and the rest had hemorrhagic stroke. The median initial GCS score at admission was 10 (IQR, 9–12). Functional independence before the index stroke was observed in 60.0% of the patients (modified Rankin Scale score = 0) (Table 1).

For the automated pupillometer parameters, the median number of pupillary measurements was 25 (IQR, 14–26) during the monitoring period. When comparing the pupillometer parameters between the lesion and contralateral sides, none of the parameters differed significantly, except the maximum pupil size. The maximum pupil size was significantly larger on the contralateral side than on the ipsilateral side at all times, although the difference was within 0.3 mm (Table 2). Table 3 shows the pupillometer

https://doi.org/10.18700/jnc.230030

Table 1. Baseline characteristics of the patients

Variable	Value (n=35)
Age (yr)	69.5±15.0
Male	22 (62.9)
Stroke type	
Ischemic stroke	22 (62.9)
Hemorrhagic stroke	13 (37.1)
Lesion side	
Right	14 (40.0)
Left	16 (45.7)
Bilateral	5 (14.3)
Initial GCS score	10 (9-12)
Hypertension	18 (51.4)
Diabetes mellitus	13 (37.1)
Dyslipidemia	8 (22.9)
Atrial fibrillation	13 (37.1)
Previous stroke	15 (42.9)
Coronary artery disease	4 (11.4)
Previous mRS score=0	21 (60.0)
Sedation during monitoring	5 (14.3)
Number of pupillometer assessments	25 (14–36)

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
GCS, Glasgow Coma Scale; mRS, modified Rankin Scale.

variables over 24 hours. Regarding the maximum pupil size, the baseline pupil size at 20:00 did not differ between the right and left pupils. At all monitoring times over 24 hours, the change in the maximum pupil size showed a significant diurnal variation (P for linear trend; right [Rt]: $P<0.001$, left [Lt]: $P=0.001$). The maximum pupil size bilaterally was significantly larger at 0:00 and 4:00 (Rt: 3.56±1.09 mm and 3.59±1.03 mm; Lt: 3.40±1.10 mm and 3.51±1.02 mm, respectively) than at 20:00 (Rt: 3.21±0.93 mm; Lt: 3.18±0.89 mm) (Table 3, Fig. 1). The baseline %CH values were similar in the bilateral pupils. As observed in the maximum pupil size, the %CH values were higher at 0:00 and 4:00 (Rt: 27.48±10.00 and 31.48±8.65; Lt: 27.56±10.51 and 31.42±9.45, respectively) than at 20:00 (Rt: 25.72±9.86, Lt: 24.98±10.45), with a significant diurnal variation observed (P for linear trend; Rt: $P<0.001$, Lt: $P<0.001$) (Table 3, Fig. 1). The LAT did not differ at any time point, regardless of the side. No significant differences in the baseline bilateral CV and MCV were observed at 20:00. The CV and MCV at 0:00 and 4:00 were significantly higher than the baseline values at 20:00, whereas those during the daytime did not change significantly. There were significant diurnal variations in the CV (P for linear trend; Rt: $P<0.001$, Lt: $P=0.001$) and MCV (P for linear trend; Rt: $P<0.001$, Lt: $P<0.001$) over 24 hours (Table 3, Fig. 1). The DV at baseline did not differ significantly between the right and left sides. Moreover, it showed a similar time trend as observed for the aforementioned parameters.

Table 2. Pupillometer parameters during the 24-hour monitoring period according to the lesion side

Time points	Ipsilateral side	Contralateral side	P-value
Maximum pupil size (mm)			
0:00	3.35±1.05	3.60±1.13	0.043
4:00	3.42±0.97	3.69±1.06	0.012
8:00	3.13±0.82	3.42±0.90	0.005
12:00	3.12±0.84	3.38±0.96	0.017
16:00	3.15±0.80	3.43±0.89	0.003
20:00	3.08±0.82	3.31±0.98	0.030
CH (%)			
0:00	27.19±9.88	27.73±10.63	0.629
4:00	31.12±8.53	31.72±9.48	0.520
8:00	25.32±9.42	27.40±10.00	0.066
12:00	25.47±9.45	27.32±9.84	0.111
16:00	26.35±9.20	27.01±10.54	0.545
20:00	25.13±9.98	25.54±10.32	0.729
LAT (sec)			
0:00	0.26±0.05	0.27±0.05	0.080
4:00	0.26±0.06	0.26±0.05	0.939
8:00	0.27±0.05	0.27±0.04	0.565
12:00	0.27±0.05	0.27±0.06	0.954
16:00	0.27±0.05	0.27±0.06	0.879
20:00	0.27±0.05	0.27±0.05	0.545
CV (mm/sec)			
0:00	1.77±0.89	1.85±0.95	0.422
4:00	1.93±0.82	2.01±0.84	0.355
8:00	1.66±0.94	1.83±0.98	0.129
12:00	1.68±0.89	1.83±0.90	0.172
16:00	1.73±0.87	1.84±0.97	0.289
20:00	1.62±0.93	1.71±0.98	0.441
MCV (mm/sec)			
0:00	3.00±1.28	3.10±1.34	0.460
4:00	3.32±1.18	3.46±1.31	0.304
8:00	2.71±1.30	2.99±1.39	0.082
12:00	2.76±1.25	2.97±1.26	0.177
16:00	2.78±1.23	2.89±1.42	0.452
20:00	2.66±1.40	2.78±1.49	0.469
DV (mm/sec)			
0:00	0.90±0.39	0.92±0.40	0.549
4:00	0.93±0.40	0.98±0.49	0.266
8:00	0.83±0.39	0.86±0.39	0.538
12:00	0.81±0.34	0.89±0.40	0.082
16:00	0.88±0.36	0.92±0.38	0.324
20:00	0.82±0.40	0.84±0.40	0.700
NPi score			
0:00	4.32±0.57	4.22±0.60	0.140
4:00	4.49±0.38	4.40±0.51	0.051
8:00	4.44±0.36	4.36±0.42	0.061
12:00	4.40±0.44	4.33±0.52	0.223
16:00	4.42±0.44	4.33±0.45	0.063
20:00	4.40±0.44	4.30±0.52	0.084

Values are presented as mean±standard deviation.
CH, constriction; LAT, latency; CV, constriction velocity; MCV, maximum constriction velocity; DV, dilation velocity; NPi, neurological pupil index.

Table 3. Change in the pupillometer parameters of acute stroke patients during 24 hours

Time points	Right eye	*P*-value[a]	Left eye	*P*-value[a]
Maximum pupil size (mm)				
20:00 (Baseline)	3.21±0.93	(ref)	3.18±0.89	(ref)
0:00	3.56±1.09	0.001	3.40±1.10	0.024
4:00	3.59±1.03	<0.001	3.51±1.02	<0.001
8:00	3.35±0.88	0.313	3.21±0.86	0.794
12:00	3.26±0.89	0.433	3.24±0.92	0.757
16:00	3.37±0.86	0.115	3.21±0.86	0.502
P for linear trend		<0.001		0.001
CH (%)				
20:00 (Baseline)	25.72±9.86	(ref)	24.98±10.45	(ref)
0:00	27.48±10.00	0.001	27.56±10.51	<0.001
4:00	31.48±8.65	<0.001	31.42±9.45	<0.001
8:00	26.67±9.13	0.122	25.80±10.16	0.340
12:00	26.42±9.61	0.349	26.47±9.81	0.461
16:00	27.13±9.60	0.282	26.24±10.18	0.391
P for linear trend		<0.001		<0.001
LAT (sec)				
20:00 (Baseline)	0.26±0.04	(ref)	0.27±0.05	(ref)
0:00	0.26±0.05	0.557	0.26±0.05	0.814
4:00	0.26±0.04	0.355	0.26±0.07	0.327
8:00	0.27±0.04	0.310	0.27±0.05	0.630
12:00	0.27±0.05	0.078	0.27±0.06	0.559
16:00	0.27±0.05	0.134	0.27±0.05	0.795
P for linear trend		0.062		0.400
CV (mm/sec)				
20:00 (Baseline)	1.68±0.94	(ref)	1.65±0.97	(ref)
0:00	1.83±0.89	0.007	1.80±0.95	0.023
4:00	1.97±0.80	<0.001	1.98±0.85	<0.001
8:00	1.78±0.93	0.234	1.70±1.00	0.805
12:00	1.73±0.85	0.311	1.78±0.94	0.397
16:00	1.82±0.91	0.129	1.75±0.94	0.437
P for linear trend		<0.001		0.001
MCV (mm/sec)				
20:00 (Baseline)	2.81±1.42	(ref)	2.65±1.50	(ref)
0:00	3.00±1.32	0.016	2.98±1.42	0.007
4:00	3.36±1.22	<0.001	3.35±1.36	<0.001
8:00	2.91±1.29	0.492	2.78±1.43	0.469
12:00	2.84±1.21	0.800	2.88±1.36	0.350
16:00	2.89±1.31	0.787	2.80±1.41	0.455
P for linear trend		<0.001		<0.001
DV (mm/sec)				
20:00 (Baseline)	0.84±0.41	(ref)	0.82±0.40	(ref)
0:00	0.90±0.42	0.026	0.88±0.42	0.143
4:00	0.97±0.50	<0.001	0.94±0.40	0.010
8:00	0.87±0.40	0.264	0.84±0.38	0.669
12:00	0.82±0.37	0.882	0.85±0.41	0.865
16:00	0.91±0.37	0.100	0.87±0.40	0.318
P for linear trend		0.002		0.038
NPi score				
20:00 (Baseline)	4.36±0.46	(ref)	4.33±0.53	(ref)
0:00	4.22±0.60	0.070	4.32±0.56	0.473
4:00	4.44±0.43	0.017	4.45±0.48	0.003
8:00	4.37±0.39	0.716	4.40±0.40	0.145
12:00	4.36±0.47	0.573	4.38±0.50	0.459
16:00	4.33±0.50	0.277	4.37±0.48	0.766
P for linear trend		0.718		0.040

Values are presented as mean±standard deviation.

ref, reference; CH, constriction; LAT, latency; CV, constriction velocity; MCV, maximum constriction velocity; DV, dilation velocity; NPi, neurological pupil index.

All *P*-values are calculated using a linear mixed-effect model with a random intercept model for repeated measures analysis. [a]*P*-value for mean difference between 20:00 (baseline) time and each time point in 24 hours.

https://doi.org/10.18700/jnc.230030

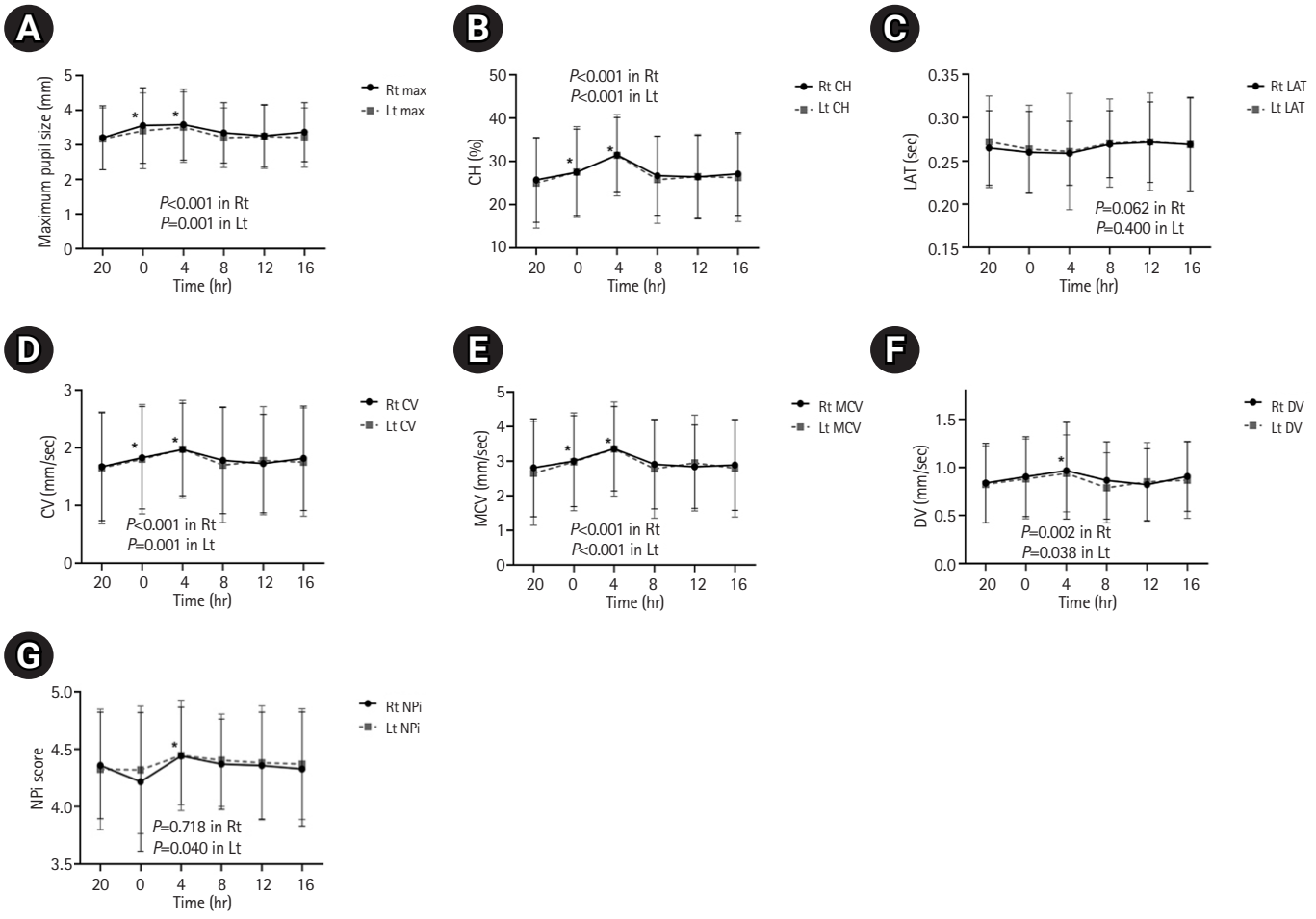

Fig. 1. Variations in the pupillometer parameters over 24 hours: (A) maximum pupil size, (B) percentage of constriction (%CH), (C) latency (LAT), (D) constriction velocity (CV), (E) maximum constriction velocity (MCV), (F) dilation velocity (DV), (G) neurological pupil index (NPi). Quantitative pupillometry was performed every 4 hours using the NPi-100 pupillometer. Significant diurnal variations are observed in the maximum pupil size, %CH, CV, MCV, and DV during the 24-hour period. The pupillometer parameters, including maximum pupil size, %CH, CV, MCV, and DV show a gradual increase after 20:00 (baseline); the values recorded at 04:00 AM are the highest, whereas those recorded at 20:00 are the lowest. *P*-value in right (Rt) and left (Lt): *P* for linear trend. **P*<0.05.

The DV at 0:00 and 4:00 was higher than that at 20:00, with a significant diurnal variation (*P* for linear trend; Rt: $P=0.002$, Lt: $P=0.038$) (Table 3, Fig. 1). The baseline NPi scores were similar on the right (4.36 ± 0.46) and left (4.33 ± 0.53) sides ($P=0.564$). No significant diurnal variations were observed in the right NPi score, although the left NPi score changed significantly over time; the left NPi score at 4:00 was higher than that at 20:00. Among the patients, five (14.3%) were administered dexmedetomidine during the monitoring period. We found that the trend of the PLR changes (largest pupil size at 04:00 and smallest size at 20:00) did not differ between the patients with and without dexmedetomidine treatment, suggesting that the dynamics of the pupillary variables were not affected by the use of dexmedetomidine (Supplementary Table 1).

DISCUSSION

This study identified the time-of-day effect on pupillary parameters in large hemispheric stroke patients with stable neurological conditions. The maximum pupil size, %CH, CV, MCV, and DV were significantly higher during the night than during the day or evening; however, no sudden drop or significant change was identified in the pupillary parameters during the 24-hour monitoring.

Serial pupil examination is a basic but critical neurological examination performed in the neuroICU. In particular, quantitative assessment of the PLR using an automated pupillometer is a reliable and objective method for monitoring pupillary reactivity. Pupillometer assessment parameters, such as the NPi and CV, are reportedly sensitive to changes in neurological deterioration,

which allows rapid diagnosis and evaluation of intracranial pathology and outcomes that assist in clinical decision-making following acute brain injuries [1-4,6,7,14-16]. Pupillometer parameters on the ipsilateral and contralateral sides were similar. However, the maximum pupil size was larger on the contralateral side than on the ipsilateral side. The maximum pupil size was within the normal range, and the observed difference between the contralateral and ipsilateral sides (less than 0.3 mm) was within the range of physiological anisocoria [17]. Changes in the PLR over 24 hours are influenced by lighting, circadian phase, balance in sympathetic and parasympathetic pathways, and sleepiness in everyday environments [13,18,19]. Previous studies investigating pupillary reactivity and pupil size over time have shown that pupil size increases at night, possibly due to alterations in the amount of light or changes in the circadian rhythm [8-10,19-21]. In contrast, other studies revealed that pupil size is dependent on the degree of sleepiness rather than the circadian phase [10,20,21]. Similarly, the relationship between pupillary dynamics and the time-of-day effect remains unclear, and no studies have investigated the diurnal variation in the pupillary parameters based on the pupillometer assessment of neurologically stable patients with large hemispheric stroke. This study revealed that pupil size was significantly larger at night, especially at 04:00, than during the day or evening (baseline value at 20:00), which corroborates the results of previous studies [8,9]. The pupillary parameters, including %CH, CV, MCV, and DV, gradually increased after 20:00; the highest values were recorded at 4:00 and the lowest at 20:00 over 24 hours, and these values could be associated with changes in pupil size. However, all pupillometer parameters had symmetric normative values with small oscillations over 24 hours.

Pupillary reactivity over 24 hours in large hemispheric stroke patients could be affected by modified circadian rhythms, light, and stimuli secondary to the environment in the neuroICU [18,19,22,23]. The circadian rhythm is affected by external stimuli, and critically ill patients commonly experience disrupted physiological circadian rhythms. Potential factors contributing to alterations in circadian rhythmicity in neuroICU patients include nocturnal light exposure, noise, altered feeding schedules, disease severity, scheduled nursing care, and sedative medications [22-24]. Therefore, pupil dynamics in the neuroICU may have been affected by the neuroICU environment influencing the patients' circadian rhythms [18,19,22-25]. Additionally, pupil dynamics during the 24-hour cycle could be influenced by ambient light levels in the neuroICU. Ambient light levels in the neuroICU are usually controlled using artificial light with minimal sunlight impact [26]. Therefore, the schedule for turning lights on and off should be considered when interpreting the results. At our center, the lights were dimmed from 0:30 to 6:00 and switched on and maintained at the same level for the remaining time. The changes in the light level during the night might have affected the maximum pupil size and robust pupillary constriction response at 4:00. However, the trend of %CH showed an increase at 0:00 compared to the baseline value at 20:00 before the light level decreased, which suggests that the pupillary changes were not merely due to alterations in ambient light. Furthermore, the amount of sedative medication should be considered when interpreting changes in the PLR in the neuroICU [1,23]. In this study, the trends of the pupillometer parameters over time were similar in patients treated with and without sedative drugs.

This study has several limitations. First, this was a retrospective study with a small number of patients; therefore, an unmeasured bias may exist. Second, we did not evaluate the actual circadian rhythms in individual patients by assessing the melatonin levels. However, all patients were subjected to the same light and dark cycles in the same neuroICU environment. Third, we did not evaluate the intensity of ambient light in the neuroICU, which may have affected the pupillary reactivity. However, the light-on/light-off timings were regular and similar for all the patients. Therefore, the time-of-day effect related to light intensity on the changes in the PLR was similar for all included patients. Fourth, the level of consciousness and sedative drugs may have affected the PLR dynamics during the monitoring period. Therefore, we adjusted the GCS score at each time point for PLR monitoring using a linear mixed model analysis to minimize these effects.

Moreover, treatment with sedation demonstrated similar time trends in the PLR of patients over 24 hours. Fifth, medical conditions and underlying diseases, such as retinopathy associated with diabetes mellitus, have the potential to affect the pupillometer parameters. Finally, the results were based on neurocritically ill patients who required repetitive pupillary assessments. Changes in pupillary dynamics may differ among healthy individuals. Additionally, most patients had a large hemispheric stroke, which may have affected the results. However, we do not think that the changes in pupillary values were merely due to alterations in neurological conditions because none of the patients experienced neurological worsening over the monitoring period, and the NPi scores did not deteriorate even with larger pupil sizes.

In conclusion, diurnal variations occurred in the pupillometer parameters over 24 hours in large hemispheric stroke patients who were in a stable neurological condition. However, all changes were within the normal ranges, with small oscillations. Therefore, transient changes in the PLR and physiological changes within normal ranges may be acceptable during neurological monitoring

https://doi.org/10.18700/jnc.230030

in neurologically critical patients. Additionally, serial monitoring of the PLR, regardless of the development of significant changes, could be a helpful tool for the neurological monitoring of large hemispheric stroke patients. Further large-scale studies are required to elucidate the relationship between the PLR parameters and time over 24 hours.

ARTICLE INFORMATION

Ethics statement

This study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (No. H-1009-062-332). The need for informed consent was waived by the IRB of Seoul National University Hospital because of the retrospective nature of the study. All methods were conducted in accordance with the relevant guidelines and regulations of the IRB of the Seoul National University Hospital.

Conflict of interest

Tae Jung Kim is the editor-in-chief, and Ji Sung Lee, Soo-Hyun Park, and Sang-Bae Ko are editorial board members of the journal. However, they were not involved in the peer reviewer selection, evaluation, or decision-making process for this article. No other potential conflicts of interest relevant to this article have been reported.

Acknowledgments

This study was supported by the Seoul National University Hospital (No. 0320210030).

ORCID

Tae Jung Kim	https://orcid.org/0000-0003-3616-5627
Ji Sung Lee	https://orcid.org/0000-0001-8194-3462
Soo-Hyun Park	https://orcid.org/0000-0003-1626-3940
Sang-Bae Ko	https://orcid.org/0000-0002-9429-9597

Author contributions

Conceptualization: TJK, SBK. Methodology: TJK, JSL, SBK. Software: TJK, JSL. Supervision: SBK. Validation: SHP. Formal analysis: TJK, JSL. Investigation: TJK, SHP. Resources: TJK, SBK. Data curation: TJK. Visualization: TJK. Project administration: TJK, SBK. Funding acquisition: SBK. Writing–original draft: TJK. Writing–review & editing: TJK, SBK.

Supplementary materials

Supplementary materials can be found via https://doi.org/10.18700/jnc.230030.

REFERENCES

1. Lussier BL, Olson DM, Aiyagari V. Automated pupillometry in neurocritical care: research and practice. Curr Neurol Neurosci Rep 2019;19:71.
2. Zhao W, Stutzman S, DaiWai O, Saju C, Wilson M, Aiyagari V. Inter-device reliability of the NPi-100 pupillometer. J Clin Neurosci 2016;33:79-82.
3. Larson MD, Singh V. Portable infrared pupillometry in critical care. Crit Care 2016;20:161.
4. Kim TJ. Quantitative assessments of pupillary light reflexes in neurocritically ill patients. J Neurocrit Care 2022;15:79-87.
5. Kim TJ, Park SH, Jeong HB, Ha EJ, Cho WS, Kang HS, et al. Neurological pupil index as an indicator of neurological worsening in large hemispheric strokes. Neurocrit Care 2020;33:575-81.
6. Chen JW, Gombart ZJ, Rogers S, Gardiner SK, Cecil S, Bullock RM. Pupillary reactivity as an early indicator of increased intracranial pressure: the introduction of the Neurological Pupil index. Surg Neurol Int 2011;2:82.
7. Oddo M, Sandroni C, Citerio G, Miroz JP, Horn J, Rundgren M, et al. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. Intensive Care Med 2018;44:2102-11.
8. Daguet I, Bouhassira D, Gronfier C. Baseline pupil diameter is not a reliable biomarker of subjective sleepiness. Front Neurol 2019;10:108.
9. Wilson MH, Edsell M, Imray C, Wright A; Birmingham Medical Research Expeditionary Society. Changes in pupil dynamics at high altitude: an observational study using a handheld pupillometer. High Alt Med Biol 2008;9:319-25.
10. Münch M, Léon L, Crippa SV, Kawasaki A. Circadian and wake-dependent effects on the pupil light reflex in response to narrow-bandwidth light pulses. Invest Ophthalmol Vis Sci 2012;53:4546-55.
11. Wilhelm B, Giedke H, Lüdtke H, Bittner E, Hofmann A, Wilhelm H. Daytime variations in central nervous system activation measured by a pupillographic sleepiness test. J Sleep Res 2001;10:1-7.
12. Eggert T, Sauter C, Popp R, Zeitlhofer J, Danker-Hopfe H; "Vigilance" of the German Society for Sleep Research and Sleep Medicine (DGSM). The pupillographic sleepiness test in adults: effect of age, gender, and time of day on pupillometric variables. Am J Hum Biol 2012;24:820-8.
13. Mathôt S. Pupillometry: psychology, physiology, and function. J Cogn 2018;1:16.

14. Couret D, Boumaza D, Grisotto C, Triglia T, Pellegrini L, Ocquidant P, et al. Reliability of standard pupillometry practice in neurocritical care: an observational, double-blinded study. Crit Care 2016;20:99.
15. Lee MH, Mitra B, Pui JK, Fitzgerald M. The use and uptake of pupillometers in the intensive care unit. Aust Crit Care 2018; 31:199-203.
16. Lussier BL, Stutzman SE, Atem F, Venkatachalam AM, Perera AC, Barnes A, et al. Distributions and reference ranges for automated pupillometer values in neurocritical care patients. J Neurosci Nurs 2019;51:335-40.
17. Payne WN, Blair K, Barrett MJ. Anisocoria [Internet]. StatPearls Publishing; 2023 [cited 2023 Oct 20]. Available from: https://pubmed.ncbi.nlm.nih.gov/29261943/
18. Biaggioni I. Circadian clocks, autonomic rhythms, and blood pressure dipping. Hypertension 2008;52:797-8.
19. Loving RT, Kripke DF, Glazner LK. Circadian rhythms in the human pupil and eyelid. Am J Physiol 1996;271(2 Pt 2): R320-4.
20. Wilhelm H, Lüdtke H, Wilhelm B. Pupillographic sleepiness testing in hypersomniacs and normals. Graefes Arch Clin Exp Ophthalmol 1998;236:725-9.
21. Van Egroo M, Gaggioni G, Cespedes-Ortiz C, Ly JQ, Vandewalle G. Steady-state pupil size varies with circadian phase and sleep homeostasis in healthy young men. Clocks Sleep 2019; 1:240-58.
22. Jobanputra AM, Scharf MT, Androulakis IP, Sunderram J. Circadian disruption in critical illness. Front Neurol 2020;11:820.
23. Telias I, Wilcox ME. Sleep and circadian rhythm in critical illness. Crit Care 2019;23:82.
24. Lusczek ER, Knauert MP. Light levels in ICU patient rooms: dimming of daytime light in occupied rooms. J Patient Exp 2021;8:23743735211033104.
25. von Gall C. The effects of light and the circadian system on rhythmic brain function. Int J Mol Sci 2022;23:2778.
26. Ong C, Hutch M, Smirnakis S. The effect of ambient light conditions on quantitative pupillometry. Neurocrit Care 2019;30: 316-21.

https://doi.org/10.18700/jnc.230030

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):77-84
https://doi.org/10.18700/jnc.230029

Journal of Neurocritical Care

Is the mechanism of synchronous cardiocerebral infarction (CCI) different from that of metachronous CCI?

Seonjeong Kim, MD[1]; Hyein Chung, MD[1]; Yoonkyung Lee, MD[1]; Byeol-A Yoon, MD, PhD[1,2]; Dae Hyun Kim, MD, PhD[1,2]; Jin-Heon Jeong, MD[1,2,3]; Jae-Kwan Cha, MD, PhD[1,2]

[1]Department of Neurology, Dong-A University Hospital, Busan, Korea
[2]Stroke Center, Dong-A University Hospital, Busan, Korea
[3]Department of Intensive Care Medicine, Dong-A University Hospital, Busan, Korea

ORIGINAL ARTICLE

Received: August 22, 2023
Revised: October 27, 2023
Accepted: October 28, 2023

Corresponding Author:
Jae-Kwan Cha, MD, PhD
Department of Neurology, Dong-A University Hospital, 26 Daesingongwon-ro, Seo-gu, Busan 49201, Korea
Tel: +82-51-240-5266
Fax +82-51-244-8338
Email: nrcjk65@gmail.com

Background: Cardiocerebral infarction (CCI) is the simultaneous occurrence of acute ischemic stroke (AIS) and myocardial infarction (MI) at the same time (synchronous), or one after another (metachronous). This study aimed to investigate the differences in the underlying mechanisms between synchronous and metachronous CCI.

Methods: This study analyzed patients with AIS registered in the Clinical Research Collaboration for Stroke in Korea Prospective Registry at a single Stroke Center from January 2019 to December 2022. Patients with synchronous and metachronous CCI (MI within 72 hours after AIS) were included. Severity at admission and modified Rankin Scale scores 3 months after treatment were assessed.

Results: Among 3,319 AIS patients, 12 (0.36%) were diagnosed with acute CCI (male, 8; mean age, 69.6±14.0 years). Of these, six (0.18%) had synchronous CCI, while the other six had metachronous CCI. The synchronous CCI group exhibited lower neurological severity at admission than the metachronous CCI group (median National Institutes of Health Stroke Scale, 3.5 vs. 12.5). Among the 12 patients, seven (58%) had ST-elevation myocardial infarction (STEMI), with five (83%) of the synchronous CCI cases presenting as STEMI. Two cases of new-onset atrial fibrillation occurred exclusively in patients with synchronous CCI. Also, one case with synchronous CCI had a thrombus in the left ventricle.

Conclusion: Acute CCI is rare and manifests with varying degrees of severity. Our study suggests that AIS in synchronous CCI may be secondary to embolism caused by a preceding MI. In contrast, metachronous CCI exhibits diverse mechanisms, including secondary myocardial injury resulting from a preceding severe AIS.

Keywords: Cardiocerebral infarction; Ischemic stroke; Myocardial infarction; Management

INTRODUCTION

Acute cardiocerebral infarction (CCI) is a rare, life-threatening condition in which both acute ischemic stroke (AIS) and myocardial infarction (MI) occur simultaneously [1,2]. Recently, researchers categorized acute CCI into two subtypes based on the timing of its occurrence: synchronous CCI and metachronous CCI [3]. Synchronous CCI is a simultaneous infarction in the cerebral and coronary vascular territories, whereas metachronous CCI occurs when one event precedes the other, regardless of the

order of AIS and MI [2]. Metachronous CCI has been documented to occur in a range of 0.9% to 12.7% [4,5], whereas synchronous CCI is extremely rare, with a prevalence rate of 0.9% [6]. In particular, in a 3-year prospective study of patients with acute cerebrovascular accidents admitted to a geriatric unit within 72 hours of onset, 12.7% were found to have what was considered to be associated with acute MI [7].

Prompt intervention and revascularization are essential for optimal treatment of both AIS and MI. However, there are currently no definitive guidelines for determining the priority of treating one condition over another. Although there are similarities in the treatment approaches for AIS and MI, slight variations in reperfusion treatment indications, medications, and dosage selection can add complexity to the emergency physician's decision-making process and hinder prompt decision making [3].

For these reasons, the mortality rate associated with acute CCI is high. However, comprehensive studies regarding this condition are lacking [8]. Furthermore, despite the distinct differences in the timing of occurrence between synchronous and metachronous CCI, it remains unclear whether there is a difference in the underlying mechanisms between these two forms of CCI. To address these uncertainties, we aimed to determine the underlying mechanisms of the two distinct forms of acute CCI, synchronous CCI and metachronous CCI, by analyzing the clinical characteristics, patterns of MI occurrence, mechanisms of AIS, and outcomes of acute CCI patients enrolled in the Clinical Research Collaboration for Stroke in Korea (CRCS-K) registry [9] at a single Stroke Center.

METHODS

This study focused on patients with AIS who were prospectively registered in the CRCS-K registry at a single Stroke Center between January 1, 2019, and December 31, 2022. This study complied with the principles of the Declaration of Helsinki.

We included adults aged 18 and above, who were diagnosed with AIS and MI. The times of occurrence and hospital admission for AIS and MI were recorded. The timing of AIS occurrence was determined based on the onset time of neurological symptoms or the last normal time, whereas the timing of MI occurrence was established using clinical symptoms, cardiac enzyme elevation, or evidence of MI on electrocardiography or echocardiography.

The participants were categorized into two groups based on the timing of occurrence. Patients who exhibited both AIS and MI simultaneously upon arrival at the emergency room were grouped as having synchronous CCI. In contrast, patients who developed MI within 72 hours of admission for AIS were grouped as having metachronous CCI. The interval between AIS and MI in metachronous CCI was determined as described by Chin et al. [7].

Demographic data, vascular risk factors, medical history, including atrial fibrillation, coronary heart disease, and prior antithrombotic use were investigated. The severity of stroke upon admission in patients with AIS was assessed using the National Institutes of Health Stroke Scale (NIHSS). Stroke type was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification with certain modifications. The TOAST classification was applied using a magnetic resonance imaging-based algorithm for AIS subtype classification (MAGIC) [10]. All patients with CCI experienced recent MI, which could be regarded as a major source of cardioembolism. However, only cases that met the differential criteria outlined by MAGIC were considered to have cardioembolic mechanisms.

We collected laboratory test results, including cardiac troponin I levels, which were within the normal range (< 0.034 ng/mL). The type of MI (ST elevation and non-ST-segment elevation) was noted. Ejection fraction (EF) was classified into preserved (EF ≥ 50%), mid-range (40%–49% EF), and reduced (< 40% EF), and presence of thrombus was confirmed on echocardiogram in the emergency room.

We reviewed the implementation of reperfusion therapies such as intravenous thrombolysis, mechanical thrombectomy, and percutaneous coronary intervention. We also investigated whether craniectomy could be performed due to the progression of brain edema in patients with malignant cerebral infarction. The functional and mortality outcomes of the participants were analyzed using the modified Rankin Scale (mRS) score at the 3-month follow-up after hospital admission. A poor functional outcome was defined as an mRS of 3–6. The cause of death was determined and documented in the deceased patients.

Variables were summarized as frequency and percentage for categorical data and mean ± standard deviation and median (range) for numeric data. Group differences were tested using Fisher's exact test for categorical data and the Mann-Whitney *U*-test for numeric data, as appropriate. Outcome incidence rates according to the CCI group were analyzed using Exact Poisson Regression. All statistical analyses were performed using STATA 18.0, statistical software (StataCorp.), and a *P*-value less than 0.05 was considered statistically significant.

RESULTS

During the study period, 3,319 patients with AIS were registered in the CRCS-K registry at a single Stroke Center. Among these, 12 (0.36%) were diagnosed with acute CCI. Of these, six patients (0.18%) were classified into the simultaneous CCI group, and the

https://doi.org/10.18700/jnc.230029

remaining six patients (0.18%) were classified into the metachronous CCI group (Table 1). Among the 12 patients with acute CCI, 7 had ST-elevation myocardial infarction (STEMI), while the remaining 5 had non–ST-elevation myocardial infarction (NSTEMI). The mean age of the 12 patients with acute CCI was 69.6±14.0 years, and the initial median NIHSS was 5, ranging from 0 to 18. The average time from onset-to-door for these patients was 531.7±511.8 minutes, ranging from 57 to 1,440 minutes.

When comparing basic demographics, clinical characteristics, and laboratory findings between patients with synchronous and metachronous CCI, no statistically significant differences were observed. However, patients with metachronous CCI had a higher prevalence of advanced age, greater burden of vascular risk factors, and a higher incidence of previous antithrombotic medication use than those with synchronous CCI. Additionally, synchronous CCI patients, with an initial median NIHSS score of 3.5, tended to have lower neurological severity at admission than metachronous CCI patients, whose initial median NIHSS score was 12.5. According to the MAGIC classification, synchronous CCI is more often associated with cardioembolism than with other mechanisms. Furthermore, the synchronous CCI group exhibited a higher incidence of STEMI than the metachronous CCI group. In our study, both cases of new-onset atrial fibrillation occurred in patients with synchronous CCI. Additionally, a left ventricular thrombus was observed in one patient with synchronous CCI on echocardiography. We also detailed the clinical characteristics of the 12 patients diagnosed with CCI (Table 2).

Reperfusion therapy for AIS was administered to six individuals (50%), four of whom had metachronous CCI (Table 3). Craniectomy was performed in one patient with metachronous CCI. All

Table 1. Clinical profile of patients with cardiocerebral infarction

Variable	Overall (n=12)	Synchronous (n=6)	Metachronous (n=6)	*P*-value
Age (yr)	69.6±14	62.3±13	76.8±12	0.09[a]
Male	8 (67)	5 (83)	3 (50)	0.55[b]
Hypertension	9 (75)	3 (50)	6 (100)	0.18[b]
Diabetes mellitus	5 (42)	2 (33)	3 (50)	1.00[b]
Dyslipidemia	6 (50)	2 (33)	4 (67)	0.57[b]
Smoking	5 (42)	3 (50)	2 (33)	1.00[b]
Pre-existing atrial fibrillation	0	0	0	-
History of coronary artery disease	3 (25)	0	3 (50)	0.18[b]
Prior use of antithrombotics				0.18[b]
None	9 (75)	6 (100)	3 (50)	
Single antiplatelet	2 (17)	0	2 (33)	
Dual antiplatelet	1 (8)	0	1 (17)	
Acute ischemic stroke onset-to-door time				1.00[b]
≤6 hr	5 (42)	3 (50)	2 (33)	
>6 hr	7 (58)	3 (50)	4 (67)	
NIHSS on admission	5 (0–18)	3.5 (0–18)	12.5 (2–17)	0.26[a]
TOAST classification				0.26[b]
Large artery atherosclerosis	4 (33)	2(33)	2 (33)	
Small vessel occlusion	1 (8)	0	1 (17)	
Cardioembolism	5 (42)	4(66)	1 (17)	
Other determined	1 (8)	0	1 (17)	
Undetermined	1 (8)	0	1 (17)	
Type of MI				0.24[b]
ST elevation MI	7 (58)	5 (83)	2 (33)	
Non-ST elevation MI	5 (42)	1 (17)	4 (67)	
Ejection fraction in echocardiogram				1.00[b]
Reduced (<40%)	5 (42)	3 (50)	2 (33)	
Mid-range (40%–50%)	3 (25)	1 (17)	2 (33)	
Preserved (≥50%)	4 (33)	2 (33)	2 (33)	
New-onset atrial fibrillation	2 (17)	2 (33)	0	0.46[b]
Presence of thrombus	1 (8)	1 (17)	0	1.00[b]

Values are presented as mean±standard deviation, number (%), or median (range).
NIHSS, National Institutes of Health Stroke Scale; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; MI, myocardial infarction.
P-values were derived using [a]Mann-Whitney's *U*-test and [b]Fisher's exact test.

Table 2. Clinical features data for 12 patients with CCI

Patient no./sex/age (yr)	Risk factor	Acute ischemic stroke				Initial V/S		Initial lab			Acute MI			Etc
		Vascular territory	Insular involvement	NIHSS	TOAST	BP	HR	Glucose (mg/dL)	LDL-C (mg/dL)	Troponin-I (ng/mL)	Type	Lesion location	EF (%)	
Synchronous CCI														
1/M/44	DM, DL	Lt. PICA	No	0	CE	130/80	104	271	130	2.395	NSTEMI	dRCA, RCA-PL	25	DCMP
2/M/81	HTN	TIA	No	2	CE	110/60	68	107	100	0.059	STEMI	dLAD	55	New AF
3/M/64	Smk	Rt. MCA	Yes	5	LAA	130/80	95	92	135	27.299	STEMI	mRCA, dLCX pLAD, mLAD	35	
4/F/71	HTN, DM, DL	Lt. ACA	No	18	CE	140/70	95	304	84	13.560	STEMI	mRCA	70	New AF
5/M/56	HTN, Smk	Lt. MCA	Yes	5	CE	130/90	77	441	116	5.503	STEMI	pLAD	30	LV thrombus
6/M/58	Smk	Rt. MCA	No	1	LAA	130/70	76	172	185	0.020	STEMI	dRCA	40	
Metachronous CCI														
7/F/86	HTN, DM, DL	Posterior circulation	No	17	LAA	180/100	72	169	117	1.198	NSTEMI	pRCA, mLAD, dLCX	40	Expired d/t sepsis
8/M/62	3VD (stent) HTN, DM, DL, Smk	Rt. MCA	Yes	14	Undetermined incomplete	140/80	88	218	93	0.003	STEMI	mLAD, LAD OS	50	Craniectomy
9/F/81	3VD (CABG) HTN, DL	Lt. MCA	Yes	2	LAA	140/90	100	146	65	1.449	NSTEMI	SVG to OM	30	
10/M/93	HTN	Lt. MCA	No	11	SVO	180/100	83	101	63	0.027	NSTEMI	dRCA	45	
11/M/69	MI (stent) HTN, DL, Smk	Multiple	No	2	Other determined (pancreatic ca)	120/80	79	175	60	0.202	NSTEMI	dRCA	55	Expired d/t sepsis
12/F/70	HTN, DM	Lt. MCA	No	15	CE	160/100	56	108	55	1.081	STEMI	LCX OS, pLAD	30	Expired d/t AHF

CCI, cardiocerebral infarction; NIHSS, National Institutes of Health Stroke Scale; TOAST, the Trial of Org 10172 in Acute Stroke Treatment; V/S, vital sign; BP, blood pressure; HR, heart rate; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; EF, ejection fraction; DM, diabetes mellitus; DL, dyslipidemia; Lt, left; PICA, posterior inferior cerebellar artery; NSTEMI, non–ST-elevation myocardial infarction; dRCA, distal segment of right coronary artery; RCA-PL, right coronary artery posterolateral segment; DCMP, dilated cardiomyopathy; HTN, hypertension; TIA, transient ischemic attack; STEMI, ST-elevation myocardial infarction; dLAD, distal segment of left anterior descending artery; AF, atrial fibrillation; Smk, smoking; Rt, right; MCA, middle cerebral artery; mRCA, middle segment of right coronary artery; dLCX, distal segment of left circumflex artery; pLAD, proximal segment of left anterior descending artery; mLAD, middle segment of left anterior descending artery; ACA, anterior cerebral artery; LV thrombus, left ventricular thrombus; pRCA, proximal segment of right coronary artery; d/t, due to; VD, vessel disease; LAD OS, left anterior descending artery ostium; CABG, coronary artery bypass grafting; SVG, saphenous vein graft; OM, obtuse marginal branch; LCX OS, left circumflex artery ostium; AHF, acute heart failure.

https://doi.org/10.18700/jnc.230029

patients with acute CCI underwent percutaneous coronary intervention. No statistically significant differences were observed when comparing reperfusion therapy between synchronous and metachronous CCI.

In the assessment of the functional outcome of 12 cases of acute CCI at 3 months, six patients (50%) experienced a poor outcome, as indicated by an mRS score of 3 to 6 (Table 4). Notably, the rate of poor functional outcomes at three months was higher in the metachronous CCI group (83%) than in the synchronous CCI group (17%). Mortality occurred in three cases, all of which were observed in patients with metachronous CCI. One of these three patients died from cardiovascular causes, while the other two patients died from sepsis. There were no statistically significant differences according to Fisher's exact test. We conducted exact Poisson regression analysis to further evaluate the outcomes. The incidence of poor functional outcome at discharge was higher in metachronous CCI group compared with synchronous CCI group (relative risk [RR], 2.00; 95% confidence interval [CI], 0.29–22.11; $P=0.69$) Also, the incidence of poor functional outcome at 3 months was higher in metachronous CCI group compared with synchronous CCI group. (RR, 5.00; 95% CI, 0.56–236.49; $P=0.22$) Finally, the incidence of all-cause mortality was higher in metachronous CCI group compared with synchronous CCI group. (RR, 3.85; 95% CI, 0.41–infinite; $P=0.25$) Although there were no statistically significant results, it was confirmed that the metachronous CCI group had a higher incidence of poor functional outcomes.

DISCUSSION

Our study showed that the incidence of acute CCI was 0.36%, with synchronous CCI accounting for 0.18% of the cases, indicating a relatively rare occurrence. While the previously reported frequency of synchronous CCI is cited as 0.009% based on Yeo's publication, upon reviewing Yeo's report [6], it is evident that out of 555 patients with AIS, five cases of synchronous CCI were observed, resulting in an accurate figure of 0.9%.

In this study, several distinct differences were observed between synchronous and metachronous CCI beyond the timing of occurrence. First, patients with synchronous CCI were younger than those with metachronous CCI and exhibited lower neurological severity at the time of AIS occurrence. Second, the incidence rate of STEMI was higher in the synchronous CCI group (83%) than in the metachronous CCI group (33%). Third, new-onset atrial fibrillation and intraventricular thrombosis on echocardiography were only found in patients with synchronous CCI.

According to a previous report by Wang et al. [1], the pathogenesis of acute CCI can be categorized into two main mechanisms. First, it can be attributed to cardiac causes such as atrial fibrillation. Secondly, this may have resulted from brain causes.

Table 3. Management of cardiocerebral infarction

Variable	Overall (n=12)	Synchronous (n=6)	Metachronous (n=6)	*P*-value
Reperfusion therapy				
Intravenous thrombolysis	3 (25)	1 (17)	2 (33)	1.00
Mechanical thrombectomy	2 (17)	1 (17)	1 (17)	1.00
Intravenous thrombolysis + mechanical thrombectomy	1 (8)	0	1 (17)	1.00
Craniectomy	1 (8)	0	1 (17)	1.00
Percutaneous coronary intervention	12 (100)	6 (100)	6 (100)	-

Values are presented as number (%). *P*-values were derived using the Fisher's exact test.

Table 4. Outcomes of patients with cardiocerebral infarction

Variable	Overall (n=12)	Synchronous (n=6)	Metachronous (n=6)	*P*-value
Functional outcome				
Poor functional outcome at discharge (mRS 3–6)	6 (50)	2 (33)	4 (67)	0.57
Poor functional outcome at 3 month (mRS 3–6)	6 (50)	1 (17)	5 (83)	0.08
Mortality outcome				
All-cause mortality	3 (25)	0	3 (50)	0.18
Cardiovascular	1 (8)	0	1 (17)	1.00
Stroke death	0	0	0	-
Others	2 (17)	0	2 (33)	0.46

Values are presented as number (%). *P*-values were derived using the Fisher's exact test.
mRS, modified Rankin Scale.

Specifically, in cases of brain damage, neurological damage caused by AIS is involved, and there is an interplay known as stroke-heart crosstalk, which includes the hypothalamic-pituitary-adrenal axis, immune and inflammatory responses, and various risk factors (such as age, sex, race, hypertension, smoking, diet, and physical inactivity) primarily involved in the pathogenesis of AIS [11,12]. Ultimately, these reactions act as cardiac burdens, leading to cardiac arrhythmias and potentially triggering MI. Indeed, myocardial damage following AIS is associated with specific brain regions such as the insular cortex. However, it is mostly observed in patients with moderate-to-severe AIS and typically occurs approximately 24 hours after stroke onset [13,14]. This suggests that metachronous CCI is associated with a higher risk of MI following a preceding stroke.

In this study, it was observed that the cardiac troponin-I levels were elevated in all acute CCI patients tested in the emergency room. Specifically, even in patients with metachronous CCI, these levels were elevated. Therefore, in patients with AIS presenting to the emergency room with an increase in cardiac troponin I levels, it is important to consider intensive cardiac evaluations, even in the absence of other findings suggestive of MI.

In this study, all three cases of new-onset atrial fibrillation occurred in patients with synchronous CCI. Atrial fibrillation has been reported as a potential cause of simultaneous CCI because it is a common source of both cerebral and coronary embolisms [4,6]. Furthermore, in synchronous CCI, echocardiography performed in the emergency room revealed the presence of a left ventricular thrombus in one patient. Additionally, the frequency of STEMI was significantly higher in the synchronous CCI group than in the metachronous CCI group.

When blood clots form at the site of cardiac muscle damage, they may cause left ventricular stenosis or a left ventricular thrombus. The incidence of left ventricular thrombus following acute MI is reported to be 20%–40%. In particular, patients with STEMI have been reported to be more likely to have a left ventricular thrombus than patients with NSTEMI (43.1% vs. 5.0%) [15]. Also, a left ventricular thrombus may be a potential risk factor for an embolic source. These findings suggest the possibility that synchronous CCI is caused by cardiac factors. However, more detailed research is required to clearly demonstrate this sequential relationship.

In this study, the mean age of patients with synchronous CCI was lower than that of patients with metachronous CCI. Considering the general fact that the average age of the patients with MI was lower than that of the patients with AIS, this suggests the possibility of a closer association between synchronous CCI and cardiac causes. Interestingly, despite the higher likelihood of synchronous CCI patients having conditions caused by cardiac factors, their neurological severity is comparatively lower, and most patients primarily complain of stroke symptoms, such as hemiparesis, rather than symptoms suggestive of MI. Symptoms such as chest pain, commonly associated with MI, may go unnoticed in stroke patients and can be attributed to the following factors. (1) Stroke-related brain damage can affect the central nervous system, leading to impaired transmission of sensory signals related to cardiac pain. (2) Stroke-induced changes in consciousness or a state of confusion can prevent the perception of cardiac pain [3,16].

In this study, 41.7% of patients with acute CCI received reperfusion therapy, such as intravenous thrombolysis or mechanical thrombectomy. This percentage was higher than that of the approximately 16% of patients who received reperfusion therapy based on the 2020 CRCS-K registry data [17]. This difference can be attributed to the fact that in this study, the average onset-to-door time for acute CCI patients was approximately 8 hours, which is significantly shorter than the average of 42 hours for all registered AIS patients in the CRCS-K registry. In a meta-analysis of Acute CCI [18], similar results were found, with over 50% of the patients with acute CCI receiving reperfusion therapy, as observed in our study.

Similar to previous studies, the frequency of poor outcomes at 90 days in patients with acute CCI in this study was >50% [3,6,18], which is higher than the 38.2% reported in the CRCS-K registry. The mortality rate was 25%, which is significantly higher than the 2.8% reported in the CRCS-K registry [17]. The high mortality rate in acute CCI can be attributed not only to the initial high severity upon admission and the higher frequency of reperfusion therapy but also to the delayed diagnosis of concomitant MI and a potential lack of comprehensive treatment guidelines for acute CCI. This delay in appropriate management could contribute to the higher mortality rates observed in patients with acute CCI.

In the present study, metachronous CCI was associated with poor functional outcomes and higher mortality rates. These results may be related to the neurological burden of the high NIHSS score and large size of the cerebral infarction in the metachronous CCI group. When the level of consciousness decreases, the airway is not protected, which increases the risk of aspiration pneumonia. In addition, severe neurological symptoms can aggravate underlying cardiac problems, resulting in death.

Our study has several limitations. First, we only included patients enrolled in the CRCS-K registry and there were no data on patients who developed AIS after MI. Second, the actual onset times of AIS and MI may differ even among the synchronous CCI groups because we classified CCI based on tests performed in the emergency room. Therefore, even if AIS and MI occur >12 hours

https://doi.org/10.18700/jnc.230029

apart, they can be classified as synchronous CCI.

This study reports a relatively rare case series of acute CCI prospectively tracked in a single-institution registry. In contrast to previous reports, MI can occur in AIS cases of varying severity and underlying mechanisms. Despite these findings, the prognosis of patients with acute CCI remains poor, with a high mortality rate. Therefore, there is a need to gather fundamental data through multicenter studies to develop response manuals and guidelines for acute CCI.

ARTICLE INFORMATION

Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board of Dong-A University on July 26, 2023 (No. 23-135). Written informed consent was obtained from all the participants.

Conflict of interest

Jin-Heon Jeong 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 conflict of interest relevant to this article was reported.

ORCID

Seonjeong Kim	https://orcid.org/0000-0001-9251-2932
Hyein Chung	https://orcid.org/0009-0008-9763-7708
Yoonkyung Lee	https://orcid.org/0000-0003-2602-6623
Byeol-A Yoon	https://orcid.org/0000-0002-4350-3551
Dae Hyun Kim	https://orcid.org/0000-0001-9761-7792
Jin-Heon Jeong	https://orcid.org/0000-0002-5878-9206
Jae-Kwan Cha	https://orcid.org/0000-0002-1049-5196

Author contributions

Conceptualization: JKC. Methodology: SK, JHJ. Formal analysis: SK, HC. Data curation: DHK, BAY, YL. Visualization: SK, YL. Project administration: JKC. Writing–original draft: SK, JKC. Writing–review & editing: SK, JKC.

REFERENCES

1. Wang X, Li Q, Wang Y, Zhao Y, Zhou S, Luo Z, et al. A case report of acute simultaneous cardiocerebral infarction: possible pathophysiology. Ann Palliat Med 2021;10:5887-90.
2. Omar HR, Fathy A, Rashad R, Helal E. Concomitant acute right ventricular infarction and ischemic cerebrovascular stroke; possible explanations. Int Arch Med 2010;3:25.
3. de Castillo LL, Diestro JD, Tuazon CA, Sy MC, Añonuevo JC, San Jose MC. Cardiocerebral infarction: a single institutional series. J Stroke Cerebrovasc Dis 2021;30:105831.
4. Akinseye OA, Shahreyar M, Heckle MR, Khouzam RN. Simultaneous acute cardio-cerebral infarction: is there a consensus for management? Ann Transl Med 2018;6:7.
5. Sakuta K, Mukai T, Fujii A, Makita K, Yaguchi H. Endovascular therapy for concurrent cardio-cerebral infarction in a patient with Trousseau syndrome. Front Neurol 2019;10:965.
6. Yeo LL, Andersson T, Yee KW, Tan BY, Paliwal P, Gopinathan A, et al. Synchronous cardiocerebral infarction in the era of endovascular therapy: which to treat first? J Thromb Thrombolysis 2017;44:104-11.
7. Chin PL, Kaminski J, Rout M. Myocardial infarction coincident with cerebrovascular accidents in the elderly. Age Ageing 1977;6:29-37.
8. Lee K, Park W, Seo KD, Kim H. Which one to do first?: a case report of simultaneous acute ischemic stroke and myocardial infarction. J Neurocrit Care 2021;14:109-12.
9. Park HK, Kim BJ, Han MK, Park JM, Kang K, Lee SJ, et al. One-year outcomes after minor stroke or high-risk transient ischemic attack: Korean multicenter stroke registry analysis. Stroke 2017;48:2991-8.
10. Ko Y, Lee S, Chung JW, Han MK, Park JM, Kang K, et al. MRI-based algorithm for acute ischemic stroke subtype classification. J Stroke 2014;16:161-72.
11. Tahsili-Fahadan P, Geocadin RG. Heart-brain axis: effects of neurologic injury on cardiovascular function. Circ Res 2017;120:559-72.
12. Scheitz JF, Nolte CH, Doehner W, Hachinski V, Endres M. Stroke-heart syndrome: clinical presentation and underlying mechanisms. Lancet Neurol 2018;17:1109-20.
13. Battaglini D, Robba C, Lopes da Silva A, Dos Santos Samary C, Leme Silva P, Dal Pizzol F, et al. Brain-heart interaction after acute ischemic stroke. Crit Care 2020;24:163.
14. Alkhachroum AM, Miller B, Chami T, Tatsuoka C, Sila C. A troponin study on patients with ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage: type II myocardial infarction is significantly associated with stroke severity, discharge disposition and mortality. J Clin Neurosci 2019;64:83-8.
15. Cruz Rodriguez JB, Okajima K, Greenberg BH. Management of left ventricular thrombus: a narrative review. Ann Transl Med 2021;9:520.
16. Park JK, Lee SH, Choi S, Jung JH, Lee N. Two patients with acute myocardial infarction presenting with simultaneous acute ischemic stroke. Korean J Med 2008;74:672-5.

17. Clinical Research Collaboration for Stroke in Korea. CRCS-K statistics 2020 report. Clinical Research Collaboration for Stroke in Korea; 2021.
18. Ng TP, Wong C, Leong EL, Tan BY, Chan MY, Yeo LL, et al. Simultaneous cardio-cerebral infarction: a meta-analysis. QJM 2022;115:374-80.

https://doi.org/10.18700/jnc.230029

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):85-93
https://doi.org/10.18700/jnc.230039

Journal of Neurocritical Care

Deep learning for prediction of mechanism in acute ischemic stroke using brain diffusion magnetic resonance image

Baik-Kyun Kim, MD[1,2,3]; Seung Park, PhD[4]; Moon-Ku Han, MD, PhD[1]; Jeong-Ho Hong, MD, PhD[5]; Dae-In Lee, MD[6]; Kyu Sun Yum, MD[7]

[1]Department of Neurology, Seoul National University Bundang Hospital, Seongnam, Korea
[2]Department of Public Health, Seoul National University Bundang Hospital, Seongnam, Korea
[3]Department of Neurology, Gyeonggi Provincial Medical Center, Icheon Hospital, Icheon, Korea
[4]Department of Biomedical Engineering, Chungbuk National University Hospital, Cheongju, Korea
[5]Department of Neurology, Keimyung University Dongsan Medical Center, Daegu, Korea
[6]Division of Cardiology, Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea
[7]Department of Neurology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea

ORIGINAL ARTICLE

Received: November 13, 2023
Revised: December 5, 2023
Accepted: December 6, 2023

Corresponding Author:
Kyu Sun Yum, MD
Department of Neurology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, 776 1sunhwan-ro, Seowon-gu, Cheongju 28644, Korea
Tel: +82-43-269-6339
Fax: +82-43-269-6196
Email: alcest@gmail.com

Background: Acute ischemic stroke is a disease with multiple etiologies. Therefore, identifying the mechanism of acute ischemic stroke is fundamental to its treatment and secondary prevention. The Trial of Org 10172 in Acute Stroke Treatment classification is currently the most widely used system, but it often has a limitations of classifying unknown causes and inadequate inter-rater reliability. Therefore, we attempted to develop a three-dimensional (3D)-convolutional neural network (CNN)-based algorithm for stroke lesion segmentation and subtype classification using only the diffusion and apparent diffusion coefficient information of patients with acute ischemic stroke.
Methods: This study included 2,251 patients with acute ischemic stroke who visited our hospital between February 2013 and July 2019.
Results: The segmentation model for lesion segmentation in the training set achieved a Dice score of 0.843±0.009. The subtype classification model achieved an average accuracy of 81.9%, with accuracies of 81.6% for large artery atherosclerosis, 86.8% for cardioembolism, 72.9% for small vessel occlusion, and 86.3% for control.
Conclusion: We developed a model to predict the mechanism of cerebral infarction using diffusion magnetic resonance imaging, which has great potential for identifying diffusion lesion segmentation and stroke subtype classification. As deep learning systems are gradually developing, they are becoming useful in clinical practice and applications.

Keywords: Deep learning; Ischemic stroke; Etiology; Diffusion magnetic resonance imaging

INTRODUCTION

Acute ischemic stroke has various causes based on the causative mechanism, consisting of large artery atherosclerosis (LAA), cardioembolism (CE), small vessel disease, stroke of other determined etiologies, or stroke of undetermined etiology. Classification of acute ischemic stroke based on the cause is important for treatment and secondary prevention. The most widely used clas-

sification system is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification [1,2]. However, this classification method shows moderate inter-rater reliability in classifying acute ischemic stroke and has a limitation of frequently classifying strokes as having an undetermined etiology [3]. To overcome this limitation, efforts are underway to develop a computerized algorithm for acute stroke diagnosis; however, these have not shown sufficient results [4,5].

Various diagnostic methods such as brain imaging and heart tests are required to determine the causative mechanisms of acute ischemic stroke. Early diagnosis of the stroke subtype using this classification system can positively affect treatment, prognosis, and secondary prevention [1]. Diffusion-weighted magnetic resonance imaging (MRI) is widely used to diagnose acute stroke. It has superior performance in detecting hyperacute lesions and very small ischemic lesions and in distinguishing chronic and acute lesions [6] compared to brain computed tomography (CT) and conventional MRI. Furthermore, simultaneous use of the apparent diffusion coefficient (ADC) map and diffusion-weighted imaging (DWI) allow for more accurate distinction of the lesion of acute ischemic stroke, providing important information about the time window of the lesion [7]. The diffusion imaging lesion pattern, which provides useful information for the early diagnosis of acute ischemic stroke, has been reported to be closely related to the stroke subtype [8,9].

Various deep learning algorithms based on convolutional neural networks (CNNs) have been proposed for diagnosing acute ischemic stroke in brain MRI images [10-21]. These studies have shown that deep learning can detect stroke lesions more accurately than traditional machine-learning techniques and can extract meaningful features for severity evaluation or prognosis prediction. Researchers have proposed lesion segmentation techniques for patients with acute ischemic stroke based on the U-Net architecture [16,17]. To efficiently exploit the contextual information of volumetric MRI data, Zhang et al. [18] proposed a stroke lesion segmentation technique using a three-dimensional (3D) fully connected-DenseNet. Although the aforementioned studies demonstrated that deep learning can classify patients with acute ischemic stroke via lesion segmentation, a classification technique for predicting the treatment mechanism of acute ischemic stroke has yet to be reported. In this study, we presented a 3D CNN-based model for stroke lesion segmentation and subtype classification using only DWI and ADC images from patients with acute ischemic stroke.

METHODS

Study population

The participants were 2,251 patients with acute ischemic stroke who visited our hospital between February 2013 and July 2019. Information on acute ischemic stroke was compiled from a registry. All patients with acute ischemic stroke were reviewed by at least three stroke specialists and classified according to the TOAST classification. There were 1,789 patients with LAA, CE, and small vessel occlusion (SVO), excluding stroke of other determined etiologies or stroke of undetermined etiology. Among them, 1,396 patients underwent DWI and ADC (Fig. 1). There were 608 patients with LAA, 441 with CE, and 359 with SVO. Among the healthy patients who visited the hospital during the same period, 400 who showed normal MRI findings at our clinic were included as controls. The patients' sex, age, National Institutes of Health Stroke Scale score, and medical history, including stroke, hypertension, diabetes mellitus, and atrial fibrillation, are listed in Table 1. In the control group, brain images without clinical information were used. Baseline characteristics were presented as frequencies (percentages). Continuous variables with normal distributions are presented as means ± standard deviation, whereas variables with non-normal distributions are presented as medians (interquartile ranges).

Imaging acquisition

MRI was performed using various machines including 1.5 T (Achieva, Philips Healthcare) and 3.0 T (Ingenia CX, Philips Healthcare; Achieva, Philips Healthcare) scanners. The parameters of the DWI sequence were as follows: repetition time, 2,500–3,000 ms; echo time, 80 ms; slice thickness, 3–5 mm; intersection gap, 1 mm; field of view, 220 × 220 mm; matrix size, 256 × 256

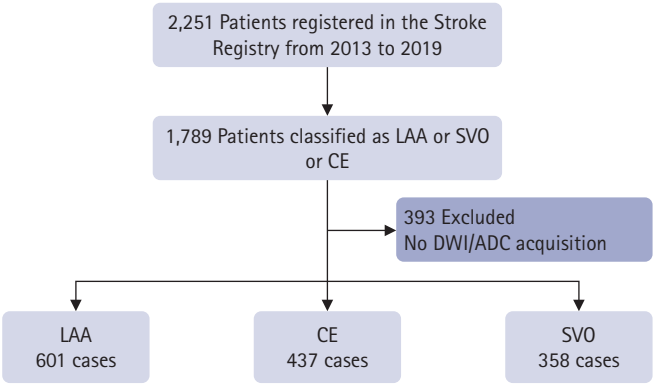

Fig. 1. Study profile. LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

https://doi.org/10.18700/jnc.230039

Table 1. Baseline characteristics of the study population according to stroke mechanism

Variable	Total	LAA	SVO	CE
Number	1,396	601	358	437
Female	591 (42.3)	250 (41.6)	136 (38.0)	205 (46.9)
Male	805 (57.7)	351 (58.4)	222 (62.0)	232 (53.1)
Age (yr)	70±12	69±12	66±13	73±11
Delayed time (min)	101 (57–198)	118 (57–213)	152 (63.25–296)	85 (55–154)
Medical history				
Stroke	276 (19.8)	113 (18.8)	64 (17.9)	99 (22.7)
Hypertension	895 (64.1)	416 (69.2)	214 (59.8)	265 (60.6)
Diabetes mellitus	475 (34.0)	222 (36.9)	131 (36.6)	122 (37.9)
Dyslipidemia	178 (12.8)	84 (14.0)	52 (14.5)	42 (9.6)
Atrial fibrillation	327 (23.4)	9 (1.5)	2 (0.6)	316 (72.3)
NIHSS	5.67±5.72	4.96±4.99	3.02±2.13	8.81±7.11

Values are presented as number (%), mean±standard deviation, or median (interquartile range).
LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism; NIHSS, National Institutes of Health Stroke Scale Rating.

(approximately 2 × 2 mm in-plane resolution); and b values, 0 and 1,000 sec/mm^2. Each apparent ADC map was generated automatically using the manufacturer's software.

Data preparation

To produce a "ground truth" reference standard for training and evaluating the subtype classification model, each patient was classified into four classes (LAA, SVO, CE, and Control) according to the TOAST classification system. Lesion areas in each DWI slide were manually annotated by two experienced neurologists using in-house annotation software. Finally, each lesion was cross-validated and labelled, with a final decision agreed upon by both raters. To address the data distribution and validation methodology in our study, we adopted a 5-fold Stratified Cross-Validation approach. This ensures the proportionality of the class distribution across each fold, which is crucial for maintaining the integrity of the validation process given the imbalanced nature of our dataset. The preprocessing pipeline was meticulously designed to normalize and standardize the MRI images obtained from various vendors with different acquisition parameters. Each patient's MRI data comprising varying numbers of slices were resampled to a uniform 3D voxel size of 256 (H) × 256 (W) × 128 (D). This resampling is pivotal for aligning the spatial dimensions across all the datasets. To address the intensity variations due to different magnetic resonance (MR) parameters and scanner calibrations, we performed intensity normalization using the window center and width values provided in the digital Imaging and communication in medicine (DICOM) file metadata. This step adjusts the pixel intensity values to a standard scale, thereby enhancing the image comparability. Additionally, DWI, which inherently have varying numbers of slices owing to different scanning protocols, were standardized by selecting a fixed number of slices that best represented the essential features required for accurate segmentation. This uniform pre-processing approach ensures that subsequent segmentation algorithms operate on data that reflect consistent anatomical structures and tissue characteristics, thereby enabling a more reliable and valid comparative analysis across all images. Practically, for each of the five folds, we allocated 60% of the data for training purposes, 20% for validation, and 20% for testing. This division was performed independently within each fold to confirm the generalizability and reliability of the model's performance.

Lesion segmentation mode

Our segmentation model, based on a 3D CNN called V-Net [22] is illustrated in Fig. 2. The model consists of an encoder that extracts feature maps from local 3D volumes and a decoder that predicts stroke lesions using feature maps. Because our model has a very deep architecture, we employed a residual block to alleviate the gradient vanishing and exploding problems. The residual block contains (1) a 3D convolutional layer with kernel size 3 × 3 × 3 and (2) a residual skip connection and two 3D convolutional layers with kernel size 3 × 3 × 3, each follo wing batch normalization and a rectified linear unit, respectively. In the network encoder, residual blocks were utilized for feature extraction and max-pooling layers, with a stride of two to reduce spectral dimensionality. In contrast, the decoder consists of up-convolutional layers with strides of two, followed by residual blocks after feature-map concatenation. Skip connections from the layers of equal resolution in the encoder provide high-resolution features to the decoder. A sigmoid activation layer was connected to the last layer of the decoder to calculate a probability map of the stroke lesions.

The model was trained over 200 epochs with an Adam optimiz-

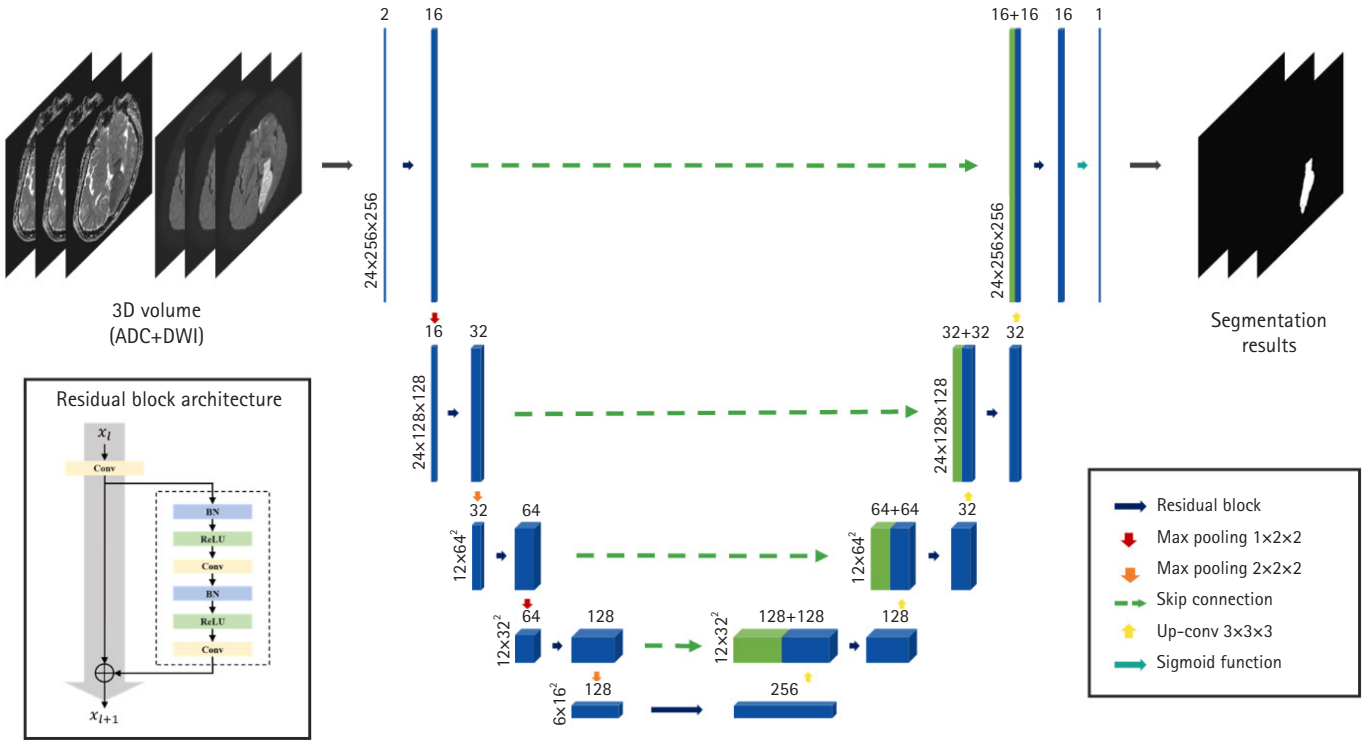

Fig. 2. Our network architecture for stroke lesion segmentation. Based on three-dimensional (3D) U-Net, the network learns the features based on a hierarchy framework starting from simple features such as edges and shapes to high-level features in the deeper levels. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; Conv, convolution; BN, batch normalization; ReLU, rectified linear unit; Up-conv, up-convolutional.

er, an initial learning rate of 1e-5, and a batch size of 8. The model was trained from scratch without using pretrained weights. We tested various loss functions such as weighted cross-entropy loss, L1 loss, and Dice loss; Dice loss achieved the best performance. Furthermore, to address the data scarcity problem, data augmentation techniques such as rigid transformation, horizontal/vertical flip, Gaussian noise, and gamma correction were randomly triggered in each training session.

Subtype classification model

As illustrated in Fig. 3, our classification model predicted the probabilities of the four classes: LAA, SVO, CE, and Control. For feature extraction, we adopted a residual block in the lesion-segmentation model. In addition, to guide the network to focus on the lesions, feature maps were enhanced using the lesion prediction results provided by the segmentation model. Specifically, the enhanced feature map Fenh is obtained by

$$\text{Fenh} = \text{F} \times (1 + \text{h}(\text{A})), \quad (1)$$

where F and A are the feature maps extracted by each residual block and lesion segmentation result, respectively. $\text{h}(\cdot)$ is a bilinear interpolation to match the spatial resolutions between F and A. This attention mechanism significantly improves the classification performance of the model by guiding the network to focus on lesion areas to predict stroke subtypes. The model was trained over 400 epochs with an Adam optimizer, an initial learning rate of 1e-5, and a batch size of 4. Categorical cross-entropy loss was utilized, and the model was trained from scratch. We used a data-augmentation technique to train the classification model.

RESULTS

Lesion segmentation model

Our segmentation model for lesion segmentation in the training set achieved a Dice score of 0.891 ± 0.034. For the test set, our model resulted in a Dice score, precision, and recall of 0.843 ± 0.009, 0.842 ± 0.012, and 0.844 ± 0.017, respectively. Fig. 4 shows some examples of lesion prediction results compared with assessments by neurologists. Our segmentation model accurately predicted extremely small lesions. Most cases of failure occurred when the lesions had very poor contrast in the diffusion images, as shown in Fig. 5.

https://doi.org/10.18700/jnc.230039

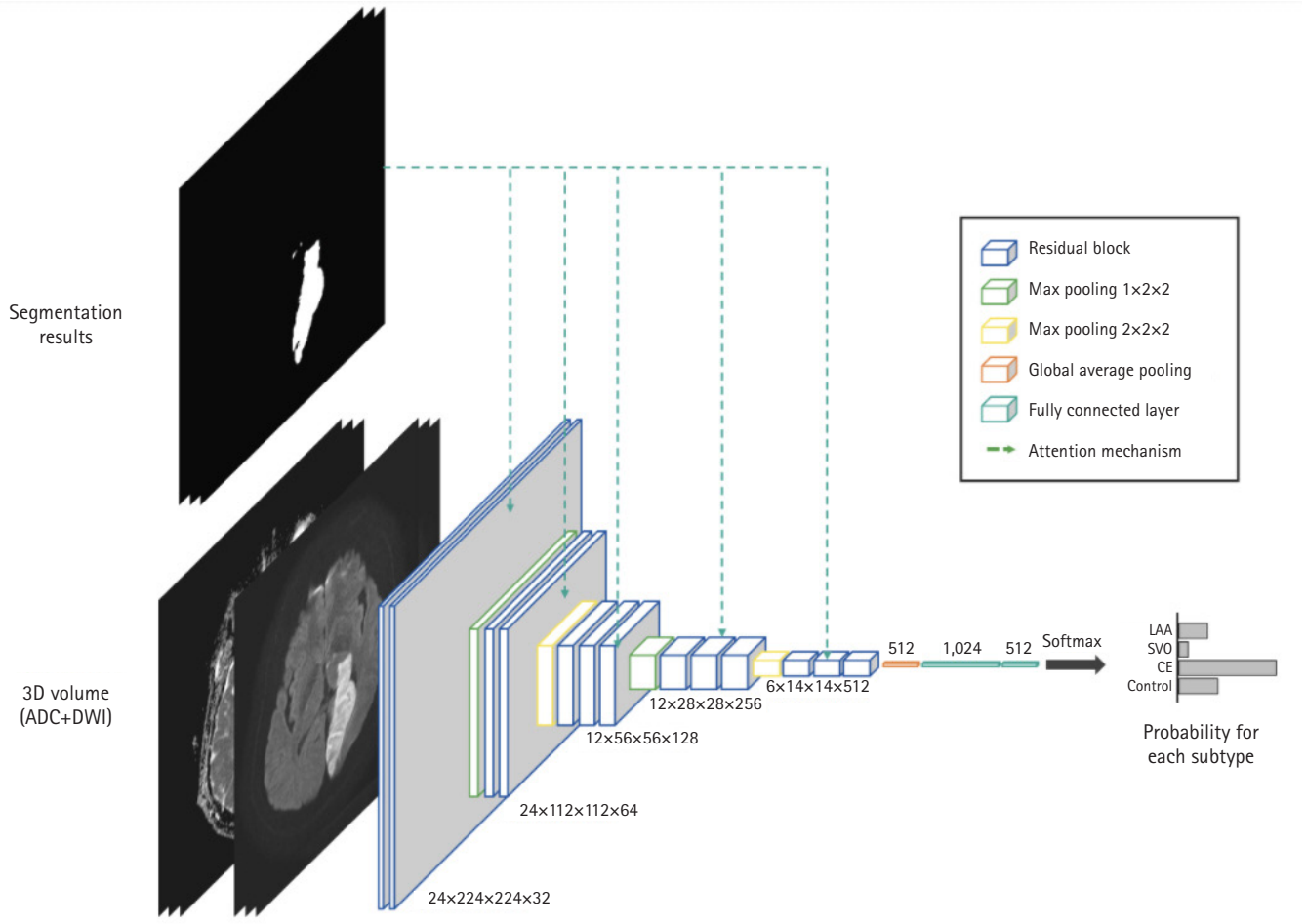

Fig. 3. Our network architecture for stroke subtype classification. To guide the network towards the lesion areas, we adopted the attention mechanism using the lesion segmentation result. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; LAA, large artery atherosclerosis; SVO, small vessel occlusion; CE, cardioembolism.

Stroke subtype classification model

To underscore the benefits of leveraging segmentation data, we integrated an enhanced feature map into our stroke-subtype classification model. By applying an enhanced feature map informed by the segmentation results, the model obtains the spatial context that the raw images lack. This context allows the model to "see" beyond mere pixel intensity, recognizing patterns and structures pertinent to stroke subtype.

This strategic modification led to a notable improvement in the performance metrics. Before integrating the segmentation information, the average classification accuracy of the model is 71.1%. However, with the incorporation of an enhanced feature map, the accuracy significantly increased to 81.9%. This effect was evident across all subtypes, with accuracies of 81.6% for LAA, 86.8% for CE, 72.9% for SVO, and 86.3% for control. The enhanced feature map sharpens the model's ability to concentrate on lesion-specific areas, thereby refining the differentiation process between various stroke subtypes.

Fig. 6 shows the confusion matrix obtained using the subtype classification model. Our model showed lower accuracy for SVO than for other subtypes, indicating that the model confused SVO with control cases owing to its poor analysis performance for small lesions.

DISCUSSION

This is the first study to perform subtype classification of stroke mechanisms by analyzing the patterns of acute ischemic stroke lesions through deep learning based on a 3D-CNN using DWI and ADC in patients with acute ischemic stroke. The main findings of this study are as follows. First, the 3D-CNN-based segmentation accuracy for acute ischemic stroke lesions was 0.843 based on the

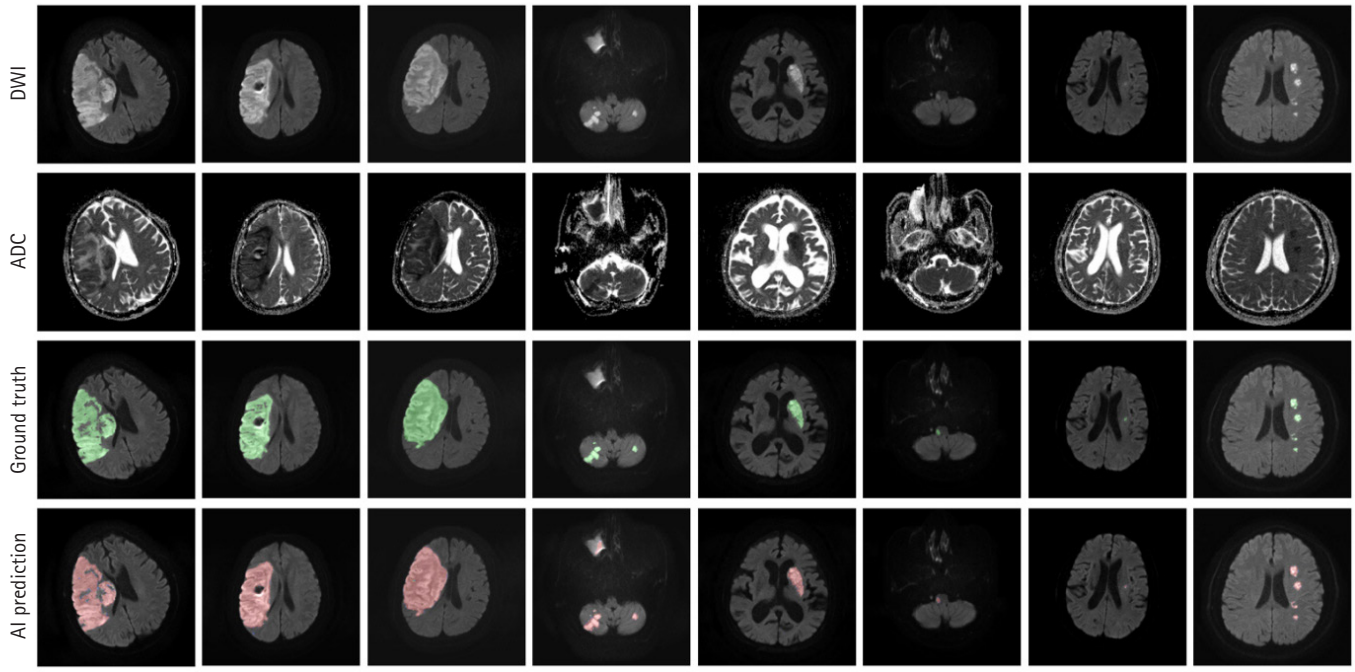

Fig. 4. Prediction outcomes using our lesion segmentation model. In each panel, the images in the first and second rows are diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) slices, respectively. The third-row images are the "ground truth" labels annotated by two neurologists, while the fourth-row images show lesion areas predicted by our model. AI, artificial intelligence.

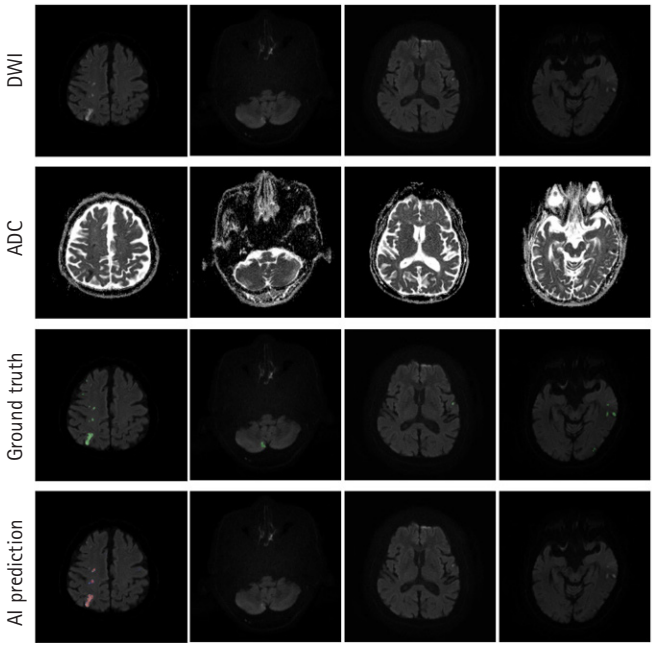

Fig. 5. Failure cases of our lesion segmentation model. Most cases have occurred when the lesions have extremely poor contrast. DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; AI, artificial intelligence.

Dice score. Second, in terms of subtyping to classify the cause of acute ischemic stroke, the predicted degree of cause classification according to the TOAST classification, which is the "ground truth," was confirmed to be 81.3% for LAA, 84.6% for SVO, and 73.0% for CE.

With technological advances, brain imaging plays a crucial role in diagnosing and identifying mechanisms underlying the development of acute ischemic stroke according to technological advances [23]. Among the various MR sequences, DWI and ADC maps are useful tools for the early detection of acute ischemic lesions and for differentiating between stroke mimics and acute ischemic stroke [24]. Several previous studies have attempted to segment the infarction volume in acute ischemic stroke using artificial intelligence (AI). Various imaging patterns of acute ischemic stroke in DWI lesions correlate with pathogenic mechanisms. In the case of cardiac embolic stroke, acute stroke lesions on DWI often show single cortical/subcortical lesions or occur multiple times in various vascular branches. Multiple unilateral lesions in the anterior circulation are characteristic findings of arteriogenic embolism. Meanwhile, small infarction (2–20 mm in diameter) lesions observed in the deep acute ischemic white matter, basal ganglia, thalamus, and pons were highly associated with SVO [8,25]. We attempted to apply a doctor's diagnostic process to determine the cause of acute ischemic stroke based on the character-

https://doi.org/10.18700/jnc.230039

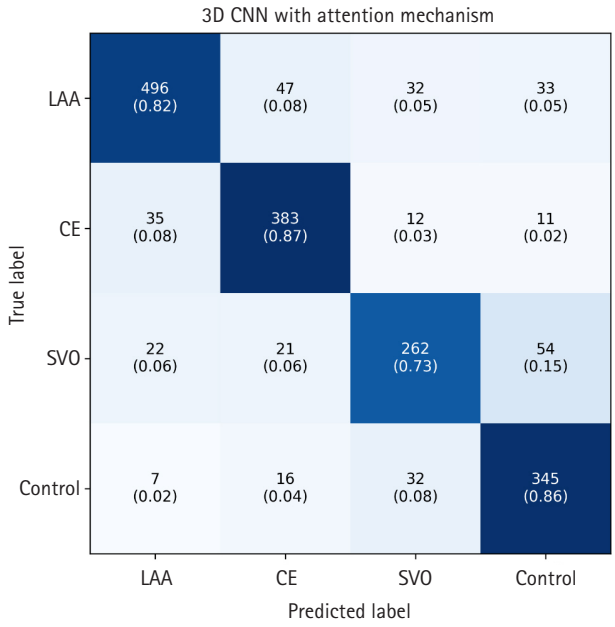

Fig. 6. Confusion matrix of our subtype classification model. Values are presented as number (ratio). 3D, three-dimensional; CNN, convolutional neural network; LAA, large artery atherosclerosis; CE, cardioembolism; SVO, small vessel occlusion.

istic findings of brain MRI using AI.

However, there are many limitations in predicting the pathogenesis of acute ischemic stroke using only DWI/ADC maps. The TOAST classification system is the most widely used system for classifying acute ischemic stroke based on its pathogenesis. Clinical findings and the results of ancillary diagnostic studies, including brain imaging and cardiac evaluation, were used to classify patients' acute ischemic stroke mechanism [1]. Although widely use and popular, its overall inter-rater agreement is moderate. Its reliability is notably lower for small-vessel occlusion and strokes of undetermined causes, especially when compared to LAA and CE [3]. To overcome this, an improved classification method that applies a new diagnostic technique was used; nevertheless, it still has limitations [4,5,26,27]. In particular, acute ischemic stroke with unknown mechanisms, such as LAA, CE, SVO, and stroke of other determined etiologies, is known as cryptogenic stroke. It is observed in approximately all the patients with acute ischemic stroke [28]. These cryptogenic strokes are often observed as embolic strokes, and are called embolic strokes of undetermined source (ESUS) [29]. There is a need to determine the mechanism of ESUS and provide proper treatment; however, a definitive method for achieving this objective remains elusive [30]. We conducted this study to diagnose acute ischemic stroke using a deep learning algorithm. To the best of our knowledge, this model is the first algorithm for identifying the mechanism of cerebral infarction in patients with ESUS. In the future, it will be necessary to create a multimodal algorithm that includes cerebrovascular imaging, laboratory data, and cardiac tests, such as transthoracic echocardiography, transesophageal echocardiography, and electrocardiography. We expect to improve the model in this study.

Our study introduces a novel approach to lesion segmentation and stroke subtype classification that significantly advances technology beyond previous methodologies [10-21]. Unlike traditional techniques [16,17] which process individual slides and therefore cannot utilize contextual information from adjacent slides, often resulting in diminished accuracy, our technique leverages a 3D CNN with a deep residual network architecture. This allowed for stable learning and improved recognition of complex patterns across multiple slides, culminating in a high Dice score of 0.845 in the test set.

Moreover, our subtype classification model exhibited an average accuracy of 81.9%, which is a notable improvement over the existing models. This is achieved through an attention mechanism that utilizes the lesion information predicted by the segmentation model, focusing on key areas for accurate prediction. This not only identified the stroke subtype but also highlighted the specific regions the model analyzed to arrive at its conclusion.

The integration of these advanced segmentation and classification models is expected to have a substantial impact on medical AI applications that rely on 3D volumetric data, such as CT and MRI scans. Our approach sets a new precedent for accuracy and reliability in medical diagnostics, offering a comprehensive solution that outperforms previous single-slice-based techniques.

This study has several limitations. First, the labeling of subtypes in the stroke prediction is unclear. Despite our meticulous process of employing the TOAST classification system and expert annotations by two experienced neurologists, the subjective nature of clinical diagnoses presents the potential for inconsistency. The difficulty in standardizing labels across different raters and cases is an inherent limitation not only in our study, but also in the broader context of machine learning applications in stroke subtype classification. This could result in variability, affecting the reliability of our model. Recognizing this limitation, we emphasize the need for continuous improvement in annotation methodologies and exploration of more objective measures in future studies to minimize such discrepancies. Second, this study lacks external validation. Therefore, there may be a bias in this model, and it is necessary to improve it by performing external validation in future studies. Third, this algorithm does not include images of cerebral infarction caused by causes other than LAA, CE, or SVO. To predict and diagnose these mechanisms, additional clinical data, such as cerebrovascular imaging, laboratory studies, and cardiological

evaluation, are required in addition to DWI/ADC. In this study, the algorithm was only trained on three mechanisms that are known to be diagnosable or predictable by DWI patterns. Therefore, it is limited in classifying cerebral infarction caused by other mechanisms. In our follow-up study, we plan to improve the algorithm by including various types of clinical data. Fourth, this study is a case-control study. The study was based on a stroke database from a single center; hence, there is a possibility of selection bias in the selection of subjects. Therefore, it is necessary to overcome this limitation using multicenter data in subsequent studies. Finally, this study was conducted using data collected from a single cohort, which limited our consideration of variations in the MR parameters. Therefore, the generalizability of our findings to datasets with different MR parameters may be limited. Specifically, our normalization approach based on Window Center and Window-Width may not be applicable to other datasets with varying imaging protocols. This limitation highlights the need for further research using diverse MRI datasets to validate and refine our methodology. Future studies should aim to incorporate data from multiple sources with varying MR parameters to ensure broader applicability and robustness of the findings.

In summary, this study aimed to predict the pathogenesis of cerebral infarction using only brain diffusion MRI and apply it clinically. Using only the initial diffusion MRI information, we present a feasible model that predicts the mechanism of occurrence by applying an algorithm based on a 3D-CNN through deep learning. The diffusion lesion volume measurement and stroke subtype classification using our proposed method showed a strong correlation with those performed by manual segmentation and subtype classification by professional neurologists. This study is significant because it is the first to predict the mechanism of acute ischemic stroke by using diffusion MRI alone. In future studies, it will be necessary to develop a multimodal algorithm that includes not only diffusion MRI, but also other brain imaging modalities and clinical data to predict the exact pathogenesis of cerebral infarction.

ARTICLE INFORMATION

Ethics statement

This single-center, retrospective case-control study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board (No. 2023-10-017), which waived the requirement for informed consent.

Conflict of interest

Moon Ku Han and Jeong-Ho Hong are editorial board members of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

Acknowledgments

This work was supported by funding from the Academic Research Program of the Chungbuk National University in 2022.

ORCID

Baik-Kyun Kim	https://orcid.org/0000-0003-1544-7713
Seung Park	https://orcid.org/0000-0003-4667-3983
Moon-Ku Han	https://orcid.org/0000-0003-0166-387X
Jeong-Ho Hong	https://orcid.org/0000-0002-8235-9855
Dae-In Lee	https://orcid.org/0000-0001-8088-3007
Kyu Sun Yum	https://orcid.org/0000-0001-9815-7652

Author contributions

Conceptualization: all authors. Methodology: BKK, SP, DIL, KSY. Formal analysis: BKK, SP, DIL, KSY. Data curation: BKK, SP, DIL, KY. Visualization: BKK, SP, DIL, KSY. Project administration: BKK, SP, DIL, KSY. Funding acquisition: KSY. Writing–original draft: BKK, SP, DIL, KY. Writing–review & editing: all authors.

REFERENCES

1. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.
2. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of stroke subtypes. Cerebrovasc Dis 2009;27:493-501.
3. Meschia JF, Barrett KM, Chukwudelunzu F, Brown WM, Case LD, Kissela BM, et al. Interobserver agreement in the trial of org 10172 in acute stroke treatment classification of stroke based on retrospective medical record review. J Stroke Cerebrovasc Dis 2006;15:266-72.
4. Goldstein LB, Jones MR, Matchar DB, Edwards LJ, Hoff J, Chilukuri V, et al. Improving the reliability of stroke subgroup classification using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. Stroke 2001;32:1091-8.
5. Ko Y, Lee S, Chung JW, Han MK, Park JM, Kang K, et al. MRI-based algorithm for acute ischemic stroke subtype classification. J Stroke 2014;16:161-72.
6. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute

https://doi.org/10.18700/jnc.230039

human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. Ann Neurol 1995; 37:231-41.
7. Lansberg MG, Thijs VN, O'Brien MW, Ali JO, de Crespigny AJ, Tong DC, et al. Evolution of apparent diffusion coefficient, diffusion-weighted, and T2-weighted signal intensity of acute stroke. AJNR Am J Neuroradiol 2001;22:637-44.
8. Wessels T, Wessels C, Ellsiepen A, Reuter I, Trittmacher S, Stolz E, et al. Contribution of diffusion-weighted imaging in determination of stroke etiology. AJNR Am J Neuroradiol 2006;27:35-9.
9. Kang DW, Chalela JA, Ezzeddine MA, Warach S. Association of ischemic lesion patterns on early diffusion-weighted imaging with TOAST stroke subtypes. Arch Neurol 2003;60:1730-4.
10. Wu O, Winzeck S, Giese AK, Hancock BL, Etherton MR, Bouts MJ, et al. Big data approaches to phenotyping acute ischemic stroke using automated lesion segmentation of multi-center magnetic resonance imaging data. Stroke 2019;50:1734-41.
11. Lee H, Lee EJ, Ham S, Lee HB, Lee JS, Kwon SU, et al. Machine learning approach to identify stroke within 4.5 hours. Stroke 2020;51:860-6.
12. Boldsen JK, Engedal TS, Pedraza S, Cho TH, Thomalla G, Nighoghossian N, et al. Better diffusion segmentation in acute ischemic stroke through automatic tree learning anomaly segmentation. Front Neuroinform 2018;12:21.
13. Yu Y, Xie Y, Thamm T, Gong E, Ouyang J, Huang C, et al. Use of deep learning to predict final ischemic stroke lesions from initial magnetic resonance imaging. JAMA Netw Open 2020;3: e200772.
14. Do LN, Baek BH, Kim SK, Yang HJ, Park I, Yoon W. Automatic assessment of ASPECTS using diffusion-weighted imaging in acute ischemic stroke using recurrent residual convolutional neural network. Diagnostics (Basel) 2020;10:803.
15. Woo I, Lee A, Jung SC, Lee H, Kim N, Cho SJ, et al. Fully automatic segmentation of acute ischemic lesions on diffusion-weighted imaging using convolutional neural networks: comparison with conventional algorithms. Korean J Radiol 2019;20:1275-84.
16. Kim YC, Lee JE, Yu I, Song HN, Baek IY, Seong JK, et al. Evaluation of diffusion lesion volume measurements in acute ischemic stroke using encoder-decoder convolutional network. Stroke 2019;50:1444-51.
17. Hui H, Zhang X, Li F, Mei X, Guo Y. A partitioning-stacking prediction fusion network based on an improved attention u-net for stroke lesion segmentation. IEEE Access 2020;8: 47419-32.
18. Zhang R, Zhao L, Lou W, Abrigo JM, Mok VC, Chu WC, et al. Automatic segmentation of acute ischemic stroke from DWI using 3-D fully convolutional DenseNets. IEEE Trans Med Imaging 2018;37:2149-60.
19. Liu X, Yang H, Qi K, Dong P, Liu Q, Liu X, et al. MSDF-net: multi-scale deep fusion network for stroke lesion segmentation. IEEE Access 2019;7:178486-95.
20. Zhang L, Song R, Wang Y, Zhu C, Liu J, Yang J, et al. Ischemic stroke lesion segmentation using multi-plane information fusion. IEEE Access 2020;8:45715-25.
21. Liu L, Wu FX, Wang J. Efficient multi-kernel dcnn with pixel dropout for stroke mri segmentation. Neurocomputing 2019; 350:117-27.
22. Milletari F, Navab N, Ahmadi SA. V-net: fully convolutional neural networks for volumetric medical image segmentation. In: 2016 fourth international conference on 3D vision (3DV); 2016; Stanford, CA, USA.
23. Bang OY, Chung JW, Son JP, Ryu WS, Kim DE, Seo WK, et al. Multimodal MRI-based triage for acute stroke therapy: challenges and progress. Front Neurol 2018;9:586.
24. Fung SH, Roccatagliata L, Gonzalez RG, Schaefer PW. MR diffusion imaging in ischemic stroke. Neuroimaging Clin N Am 2011;21:345-77.
25. Lee LJ, Kidwell CS, Alger J, Starkman S, Saver JL. Impact on stroke subtype diagnosis of early diffusion-weighted magnetic resonance imaging and magnetic resonance angiography. Stroke 2000;31:1081-9.
26. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz WJ. An evidence-based causative classification system for acute ischemic stroke. Ann Neurol 2005;58:688-97.
27. Ay H, Benner T, Arsava EM, Furie KL, Singhal AB, Jensen MB, et al. A computerized algorithm for etiologic classification of ischemic stroke: the Causative Classification of Stroke System. Stroke 2007;38:2979-84.
28. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. Stroke 2017;48:867-72.
29. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13: 429-38.
30. Healey JS, Gladstone DJ, Swaminathan B, Eckstein J, Mundl H, Epstein AE, et al. Recurrent stroke with rivaroxaban compared with aspirin according to predictors of atrial fibrillation: secondary analysis of the NAVIGATE ESUS randomized clinical trial. JAMA Neurol 2019;76:764-73.

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):94-100
https://doi.org/10.18700/jnc.230031

Journal of Neurocritical Care

Effects of sufficient anticoagulation on ischemic stroke outcomes in patients with nonvalvular atrial fibrillation

Tae Jung Kim, MD, PhD[1,2]; Soo-Hyun Park, MD, PhD[3]; Youngjoon Kim, MD[1]; Sang-Bae Ko, MD, PhD[1,2]

[1]Department of Neurology, Seoul National University College of Medicine, Seoul, Korea
[2]Department of Critical Care Medicine, Seoul National University Hospital, Seoul, Korea
[3]Department of Neurology, Kangdong Sacred Heart Hospital, Seoul, Korea

ORIGINAL ARTICLE

Received: September 9, 2023
Revised: October 27, 2023
Accepted: November 3, 2023

Corresponding Author:
Sang-Bae Ko, MD, PhD
Departments of Neurology and Critical Care Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-2278
Fax: +82-2-3672-7553
Email: sangbai1378@gmail.com

Background: Optimal anticoagulation therapy reduces the risk of ischemic stroke in patients with nonvalvular atrial fibrillation (AF). Therefore, we aimed to evaluate the effects of prior anticoagulation therapy with vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) on ischemic stroke outcomes in patients with nonvalvular AF.

Methods: We enrolled 487 patients with ischemic stroke and nonvalvular AF between January 2013 and August 2020. The infarct volume was semi-automatically evaluated using diffusion-weighted magnetic resonance imaging. Patients were categorized into no anticoagulation, undertreated anticoagulation, and sufficient anticoagulation (with VKA or DOAC) groups based on their pre-admission anticoagulant use, and the clinical characteristics were compared between the groups.

Results: Among the included patients, 374 (76.8%), 50 (10.3%), 10 (2.1%), and 53 (10.9%) patients received no anticoagulants, were undertreated with a VKA, were sufficiently treated with a VKA, and received DOACs, respectively, before stroke. Multivariate analysis revealed that optimal anticoagulation was independently associated with a low risk of severe stroke (odds ratio, 0.553; 95% confidence interval, 0.308–0.992; *P*=0.047). Additionally, the DOAC group had a significantly smaller mean infarct volume than the other groups (45.8±73.2, 45.0±69.1, 30.9±24.7, and 12.6±24.9 mL in the no anticoagulation, insufficient VKA, sufficient VKA, and DOAC groups, respectively; *P*=0.011).

Conclusion: Sufficient pre-stroke anticoagulation is associated with mild stroke severity and good outcomes at 3 months post-stroke. Additionally, pre-stroke DOAC treatment is associated with smaller infarct volume in patients with ischemic stroke and nonvalvular AF.

Keywords: Anticoagulants; Atrial fibrillation; Cerebral infarction

INTRODUCTION

Atrial fibrillation (AF) is an important risk factor for ischemic stroke, and 10%–15% of all ischemic strokes occur in patients with AF [1]. Previous studies have demonstrated that optimal anticoagulation using vitamin K antagonists (VKAs), warfarin, and direct oral anticoagulants (DOACs) reduces the risk of ischemic stroke in patients with AF [2-7]. Therefore, international guidelines recommend sufficient anticoagulation with VKAs and DOACs for primary and secondary prevention, respectively, of cardi-

oembolic ischemic stroke in patients with nonvalvular AF [8,9]. Moreover, compared to no anticoagulation therapy, sufficient VKA and DOAC therapy reportedly reduced ischemic stroke severity and improved clinical outcomes in patients with AF [10-14]. Furthermore, previous studies reported that DOAC therapy reduced the initial severity of ischemic stroke similar to sufficient VKA treatment [15,16]. However, the clinical impact of optimal anticoagulation with different treatment modalities, such as VKAs and DOACs, on initial stroke severity, infarct volume, and short-term outcomes in patients with acute cardioembolic ischemic stroke and nonvalvular AF remains unknown. Therefore, we aimed to investigate the association of pre-stroke anticoagulation therapy with VKAs and DOACs as well as stroke severity and outcomes in patients with ischemic stroke and non-valvular AF.

METHODS

Study population

We retrospectively included patients who were admitted to our hospital with acute ischemic stroke within 7 days of symptom onset, between January 2013 and August 2020. Of the 603 patients with cardioembolic ischemic stroke and AF who were initially enrolled, those with valvular AF (n = 69) and those who did not undergo diffusion-weighted imaging (DWI) during hospitalization after ischemic stroke (n = 37) were excluded. Finally, 487 patients with ischemic stroke and nonvalvular AF were included.

Baseline characteristics and clinical information

Clinical data regarding patient demographics, vascular risk factors, location of vessel occlusion, lesion location, reperfusion therapy, medication history, and laboratory findings were retrieved from the electronic medical records. All patients underwent laboratory examinations, including glucose and lipid profiling, blood cell counts, high-sensitivity C-reactive protein analysis, prothrombin time-international normalized ratio (PT-INR), and activated partial thromboplastin time, at admission. For the purpose of this study, pre-admission anticoagulation treatments were categorized into four groups: (1) no anticoagulation therapy, (2) undertreated anticoagulation (subtherapeutic dose of VKA with a PT-INR of < 2 at admission), (3) sufficient VKA therapy (therapeutic dose of VKA with a PT-INR of ≥ 2 at admission) [8,9], or those on DOACs. Sufficient anticoagulation therapy was classified as sufficient VKA and sufficient DOAC. The National Institutes of Health Stroke Scale (NIHSS) score, which was the primary outcome at discharge, was used to measure stroke severity at admission, which was the primary outcome, and at discharge. Patients with an NIHSS score of ≥ 5 were classified as having moderate to severe stroke [17]. The functional outcome at 3 months post-stroke, which was the secondary outcome, was evaluated using the modified Rankin Scale (mRS). Patients were assigned to either the "good outcome" (mRS score ≤ 2) or "poor outcome" (mRS score ≥ 3) group. Additionally, infarct volume was analyzed according to the pre-admission anticoagulation therapy received by the patients.

Radiological assessment

Brain magnetic resonance (MR) images were obtained using a 1.5 T (Signa HDxt, GE Healthcare [n = 114]) or 3.0 T (Verio, Siemens [n = 91]; Discovery 750, GE Healthcare [n = 158]; Magnetom Skyra, Siemens [n = 51]; Ingenia CX, Philips [n = 73]) machine. Moreover, we extensively acquired MR images using DWI (repetition time/echo time: 6,000–10,000/65–80 for 3.0 T and 5,000–9,000/65–75 for 1.5 T) [18-20]. The lesion locations were classified as anterior circulation, posterior circulation, or multiple territories. The cerebral infarct volumes of the lesions were analyzed on DWI using Medical Imaging Processing, Analysis, and Visualization (MIPAV, ver. 10.0.0; National Institutes of Health) [21], by an investigator blinded to the clinical information. Large-vessel occlusion was evaluated using brain computed tomography angiography or MR angiography.

Statistical analysis

Baseline characteristics are presented as frequencies (percentages). Continuous variables with normal distributions are presented as means ± standard deviations, whereas variables with non-normal distributions are presented as medians (interquartile ranges). In the univariate analysis, the proportions of categorical variables were compared using Pearson chi-square test or Fisher's exact test, as appropriate. The relationships between continuous variables and anticoagulation therapies were analyzed using the Kruskal-Wallis test or one-way analysis of variance. Associations between outcomes and the levels of anticoagulation therapy were analyzed using logistic regression analysis. Covariates with a significance level of $P < 0.05$ in the univariate analyses or clinically important variables were used for adjusting the multivariate analysis. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using IBM SPSS ver. 25.0 (IBM Corp.) and GraphPad Prism ver. 9 (GraphPad Software).

RESULTS

Of the 487 patients included in this study, 374 (76.8%) received no anticoagulant medication, 50 (10.3%) were undertreated with VKA, and 63 (12.9%) received sufficient anticoagulation (10

[2.1%] received VKAs and 53 [10.9%] received DOACs). Table 1 presents the clinical characteristics of the included patients. Their mean age was 73.8±9.9 years, and 294 (60.4%) of them were men. There were significantly more patients with a history of stroke/transient ischemic attack and dyslipidemia in the undertreated and sufficient anticoagulation groups than that in the no anticoagulation group ($P<0.001$). Patients who received prestroke anticoagulation therapy were less likely to undergo intravenous thrombolysis upon admission ($P=0.002$). There were no significant differences in lesion location or vessel occlusion among the four groups (Table 1). The sufficient anticoagulation group had a lower initial NIHSS score, better outcomes at 3 months post-stroke, and lower infarct volume than the no anticoagulation and undertreated VKA groups (no anticoagulation vs. undertreated VKA vs. sufficient anticoagulation: NIHSS score: 6.0 [2.0–15.0] vs. 5.5 [1.0–16.3] vs. 4.0 [1.0–9.0], $P=0.008$; good outcomes at 3 months: 52.7% vs. 50.0% vs. 73.0%, $P=0.008$; infarct volume: 45.8±73.2 vs. 45.0±69.1 vs. 15.5±25.6 mL, $P=0.005$ (Table 1). Additionally, the DOAC group had a lower initial NIHSS score ($P=0.018$) and better outcomes at 3 months post-stroke ($P=0.015$) than the VKA group (Table 2). Furthermore, the DOAC group had the lowest infarct volume among the four treatment groups (no anticoagulation vs. undertreated VKA vs. sufficient VKA vs. DOAC: 45.8±73.2 mL vs. 45.0±69.1 mL vs.

Table 1. Baseline characteristics of the included patients

Variable	Total (n=487)	No anticoagulant (n=374, 76.8%)	Undertreated anticoagulation (n=50, 10.3%)	Sufficient anticoagulation (n=63, 12.9%)	*P*-value
Age (yr)	73.8±9.9	74.2±9.9	72.3±11.6	72.6±7.9	0.244
Male	294 (60.4)	220 (58.8)	30 (60.0)	44 (69.8)	0.254
Hypertension	353 (72.5)	270 (72.2)	35 (70.0)	48 (76.2)	0.739
Diabetes mellitus	164 (33.7)	123 (32.9)	14 (28.0)	27 (42.9)	0.202
Dyslipidemia	184 (37.8)	137 (36.6)	15 (30.0)	32 (50.8)	0.049
Previous stroke	135 (27.7)	84 (22.5)	23 (46.0)	28 (44.4)	<0.001
Coronary artery disease	88 (18.1)	72 (19.3)	10 (20.0)	6 (8.5)	0.166
Smoking	142 (29.2)	110 (29.4)	15 (30.0)	17 (27.0)	0.917
Initial NIHSS	5.0 (2.0–15.0)	6.0 (2.0–15.0)	5.5 (1.0–16.3)	4.0 (1.0–9.0)	0.008
Initial moderate to severe stroke (NIHSS ≥5)	243 (49.9)	195 (52.1)	25 (50.0)	23 (36.5)	0.072
Discharge NIHSS	2.5 (1.0–9.0)	3.0 (1.0–10.0)	3.0 (0.8–9.0)	2.0 (0.0–5.0)	0.074
Prestroke mRS=0	375 (77.0)	294 (78.6)	312 (64.0)	49 (77.8)	0.069
Lesion locations					0.638
Anterior	327 (67.1)	257 (68.7)	33 (66.0)	37 (58.7)	
Posterior	99 (20.3)	72 (19.3)	11 (22.0)	16 (25.4)	
Multiple	61 (12.5)	45 (12.0)	6 (12.0)	10 (15.9)	
Vessel occlusion					0.668
None	259 (53.2)	192 (51.3)	28 (56.0)	39 (61.9)	
Anterior	181 (37.2)	146 (39.0)	17 (34.0)	18 (28.6)	
Posterior	42 (8.6)	31 (8.3)	5 (10.0)	6 (9.5)	
Multiple	5 (1.0)	5 (1.3)	0	0	
Intravenous thrombolysis	65 (13.3)	61 (16.3)	2 (4.0)	2 (3.2)	0.002
Endovascular reperfusion therapy	99 (20.3)	79 (21.1)	10 (20.0)	10 (15.9)	0.631
Fasting glucose level (mg/dL)	109.8±38.5	111.4±41.4	102.4±28.0	106.9±24.9	0.266
Good outcome at 3 months	268 (55.0)	197 (52.7)	25 (50.0)	46 (73.0)	0.008
Laboratory information					
Hemoglobin (g/dL)	13.4±2.1	13.4±2.1	13.1±2.3	13.8±1.9	0.159
Platelet (×1,000/μL)	206.4±65.2	207.3±66.6	203.0±62.6	204.2±59.6	0.873
Creatinine (mg/dL)	1.15±0.94	1.14±0.95	1.32±1.30	1.10±0.43	0.389
Total cholesterol (mg/dL)	158.4±36.8	159.6±37.3	154.4±34.5	154.5±36.1	0.444
hs-CRP (mg/dL)	1.39±2.98	1.45±3.03	1.93±3.91	0.62±1.27	0.052
PT-INR	1.13±0.35	1.04±0.11	1.33±0.28	1.50±0.76	<0.001
aPTT (sec)	32.2±17.9	31.4±19.9	33.6±6.4	35.7±8.3	0.179
Infarct volume (mL)	41.8±69.2	45.8±73.2	45.0±69.1	15.5±25.6	0.005

Values are prsesented as mean±standard deviation, number (%), or median (interquartile range).
NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; hs-CRP, high-sensitivity C-reactive protein; PT-INR, prothrombin time-international normalized ratio; aPTT, activated partial thromboplastin time.

https://doi.org/10.18700/jnc.230031

Table 2. Baseline characteristics according to anticoagulation

Variable	Total (n=487)	No anticoagulant (n=374, 76.8%)	Undertreated VKA (n=50, 10.3%)	Sufficient VKA (n=10, 2.1%)	DOAC (n=53, 10.9%)	*P*-value
Age (yr)	73.8±9.9	74.2±9.9	72.3±11.6	75.0±9.3	72.2±7.6	0.318
Male	294 (60.4)	220 (58.8)	30 (60.0)	8 (80.0)	36 (67.9)	0.357
Hypertension	353 (72.5)	270 (72.2)	35 (70.0)	8 (80.0)	40 (75.5)	0.884
Diabetes mellitus	164 (33.7)	123 (32.9)	14 (28.0)	4 (40.0)	23 (43.4)	0.368
Dyslipidemia	184 (37.8)	137 (36.6)	15 (30.0)	3 (30.0)	29 (54.7)	0.040
Previous stroke	135 (27.7)	84 (22.5)	23 (46.0)	4 (40.0)	24 (45.3)	<0.001
Coronary artery disease	88 (18.1)	72 (19.3)	10 (20.0)	0	6 (11.3)	0.223
Smoking	142 (29.2)	110 (29.4)	15 (30.0)	3 (30.0)	14 (26.4)	0.982
Initial NIHSS	5.0 (2.0–15.0)	6.0 (2.0–15.0)	5.5 (1.0–16.3)	5.0 (1.0–14.5)	4.0 (1.0–8.0)	0.018
Initial moderate to severe stroke (NIHSS ≥ 5)	243 (49.9)	195 (52.1)	25 (50.0)	5 (50.0)	18 (34.0)	0.105
Discharge NIHSS	2.5 (1.0-9.0)	3.0 (1.0–10.0)	2.0 (0.0–11.0)	2.0 (0.0–4.5)	2.0 (0.0–5.0)	0.150
Prestroke mRS=0	375 (77.0)	294 (78.6)	312 (64.0)	8 (80.0)	41 (77.4)	0.143
Lesion locations						0.821
Anterior	327 (67.1)	257 (68.7)	33 (66.0)	6 (60.0)	31 (58.5)	
Posterior	99 (20.3)	72 (19.3)	11 (22.0)	3 (30.0)	13 (24.5)	
Multiple	61 (12.5)	45 (12.0)	6 (12.0)	1 (10.0)	9 (17.0)	
Vessel occlusion						0.851
None	259 (53.2)	192 (51.3)	28 (56.0)	6 (60.0)	33 (62.3)	
Anterior	181 (37.2)	146 (39.0)	17 (34.0)	3 (30.0)	15 (28.3)	
Posterior	42 (8.6)	31 (8.3)	5 (10.0)	1 (10.0)	5 (9.4)	
Multiple	5 (1.0)	5 (1.3)	0	0	0	
Intravenous thrombolysis	65 (13.3)	61 (16.3)	2 (4.0)	1 (10.0)	1 (1.9)	0.005
Endovascular reperfusion therapy	99 (20.3)	79 (21.1)	10 (20.0)	1 (10.0)	9 (17.0)	0.763
Fasting glucose level (mg/dL)	109.8±38.5	111.4±41.4	102.4±28.0	107.6±23.5	106.8±25.5	0.449
Good outcome at 3 months	268 (55.0)	197 (52.7)	25 (50.0)	6 (60.0)	40 (75.5)	0.015
Laboratory information						
Hemoglobin (g/dL)	13.4±2.1	13.4±2.1	13.1±2.3	14.1±1.3	13.8±2.0	0.265
Platelet (×1,000/μL)	206.4±65.2	207.3±66.6	203.0±62.6	214.0±55.0	202.3±60.7	0.910
Creatinine (mg/dL)	1.15±0.94	1.14±0.95	1.32±1.30	1.18±0.35	1.09±0.44	0.578
Total cholesterol (mg/dL)	158.4±36.8	159.6±37.3	154.4±34.5	168.2±30.1	152.0±36.8	0.376
hs-CRP (mg/dL)	1.39±2.98	1.45±3.03	1.93±3.91	0.42±0.64	0.66±1.36	0.113
PT-INR	1.13±0.35	1.04±0.11	1.33±0.28	2.84±0.87	1.25±0.38	<0.001
aPTT (sec)	32.2±17.9	31.4±19.9	33.6±6.4	42.1±12.2	34.5±6.8	0.175
Infarct volume (mL)	41.8±69.2	45.8±73.2	45.0±69.1	30.9±24.7	12.6±24.9	0.011

Values are prsesented as mean±standard deviation, number (%), or median (interquartile range).
VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; hs-CRP, high-sensitivity C-reactive protein; PT-INR, prothrombin time-international normalized ratio; aPTT, activated partial thromboplastin time.

30.9±24.7 mL vs. 12.6±24.9 mL, $P=0.011$) (Table 2, Fig. 1). However, sufficient anticoagulation was negatively associated with initial stroke severity (NIHSS score ≥5) and poor outcome in univariate analysis (Table 3), and was independently negatively correlated with initial moderate to severe stroke (odds ratio [OR], 0.467; 95% confidence interval [CI], 0.236–0.888; $P=0.021$) and poor outcome at 3 months post-stroke (OR, 0.377; 95% CI, 0.155–0.920; $P=0.032$) (Table 3) in multivariate analysis.

DISCUSSION

This study showed that compared to no or undertreated anticoagulation, sufficient pre-stroke anticoagulation with VKA and DOAC was associated with milder stroke and was independently related to a better outcome at 3 months post-stroke in patients with nonvalvular AF. Additionally, the DOAC group had the lowest initial NIHSS score and smallest infarct volume among the four anticoagulation therapy groups.

Patients with AF who receive sufficient pre-stroke VKA therapy have a lower risk and severity of stroke, and better outcomes than those who do not receive anticoagulation [10-14]. Moreover, DOAC therapy was more effective than other anticoagulant therapies in reducing infarct volume, arterial occlusion, and stroke severity in patients with AF who experienced anterior circulation ischemic stroke [15,16]. Although previous studies have reported the occurrence of major artery occlusion leading to ischemic

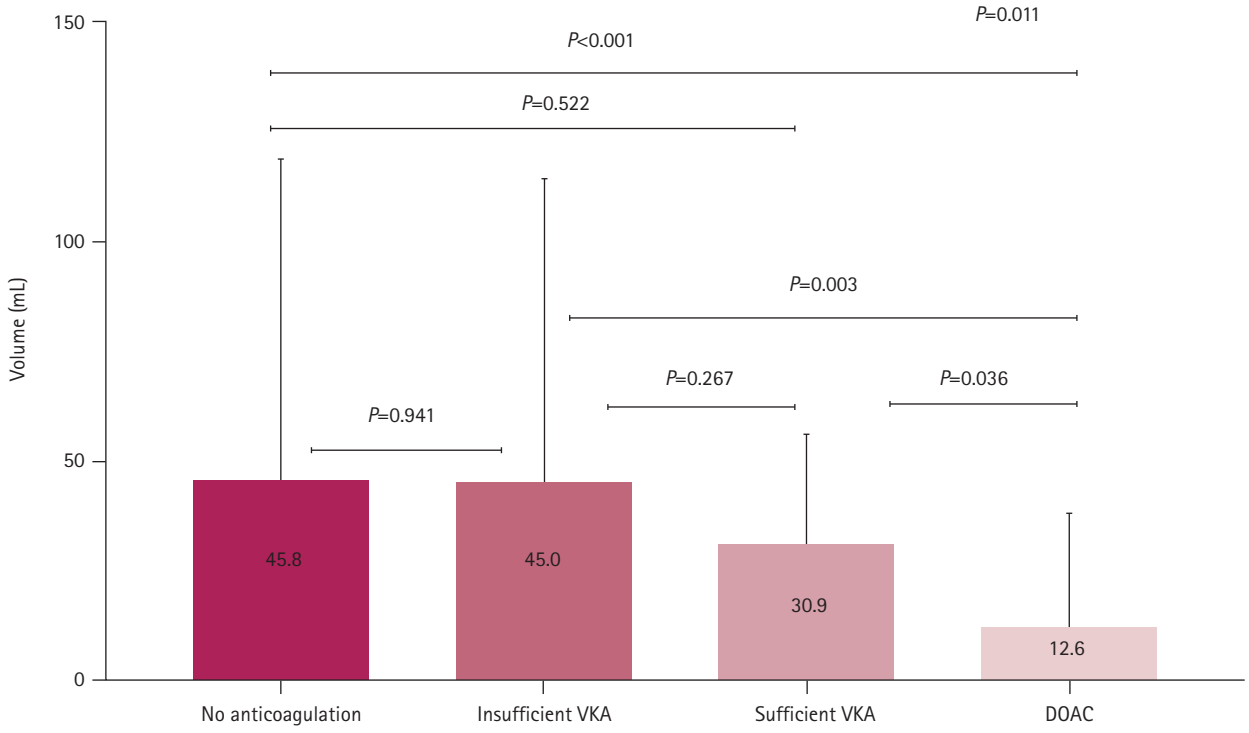

Fig. 1. Comparison of infarct volume according to pre-stroke anticoagulation. The sufficient anticoagulation group (sufficient vitamin K antagonist [VKA] and direct oral anticoagulants [DOACs]) had a lower infarct volume than no anticoagulation and undertreated VKA groups. Furthermore, the DOAC group had the lowest infarct volume by a significant margin among the four treatment groups.

Table 3. Association between anticoagulation and short-term outcome in ischemic stroke patients with nonvalvular atrial fibrillation

Variable	Crude odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Initial NIHSS ≥5[a]				
Age	1.040 (1.020–1.060)	<0.001	1.032 (1.008–1.056)	0.009
Sufficient anticoagulation	0.463 (0.269-0.797)	0.005	0.457 (0.236–0.888)	0.021
Poor outcome at 3 months[b]				
Initial NIHSS	1.244 (1.197–1.293)	<0.001	1.340 (1.256–1.143)	<0.001
Sufficient anticoagulation	0.406 (0.226–0.731)	0.003	0.377 (0.155–0.920)	0.032

CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale.
[a]Adjusted for previous stroke, age, hypertension, diabetes mellitus, prestroke modified Rankin Scale, locations of lesions, vessel occlusion, sufficient anticoagulation; [b]Adjusted for initial NIHSS, endovascular reperfusion therapy, intravenous thrombolysis, previous stroke, hypertension, diabetes mellitus, dyslipidemia, vessel occlusion, fasting glucose level, prestroke modified Rankin Scale, locations of lesions, anticoagulation.

stroke in patients with AF and negative associations between VKA or DOAC therapy and initial stroke volume, few studies have evaluated the relationship between sufficient anticoagulation and initial stroke severity, functional outcome, and infarct volume according to the type of pre-stroke anticoagulation therapy in patients with AF and ischemic stroke in different vascular territories. In our study, sufficient pre-stroke anticoagulation reduced stroke severity and infarct volume, and improved functional outcomes in patients with nonvalvular AF, regardless of the vascular territory involved. Moreover, DOAC therapy resulted in decreased stroke severity and improved functional outcomes, consistent with the findings of previous studies [15,16].

Sufficient anticoagulation therapy leads to a decrease in the size of thrombi and emboli, thereby preventing large artery occlusion and decreasing the infarct volume, resulting in mild initial symptoms of acute ischemic stroke [13,22,23]. Small thrombi, which occur in patients consistently receiving sufficient anticoagulation, are indirectly related to the ultra-early recanalization of vulnerable thrombi, thereby preventing large artery occlusion. Owing to minimal fluctuations in its anticoagulation effect, DOAC therapy consistently provides optimal anticoagulation therapy compared to VKA therapy. Therefore, DOAC therapy is at least as effective as VKA therapy in preventing stroke occurrence and reducing initial stroke severity [15,16]. Consequently, the recommended an-

https://doi.org/10.18700/jnc.230031

ticoagulation strategy for the secondary prevention of ischemic stroke in patients with AF has been changed from VKA to DOAC, and additional indications for DOAC use have been suggested [4-9]. Sufficient anticoagulation can be attributed to the inhibition of the thrombotic system through the acceleration of thrombolysis, which may lead to gradual fibrinolysis in the thrombi. Therefore, therapeutic anticoagulation can reduce infarct size by preventing microvascular thrombosis after ischemic stroke [24], which may explain the lower stroke severity and better outcomes in the DOAC group than that in the VKA group.

In our study, stroke severity, infarct volume, and outcomes of the insufficient anticoagulation group were similar to those of the no anticoagulation group. In contrast, subtherapeutic anticoagulation with VKA was associated with poor medication adherence. A PT-INR in the subtherapeutic range in patients receiving VKAs may lead to a transient hypercoagulable state due to the difference in plasma half-life between procoagulation factors II and X and anticoagulant proteins C and S [25,26]. Therefore, it is pharmacokinetically possible that, compared to the no anticoagulation group, the subtherapeutic group had similarly sized or larger thrombi, which may have resulted in an increased infarct volume [27]. Hence, well-managed oral anticoagulant treatment may reduce stroke severity and improve functional outcomes of ischemic stroke in patients with nonvalvular AF.

However, this study had some limitations. First, this was a retrospective study; therefore, there is a possibility of selection bias and uncontrolled factors in the clinical scenario. Second, pre-stroke anticoagulant status was defined based on prescription information, whereas drug adherence data for DOACs were not systematically collected. Third, we did not measure the DOAC plasma levels using calibrated Xa activity or hemoclot assays, which may have affected the findings in the DOAC treatment group. Finally, we did not differentiate between paroxysmal, persistent, or permanent AF. However, all AF types are high-risk factors for embolic vascular events.

In conclusion, sufficient anticoagulation therapy is associated with decreased stroke severity and infarct volume, and improved functional outcomes. Patients with valvular AF who received DOAC treatment prior to ischemic stroke onset showed small infarct volumes and good functional outcomes at 3 months post-stroke. Therefore, sufficient anticoagulation with VKAs and DOACs could improve ischemic stroke outcomes in patients with nonvalvular AF. However, further large-scale clinical studies are required to determine what constitutes sufficient anticoagulation and to evaluate stroke severity and outcomes after ischemic stroke caused by nonvalvular AF.

ARTICLE INFORMATION

Ethics statement

This study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (No. H-1009-062-332). The need for informed consent was waived by the board because of the retrospective nature of the study. All the procedures were performed in accordance with the relevant guidelines and regulations of the IRB of the Seoul National University Hospital.

Conflict of interest

Tae Jung Kim is an editor-in-chief, and Soo-Hyun Park and Sang-Bae Ko are editorial board members of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflict of interest relevant to this article was reported.

ORCID

Tae Jung Kim https://orcid.org/0000-0003-3616-5627
Soo-Hyun Park https://orcid.org/0000-0003-1626-3940
Youngjoon Kim https://orcid.org/0000-0001-6180-9282
Sang-Bae Ko https://orcid.org/0000-0002-9429-9597

Author contributions

Conceptualization: TJK, SBK. Methodology: TJK, SBK. Software: TJK, SHP. Validation: YK, SHP. Formal analysis: TJK. Investigation: TJK, YK, SHP. Resources: TJK, SBK. Data curation: TJK. Visualization: TJK. Supervision: SBK. Project administration: TJK, SBK. Writing–original draft: TJK. Writing–review & editing: TJK, SBK.

REFERENCES

1. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. Circulation 2022;145:e153-639.
2. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ. Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 Suppl):429S-456S.
3. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131:492-501.
4. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.

5. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
6. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104.
7. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
8. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke 2021;52:e364-467.
9. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:2160-236.
10. Wang C, Wang Y, Wang C, Zhao X, Liu L, Liu G, et al. Anticoagulation-related reduction of first-ever stroke severity in Chinese patients with atrial fibrillation. J Clin Neurosci 2014;21:1755-60.
11. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, Singer DE. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 2003;349:1019-26.
12. O'Donnell M, Oczkowski W, Fang J, Kearon C, Silva J, Bradley C, et al. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. Lancet Neurol 2006;5:749-54.
13. Matsumoto M, Okazaki S, Sakaguchi M, Ohara N, Furukado S, Nagano K, et al. Preadmission therapeutic anticoagulation reduces cerebral infarct volume in patients with nonvalvular atrial fibrillation. Eur Neurol 2011;66:277-82.
14. Schwammenthal Y, Bornstein N, Schwammenthal E, Schwartz R, Goldbourt U, Tsabari R, et al. Relation of effective anticoagulation in patients with atrial fibrillation to stroke severity and survival (from the National Acute Stroke Israeli Survey [NASIS]). Am J Cardiol 2010;105:411-6.
15. Sakamoto Y, Okubo S, Sekine T, Nito C, Suda S, Matsumoto N, et al. Prior direct oral anticoagulant therapy is related to small infarct volume and no major artery occlusion in patients with stroke and non-valvular atrial fibrillation. J Am Heart Assoc 2018;7:e009507.
16. Sakamoto Y, Okubo S, Nito C, Suda S, Matsumoto N, Abe A, et al. The relationship between stroke severity and prior direct oral anticoagulant therapy in patients with acute ischaemic stroke and non-valvular atrial fibrillation. Eur J Neurol 2017;24:1399-406.
17. Kenmuir CL, Hammer M, Jovin T, Reddy V, Wechsler L, Jadhav A. Predictors of outcome in patients presenting with acute ischemic stroke and mild stroke scale scores. J Stroke Cerebrovasc Dis 2015;24:1685-9.
18. Kang KM, Sohn CH, Choi SH, Jung KH, Yoo RE, Yun TJ, et al. Detection of crossed cerebellar diaschisis in hyperacute ischemic stroke using arterial spin-labeled MR imaging. PLoS One 2017;12:e0173971.
19. Nam KW, Kim CK, Ko SB, Yoon BW, Yoo RE, Sohn CH. Regional arterial spin labeling perfusion defect is associated with early ischemic recurrence in patients with a transient ischemic attack. Stroke 2020;51:186-92.
20. Nam KW, Kim TJ, Kim CK, Mo H, Jeong HY, Kang MK, et al. Temporal changes in the neutrophil to lymphocyte ratio and the neurological progression in cryptogenic stroke with active cancer. PLoS One 2018;13:e0194286.
21. McAuliffe MJ, Lalonde FM, McGarry D, Gandler W, Csaky K, Trus BL. Medical image processing, analysis and visualization in clinical research. In: Proceedings of the 14th IEEE Symposium on Computer-Based Medical Systems; 2001 Jul 26-27; Bethesda, MD. CBMS; 2001. p. 381-6.
22. Ay H, Arsava EM, Gungor L, Greer D, Singhal AB, Furie KL, et al. Admission international normalized ratio and acute infarct volume in ischemic stroke. Ann Neurol 2008;64:499-506.
23. Wakita M, Yasaka M, Minematsu K, Yamaguchi T. Effects of anticoagulation on infarct size and clinical outcome in acute cardioembolic stroke. Angiology 2002;53:551-6.
24. Corrado G, Tadeo G, Beretta S, Tagliagambe LM, Manzillo GF, Spata M, et al. Atrial thrombi resolution after prolonged anticoagulation in patients with atrial fibrillation. Chest 1999;115:140-3.
25. Takano K, Iino K, Ibayashi S, Tagawa K, Sadoshima S, Fujishima M. Hypercoagulable state under low-intensity warfarin anticoagulation assessed with hemostatic markers in cardiac disorders. Am J Cardiol 1994;74:935-9.
26. Sakamoto Y, Okubo S, Nito C, Suda S, Matsumoto N, Nishiyama Y, et al. Insufficient warfarin therapy is associated with higher severity of stroke than no anticoagulation in patients with atrial fibrillation and acute anterior-circulation stroke. Circ J 2018;82:1437-42.
27. Harrison L, Johnston M, Massicotte MP, Crowther M, Moffat K, Hirsh J. Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. Ann Intern Med 1997;126:133-6.

https://doi.org/10.18700/jnc.230031

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):101-106
https://doi.org/10.18700/jnc.230034

Journal of Neurocritical Care

A case report of pitfall of fever and altered mental status: cerebral malaria due to *Plasmodium falciparum* in an adult traveler returning from Congo

Soo-Hyun Park, MD, PhD[1,2]; Yerim Kim, MD, PhD[1]; Yeo Jin Kim[1]; Jong Seok Bae, MD, PhD[1]; Ju-Hun Lee, MD, PhD[1]

[1]Department of Neurology, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea
[2]Department of Critical Care Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Korea

CASE REPORT

Received: September 27, 2023
Revised: October 24, 2023
Accepted: October 27, 2023

Corresponding Author:
Yerim Kim, MD, PhD
Departments of Neurology and Critical Care Medicine, Kangdong Sacred Heart Hospital, 150 Seongan-ro, Gangdong-gu, Seoul 05355, Korea
Tel: +82-2-2152-1027
Fax : +82-2-2152-1204
Email: brainyrk@gmail.com

Background: Cerebral malaria, caused by *Plasmodium falciparum*, can lead to severe neurological complications. It is more frequently observed in children than in adults. Because cerebral malaria is rare and has no specific symptoms or neurologic findings, it is not easy to diagnose.

Case Report: We report a case of a 61-year-old male who returned from the Democratic Republic of the Congo with fever, fatigue, and confusion. With considering cerebral malaria, a peripheral blood smear confirmed *P. falciparum* infection (initial parasite load, 760,800/μL; ring form, 100%). Cerebrospinal fluid analyses showed high protein level (103.2 mg/dL). Electroencephalograms showed background slowing activity. Brain magnetic resonance imaging showed signal changes and cerebral swelling. The initial doxycycline and quinidine treatment for malaria was successful without sequalae.

Conclusion: Physicians must have high suspicion about the symptoms and the necessity for screening in individuals traveling to malaria-endemic regions when experiencing changes in consciousness.

Keywords: Malaria; Cerebral malaria; *Plasmodium falciparum*; Altered mental status; Doxycycline; Quinidine

INTRODUCTION

Cerebral malaria is a rare symptom of *Plasmodium falciparum* [1]. This disease destroys the integrity of the blood-brain barrier through various mechanisms [2]. Cerebral malaria occurs mainly in children in endemic areas or in adult travelers who have not developed immunity. Therefore, clinicians should consider diagnosing cerebral malaria in patients with neurological symptoms and a history of travel to malaria-endemic areas [3]. Moreover, cerebral malaria is associated with severe neurological complications and a high mortality rate of approximately 15% [3]. The incidence of cerebral malaria is high in pediatric populations, particularly in those younger than 5 years, in sub-Saharan Africa, whereas cerebral malaria is relatively rare in adults [1]. Given the potential for sequelae, particularly in adults, early diagnosis and prompt treatment are critical for reducing the disease burden. In this report, we describe a case of decreased consciousness caused by *P. falciparum* infection in a patient who was transferred to the intensive care unit (ICU).

CASE REPORT

A 61-year-old man was admitted to the hospital with a fever of 38.9 °C, progressive headache, and altered mental status. The patient had resided in the Democratic Republic of the Congo for business for 6 months before his admission and had recently returned to Korea. The patient received doxycycline for malarial prophylaxis along with vaccinations for yellow fever and typhoid disease.

Two days before the emergency room visit, he was confused, disoriented, and unable to recognize his house. His symptoms were intermittent and worsened upon awakening. The patient became increasingly delirious, and his violent behavior made it difficult for him to provide a comprehensive medical history. He had minimal oral intake for 4 days. His wife said that his symptoms started 2 weeks before presentation while he was in the Democratic Republic of the Congo. He experienced diarrhea but did not have any hematochezia or black stools. In addition, he had a cough without experiencing dyspnea or chest pain. The patient experienced nausea and vomiting, however, did not complain of visual disturbances, numbness, or focal weakness.

Upon arriving at the hospital, his vital signs revealed significant hypotension (blood pressure of 102/63 mm Hg), tachycardia (123 beats/min), a fever (38.9 °C), and an oxygen saturation level of 94% while breathing room air. The initial electrocardiogram (ECG) revealed sinus tachycardia with a QTc interval of 454 ms. He was admitted to the neuro-ICU for the management and continuous monitoring of his mental status, which included regular laboratory tests and ECGs. Several evaluations were performed for the diagnosis, and tropical infections were considered. Laboratory tests revealed pancytopenia, elevated C-reactive protein levels, and hyperlactatemia. Evaluation of cerebrospinal fluid (CSF) revealed no evidence of meningitis with elevated CSF protein level (103.2 mg/dL; normal range, 15.0–40.0 mg/dL) and normal adenosine deaminase (ADA) level (10 IU/L; normal range, 5.0–20.0 IU/L).

Further examination revealed no evidence of meningitis, enteric fever, Ebola virus disease, schistosomiasis, tick-borne Rickettsiae, filariasis, yellow fever, dengue, or chikungunya. Two days after admission, he developed continuous drowsiness (Glasgow Coma Scale [GCS] score, E3V4M6) and confusion (Fig. 1). Neurocognitive assessment yielded a score of 14/30 on the Mini-Mental State Examination (MMSE), 13/30 on the Montreal Cognitive Assessment (MoCA), and poor visuospatial and executive skills (Fig. 1). Phonemic and semantic paraphrasic fluency errors were present with mild ideomotor apraxia when following commands in motor tasks. No evidence of cerebellar dysfunction, frontal release signs, or depression was observed. Electroencephalography (EEG) was used to differentiate seizures, and EEG was performed. The EEG displayed background slowing activity (Fig. 2).

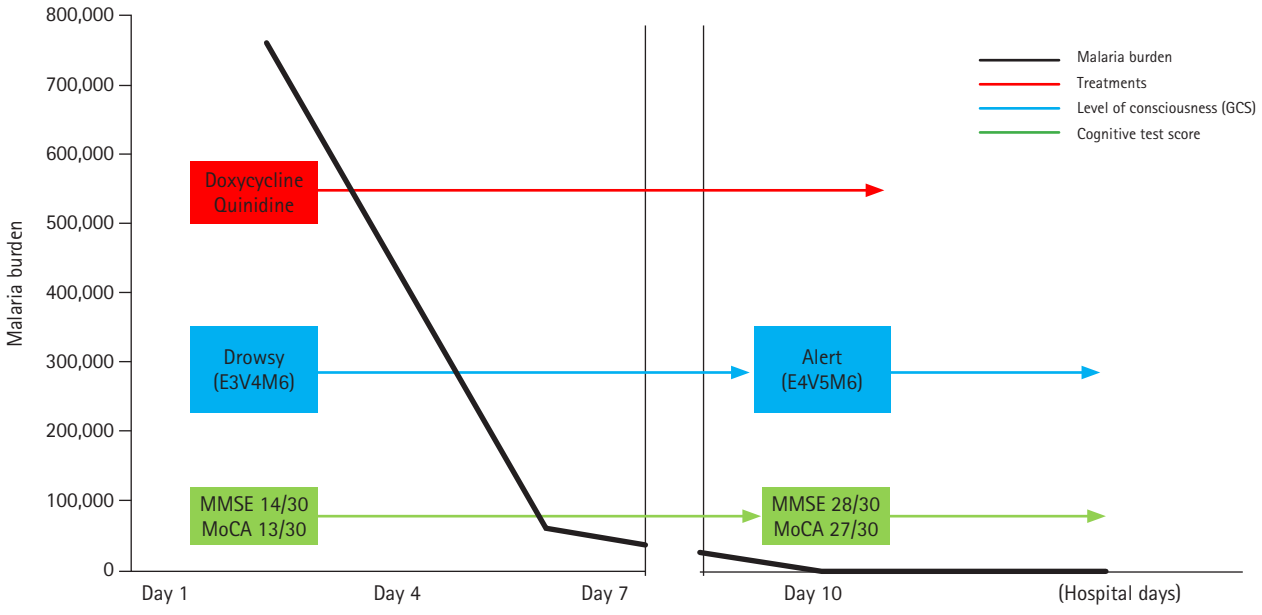

Fig. 1. Timeline of malaria burden and symptoms progression. The measured malaria burden (black line), level of consciousness (blue line), and cognitive function test results (green line) are related to the treatment. GCS, Glasgow Coma Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

https://doi.org/10.18700/jnc.230034

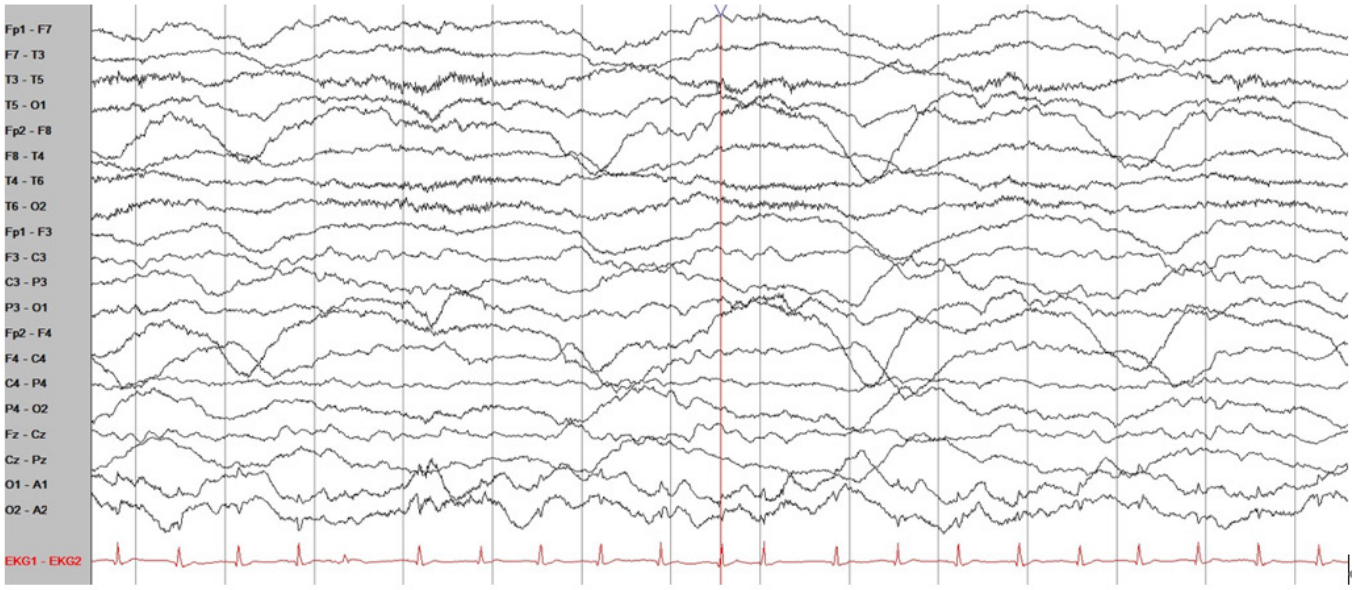

Fig. 2. Patient's electroencephalography (EEG). EEG displays background slowing activity.

Brain magnetic resonance imaging (MRI) revealed subtle changes with high signal intensity on the diffusion-weighted image (DWI) and swelling of the hippocampal, limbic, and parieto-occipital cortical lesions (Fig. 3). A peripheral blood smear isolated malarial parasites and confirmed *P. falciparum* infection (initial parasite load, 760,800/μL; ring form, 100%) under a microscope with multiple invasions of ring form in red blood cells (RBCs). Finally, cerebral malaria was diagnosed based on the patient's clinical course and laboratory results.

The patient was treated for cerebral malaria with doxycycline and intravenous quinidine. Clinicians monitored drug toxicity. As intravenous quinidine can evoke hyperinsulinemia due to hypoglycemia, hourly blood glucose levels were assessed. Quinidine may also prolong the QT interval. Consequently, continuous ECG monitoring was required. In addition, clinicians consider discontinuing quinidine if QTc prolongs over 50% of the patient's initial QTc and holding it until the QTc falls below 25% of the initial baseline value.

His consciousness continued to worsen and eventually declined. Following 6 days of intravenous quinidine treatment, a peripheral blood smear indicated a malarial load of 60,775/μL. His mental status improved (GCS, E4V4M6) as the malarial load decreased (250/μL) (Fig. 1). The patient's violent tendencies also disappeared.

Ten days later, the patient was transferred to the general ward. His MMSE and MoCA scores improved to 28/30 and 27/30, respectively, with good visuospatial and executive skills (Fig. 4). His phonemic and semantic fluencies also improved. The patient was discharged on the 14th day of admission with no detectable parasite load (0/μL). His mental status and follow-up EEG findings were normal, and he could perform activities of daily living independently after discharge.

DISCUSSION

Here, we report an uncommon case of cerebral malaria in a patient with various neurological symptoms in Korea. In this case, the patient was properly diagnosed and treated, but when the medical staff initially met the patient, his symptoms were not specific. Therefore, we almost missed the first time and did not include the diagnostic criteria for cerebral malaria by *P. falciparum*.

Cerebral malaria poses a diagnostic challenge because of the nonspecific clinical features that may overlap with those of other conditions, leading to altered consciousness. Only *P. falciparum*, and no other malaria-causing pathogens, can cause cerebral malaria. The World Health Organization defines cerebral malaria as a clinical syndrome characterized by altered consciousness resulting from malarial infection that cannot be attributed to non-malarial causes [1]. As a result, cerebral malaria exhibits a heterogeneous array of symptoms rather than a homogenous syndrome [2].

Cerebral malaria caused by *P. falciparum* is a severe form that affects the brain and results in altered consciousness, neurological deficits, and death [3]. This condition is highly prevalent in endemic regions of Africa and has a significant impact on young

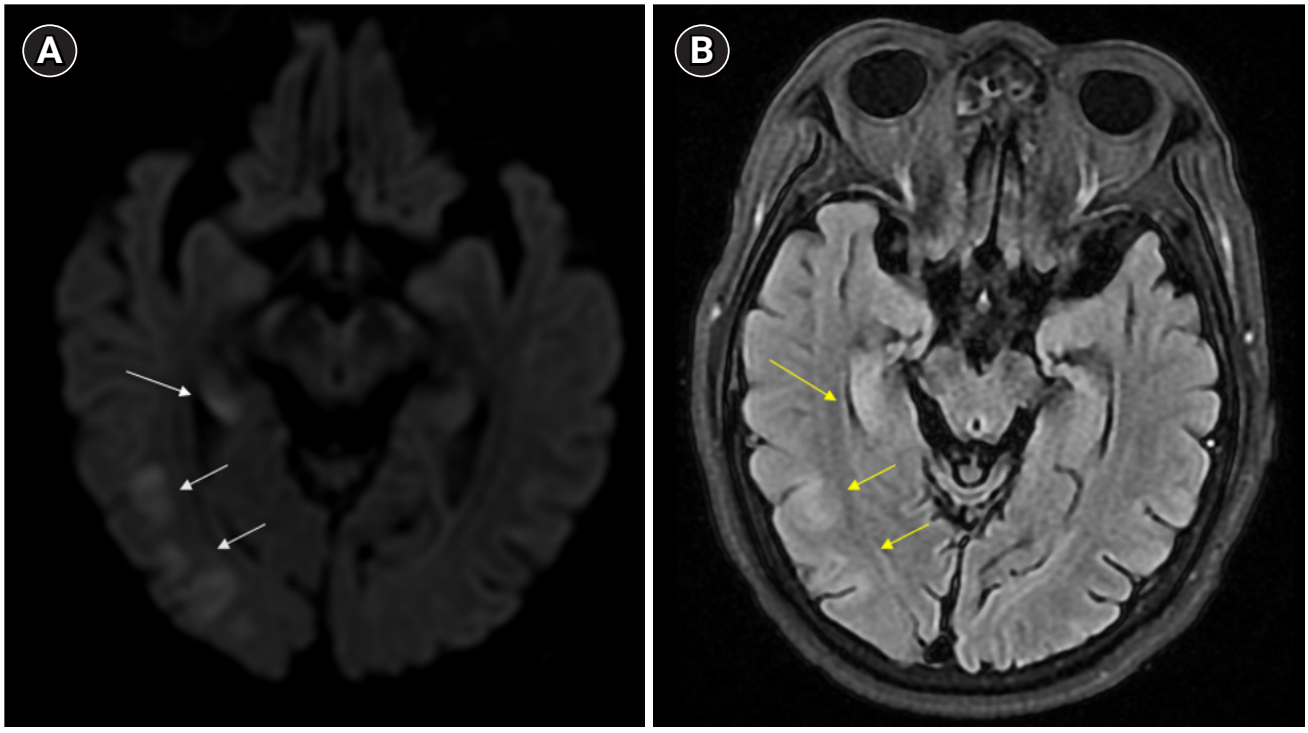

Fig. 3. Brain magnetic resonance imaging. Diffusion-weighted image (A) displaying high signal intensities in the right hippocampal, limbic, and parieto-occipital cortices (white arrows). The fluid attenuated inversion recovery (B) exhibits high signal intensity in the same region (yellow arrows).

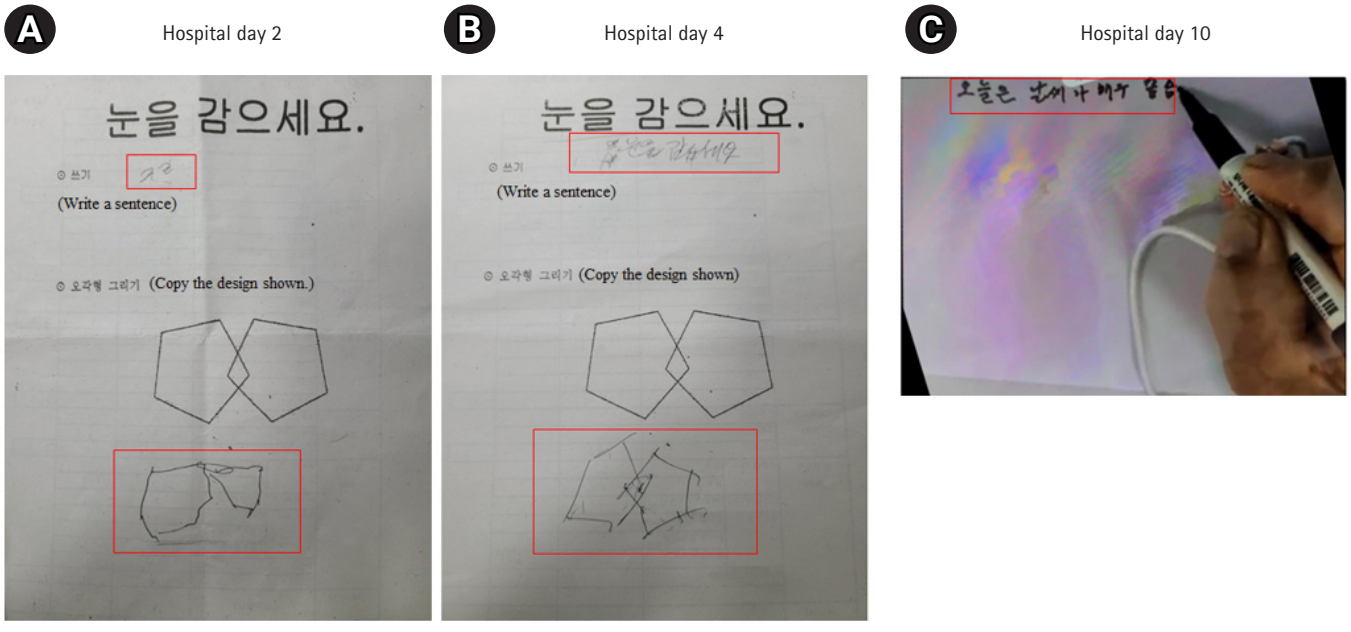

Fig. 4. Results of visuospatial and executive function test. The result of visuospatial and executive function improved after malaria treatment (B) compared before (A). On the 10th hospital day, the patient could write complete sentences (C).

https://doi.org/10.18700/jnc.230034

children, with an estimated incidence of 1,120 per 100,000 per year and a peak incidence in preschool children [4]. Moreover, an estimated 575,000 children in Africa develop cerebral malaria annually [5].

Cerebral malaria presents with symptoms such as fever, headache, and body aches and can progress to altered consciousness (coma). Although neurological deficits, including blindness, ataxia, and hypotonia, have demonstrated improvement over time in some patients, approximately 25% of individuals have long-term impairments, including cognitive, motor, and behavioral dysfunctions, and a 10% incidence of epilepsy [3]. Contrary to its name, cerebral malaria does not involve *P. falciparum* invading the brain tissue. Other commonly observed systemic complications include anemia, metabolic acidosis, electrolyte imbalance, hypoglycemia, and shock. Evidence suggests that cerebral malaria is associated with multiple organ involvement [3].

The pathophysiology of cerebral malaria involves the sequestration of parasitized RBCs (pRBCs) in the cerebral microcirculation, leading to hypoxia and inadequate tissue perfusion. The sequestration of pRBCs in the cerebral microvasculature causes endothelial damage, cell apoptosis, and brain-blood-barrier dysfunction [6]. These events are associated with intracranial hypertension and brain swelling [7]. Cortical infarction and cerebral venous thrombosis can also occur due to disordered coagulation [8]. Severe metabolic factors, such as inflammatory cytokines and chemokines (tumor necrosis factor [TNF], interleukin [IL]-1b, IL-6, and IL-10) and mediators (quinolinic and kynurenic acid), may also exacerbate injury [9].

In addition, CSF examinations should exclude other causes of central nervous system infection. Furthermore, CSF results for cerebral malaria are generally within the normal range. Mild pleocytosis (10–50 cells/mm^3), increased protein (up to 200 mg/dL), and/or ADA levels may sometimes be observed during CSF examination [10]. Our patient also demonstrated elevated CSF protein levels without central nervous system infection.

General conditions such as fever, nutritional status, diarrhea, mood, and medical conditions can affect a patient's cognitive function [11]. Unlike in our case, the evaluation of cognitive function tests presents challenges in cases of cerebral malaria. Therefore, brain MRI can reveal additional information to determine the disease severity and brain injury in patients with cerebral malaria [12]. Brain MRI abnormalities are present in 78% of the patients with cerebral malaria and include signs of cerebral edema, infarcts, and subcortical white matter changes [13]. Brain swelling is related to venous congestion of sequestered pRBCs, causing increased cerebral blood volume [14]. Additionally, DWI abnormalities were few due to cytotoxic edema. In particular, fatal cases are associated with increased brain volume, leading to elevated cerebral pressure. In addition, predominant posterior cerebral swelling, such as in posterior reversible encephalopathy syndrome, has been reported [9]. Changes in MRI were related to the observed neurological symptoms. Compared to computed tomography, MRI is more sensitive for detecting brain abnormalities in patients with cerebral malaria. In addition, EEG findings have been associated with long-term neurocognitive morbidity in cerebral malaria [13]. Moreover, EEG findings suggest neurocognitive outcomes. A high average background voltage, fast dominant rhythm frequency, and vertex sharp waves are associated with better cognitive function [15].

Most patients regained consciousness within 48–72 hours of treatment initiation (median time, 32.3 hours) [1]. Therefore, cerebral malaria treatment aims to lower the malaria burden and reduce brain injury. Additionally, the signs of edema disappeared remarkably after antimalarial treatment within 72 hours in the brain MRI [9,14]. The clinical outcome of cerebral malaria may depend on the appropriate treatment of the disease mechanism to reduce complications. Recommended treatments for malaria include doxycycline and quinidine [2]. However, quinidine is requied caution when treating, because it can lead to torsades de pointes due to a prolonged QT interval and can also result in hypoglycemia due to hyperinsulinemia [2].

Several studies have investigated methods for preventing endothelial damage and improving blood flow. These include interventions targeting the pathogenesis and risk factors for brain injury [1]. Trials have been conducted on steroids, immunoglobulins, anti-TNF agents, micronutrients, and prophylactic anticonvulsants. Combining these adjuvant therapies may enhance neurocognitive outcomes [1].

This was a rare case of an adult with cerebral malaria who presented with altered mental status, behavioral changes, cognitive impairment, and decreased fluency. To diagnose this condition early, clinicians should be vigilant of neurocognitive deficits and neuropsychiatric symptoms. Moreover, individuals returning from malaria-endemic regions should undergo screening when they exhibit changes in their levels of consciousness. The patient's symptoms improved with immediate and appropriate cerebral malaria treatment. For cerebral malaria identification, a travel history to endemic areas, including sub-Saharan Africa, and observation of the peripheral blood smear under a microscope is essential. We also attempted to identify the *P. falciparum* parasite, ring form (multiple invasions), or banana-shaped gametocytes in the blood smear.

ARTICLE INFORMATION

Ethics statement

This study complied with the principles of the Declaration of Helsinki. The study's protocol was reviewed and approved by the Institutional Review Board of Inha University Hospital (IRB No. 2022-08-007-006). The IRB waived the requirement to obtain written informed consent from patients.

Conflict of interest

Soo-Hyun Park is editorial board member of the journal, but she was not involved in the peer reviewer selection, evaluation, or decision-making process for this article. No other potential conflicts of interest relevant to this article have been reported.

ORCID

Soo-Hyun Park	https://orcid.org/0000-0003-1626-3940
Yerim Kim	https://orcid.org/0000-0002-7108-6302
Jong Seok Bae	https://orcid.org/0000-0002-4313-1786
Ju-Hun Lee	https://orcid.org/0000-0001-6831-7248

Author contributions

Conceptualization: SHP. Data curation: SHP, YK. Formal analysis: JHL. Investigation: SHP. Methodology: YK. Software: YK. Validation: BJS. Visualization: YK. Writing–original draft: SHP. Writing–review & editing: SHP, JSB, JHL.

REFERENCES

1. Roberson MT, Smith AT. Cerebral malaria in a patient with recent travel to the Congo presenting with delirium: a case report. Clin Pract Cases Emerg Med 2020;4:533-6.
2. Marsh K, English M, Crawley J, Peshu N. The pathogenesis of severe malaria in African children. Ann Trop Med Parasitol 1996;90:395-402.
3. Idro R, Marsh K, John CC, Newton CR. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. Pediatr Res 2010;68:267-74.
4. Breman JG. The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden. Am J Trop Med Hyg 2001;64(1-2 Suppl):1-11.
5. van Hensbroek MB, Palmer A, Jaffar S, Schneider G, Kwiatkowski D. Residual neurologic sequelae after childhood cerebral malaria. J Pediatr 1997;131(1 Pt 1):125-9.
6. Storm J, Craig AG. Pathogenesis of cerebral malaria: inflammation and cytoadherence. Front Cell Infect Microbiol 2014;4:100.
7. Sein KK, Maeno Y, Thuc HV, Anh TK, Aikawa M. Differential sequestration of parasitized erythrocytes in the cerebrum and cerebellum in human cerebral malaria. Am J Trop Med Hyg 1993;48:504-11.
8. Schiess N, Villabona-Rueda A, Cottier KE, Huether K, Chipeta J, Stins MF. Pathophysiology and neurologic sequelae of cerebral malaria. Malar J 2020;19:266.
9. Mohanty S, Benjamin LA, Majhi M, Panda P, Kampondeni S, Sahu PK, et al. Magnetic resonance imaging of cerebral malaria patients reveals distinct pathogenetic processes in different parts of the brain. mSphere 2017;2:e00193-17.
10. Misra UK, Kalita J, Prabhakar S, Chakravarty A, Kochar D, Nair PP. Cerebral malaria and bacterial meningitis. Ann Indian Acad Neurol 2011;14(Suppl 1):S35-9.
11. Gure TR, Langa KM, Fisher GG, Piette JD, Plassman BL. Functional limitations in older adults who have cognitive impairment without dementia. J Geriatr Psychiatry Neurol 2013;26:78-85.
12. Kumral E, Bayam FE, Köken B, Erdoğan CE. Clinical and neuroimaging determinants of minimally conscious and persistent vegetative states after acute stroke. J Neurocrit Care 2019;12:37-45.
13. Kampondeni SD, Potchen MJ, Beare NA, Seydel KB, Glover SJ, Taylor TE, et al. MRI findings in a cohort of brain injured survivors of pediatric cerebral malaria. Am J Trop Med Hyg 2013;88:542-6.
14. Karimi M, Nazari S, Shirani F, Alivirdiloo V, Siahposht-Khachaki A, Edalatkhah S, et al. Neuroprotective effects of chloroquine on neurological scores, blood-brain barrier permeability, and brain edema after traumatic brain injury in male rats. J Neurocrit Care 2023;16:18-27.
15. Clark DJ, Bond C, Andrews A, Muller DJ, Sarkisian A, Opoka RO, et al. Admission clinical and EEG features associated with mortality and long-term neurologic and cognitive outcomes in pediatric cerebral malaria. Neurology 2023;101:e1307-18.

https://doi.org/10.18700/jnc.230034

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):107-110
https://doi.org/10.18700/jnc.230035

Journal of Neurocritical Care

Disseminated nocardiosis including cerebral nocardiosis caused by *Nocardia farcinica*: a case report

Baeseoup Song, MD[1,*]; Dong Youn Kim, MD, PhD[2,*]; Young Jin Kim, MD, PhD[3]; Ho Geol Woo, MD, PhD[1]

[1]Department of Neurology, College of Medicine, Kyung Hee University, Seoul, Korea
[2]Division of Infectious Diseases, Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Korea
[3]Department of Laboratory Medicine, College of Medicine, Kyung Hee University, Seoul, Korea

CASE REPORT

Received: October 5, 2023
Revised: October 16, 2023
Accepted: October 27, 2023

Corresponding Author:
Ho Geol Woo, MD, PhD
Department of Neurology, Kyung Hee University Hospital, College of Medicine, Kyung Hee University, 23 Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Korea
Tel: +82-2-958-8491
Fax: +82-2-958-8490
Email: nr85plasma@naver.com

*These authors contributed equally to this work.

Background: As nocardiosis presents with nonspecific symptoms, its diagnosis is often difficult, resulting in high mortality. Here, we report a rare case of disseminated *Nocardia farcinica* infection that was successfully managed with a combination of antibiotic therapies.

Case Report: A 71-year-old man with idiopathic thrombocytopenia purpura presented with sudden-onset motor aphasia, motor weakness of the right limb, and fever. Brain magnetic resonance imaging revealed multiple scattered diffusion-restricted lesions. Multiple cutaneous and peritoneal nodules were also identified. We performed full-length 16S ribosomal ribonucleic acid (rRNA) sequencing and obtained basic local alignment search tool results against the National Center for Biotechnology Information 16S rRNA database, which showed the best match to be *N. farcinica*. After maintaining the antibiotics for approximately 56 days, the patient recovered full consciousness, and the motor weakness of the right limb improved.

Conclusion: Timely diagnosis of disseminated or cerebral nocardiosis and treatment with appropriate antibiotics are crucial for a desirable clinical outcome.

Keywords: Nocardiosis; Brain abscess; 16S rRNA; Sequence analysis

INTRODUCTION

Nocardiosis is an infectious disease that can be either localized or disseminated. Nocardiosis typically occurs in adults aged 30–50 years, with male predominance, and primarily affects individuals with severe immune dysfunction [1,2]. Because the symptoms of nocardiosis are nonspecific, diagnosis is often challenging and easily missed, with high mortality (>50%) in patients with disseminated or cerebral nocardiosis [1]. The infection is usually confined to the lungs and disseminated or cerebral nocardiosis is relatively rare. Here, we report a rare case of disseminated *Nocardia farcinica* infection, including cerebral nocardiosis, in an immu-

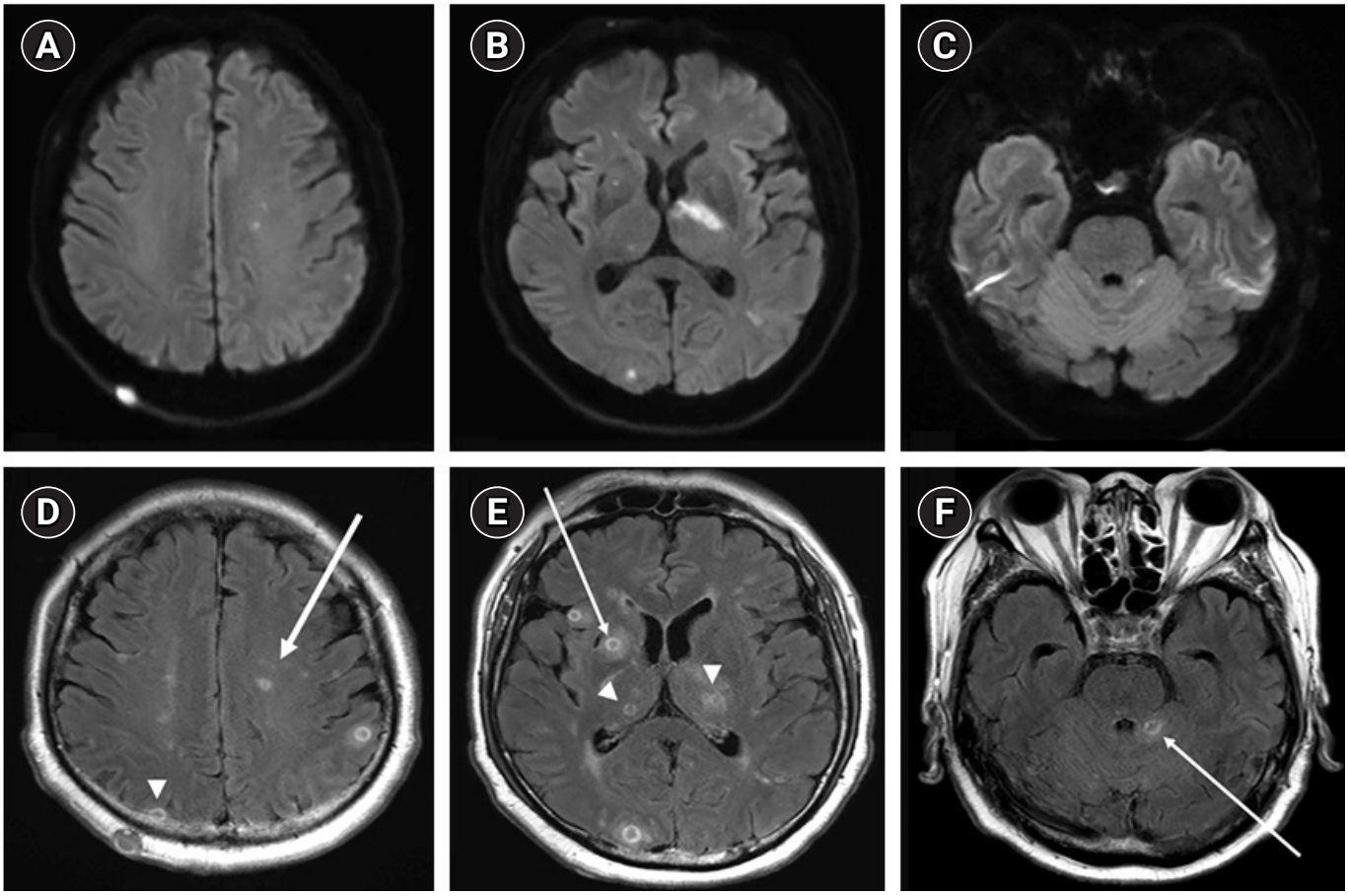

Fig. 1. Magnetic resonance imaging of the patient. (A-C) Multiple scattered diffusion-restricted lesions in both hemispheres, thalami, cerebella, and right basal ganglia are observed on the initial diffusion-weighted image. (D-F) Rim-enhancing lesions (arrows and arrowheads) with associated edema on T1 weighted imaging and a dark signal on T2 weighted imaging and consistent wall thickness suggest a brain abscess.

nosuppressed man, who was successfully managed with a combination of antibiotics.

CASE REPORT

A 71-year-old man presented with sudden-onset motor aphasia, motor weakness of the right limb, and fever (38.3 °C). The patient had a history of hypertension and idiopathic thrombocytopenia purpura (ITP) 5 years prior to admission and was taking 7.5 mg prednisolone per day and 50 mg azathioprine per day for ITP. One month before the onset of the present illness, chest radiography revealed heterogeneous opacities with consolidation in both the lower lobes. A wedge resection was performed to exclude the possibility of lung cancer. Cytomegalovirus pneumonia was confirmed and the patient was treated accordingly. Initial brain magnetic resonance imaging revealed multiple scattered diffusion-restricted lesions, which were present in both hemispheres, thalami, cerebella, and right basal ganglia (Fig. 1A-C). The lesions demonstrated central hypointense signals on T1 weighted imaging with corresponding hyperintense signals on T2 weighted imaging with ring enhancement (Fig. 1D-F).

Initial blood tests showed leukocytosis (19,170/mm^3), including 89% polymorphonuclear cells, and elevated C-reactive protein (16.10 mg/dL). A white blood cell count of 580/mm^3 (80% neutrophils) and protein level of 152 mg/dL were observed in the initial cerebrospinal fluid test. The brain lesions were thought to be brain abscesses with meningitis and treatment was initiated with ceftriaxone, vancomycin, and metronidazole. One week later, his condition rapidly deteriorated with altered consciousness. Second cerebrospinal fluid analysis confirmed white blood cell count of 684/mm^3 and protein level of 107 mg/dL. Abdominopelvic and chest computed tomography revealed multiple cutaneous and peritoneal nodules resulting from hematogenous spread (Supplementary Fig. 1). We made an incision and drained the nodules on

https://doi.org/10.18700/jnc.230035

the skin. Initially, filamentous acid-fast bacilli (AFB) were not observed in the AFB stains. Moreover, the AdvanSure tuberculosis/nontuberculous mycobacteria real-time PCR kit (AdvanSure; LG Life Science) yielded negative results. However, for suspected nocardiosis, we rechecked the tuberculosis culture media obtained during a previous hospitalization and found growing species in the tuberculosis culture media. Additional testing was required, and filamentous AFB were observed in the modified AFB stains of the specimens (Supplementary Fig. 2). Attempts to identify the organism using matrix-associated laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS, Bruker Daltonics) in the *in vitro* diagnostic mode yielded no results. However, *N. farcinica* was identified only in the research use only (RUO) mode. To confirm the results obtained in the RUO mode, we immediately performed full-length 16S ribosomal ribonucleic acid (rRNA) sequencing and obtained basic local alignment search tool (BLAST) results against the National Center for Biotechnology Information 16S rRNA database, which showed the best match to be *N. farcinica* (1,389/1,389, 100%). We re-evaluated the previously resected lung specimens and confirmed the presence of *N. farcinica*. As the guardian refused a brain biopsy, stereotactic cerebral biopsy could not be performed. We changed the antibiotics to imipenem and trimethoprim-sulfamethoxazole (TMP/SMX) to treat the disseminated nocardiosis, including cerebral nocardiosis. We identified antimicrobial susceptibility to TMP/SMX. After maintaining the antibiotics for approximately 56 days, the patient recovered full consciousness, and the motor weakness of the right limb improved.

DISCUSSION

Nocardiosis is a rare infection caused by weakly acid-fast gram-positive bacteria belonging to the Mycobacteriaceae family [3]. Although 54 species of *Nocardia* have been implicated in human infections, *N. farcinica* is one of the six most common species [4]. Cerebral abscesses caused by *N. farcinica* have been increasingly diagnosed because of the growing population of immunosuppressed hosts and improvements in diagnostic capabilities [3]. However, cerebral abscesses are relatively rare and account for approximately 2% of all cerebral abscesses [5]. Retroperitoneal abscesses are also rare [6]. To detect *Nocardia*, the culture identification of *Nocardia* is traditionally carried out through biochemical tests and phenotypic methods including Gram staining, modified acid-fast staining, and chromatography. However, these methods are limited in terms of species-level identification. Using MALDI-TOF MS, it is possible to rapidly and accurately identify microorganisms in a database. However, for relatively rare microorganisms, the results may not be definitive owing to the possible absence of a reference spectrum in the database. According to previous studies, species-level identification has been reported in only 14.9%–80.4% of *Nocardia* isolates [7,8]. Therefore, we identified *Nocardia*, a relatively rare microorganism, using 16S rRNA sequencing in conjunction with MALDI-TOF MS. Although requiring more time and cost, 16S rRNA sequencing and BLAST analysis can provide additional information for the identification of detailed differences between species. A previous study showed that stereotactic cerebral biopsy should be considered early in the diagnostic workup of immunocompromised patients owing to the aggressive course of cerebral nocardiosis [9]. However, because the patient's guardian refused a cerebral biopsy, stereotactic cerebral biopsy could not be performed. *N. farcinica* is usually resistant to multiple antimicrobial agents, particularly broad-spectrum cephalosporins, which makes treatment difficult [10]. TMP/SMX is the most effective treatment for central nervous system infections caused by *Nocardia* [10]. Numerous agents, including imipenem, are considered acceptable second-line treatments. Combination therapy should be considered for patients with severe disseminated central nervous system infections. Prognosis is related to the severity of the underlying disease, site of infection, patient immune function, and presence of drug resistance. The present study had several limitations. First, this was a single-patient single-center study. Additionally, no microorganisms were detected in the brain. Another important limitation is the lack of understanding of the molecular and cellular mechanisms that lead to disseminated infection.

As the use of immunosuppressants increases, the accurate identification of *N. farcinica* is important.

ARTICLE INFORMATION

Ethics statement

This case was reviewed and approved by the Ethics Committee of Kyung Hee University Medical Center (No. KMC IRB 2009-12-301). 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.

Acknowledgments

This work was supported by the National Research Foundation of Korea grant funded by the Korean Government (MSIT) (No. RS-2023-00239251 to HGW).

ORCID

Baeseoup Song https://orcid.org/0000-0002-7697-8449
Dong Youn Kim https://orcid.org/0009-0004-2675-748X
Young Jin Kim https://orcid.org/0000-0001-8182-2433
Ho Geol Woo https://orcid.org/0000-0001-6489-0100

Author contributions

Conceptualization: all authors. Investigation: all authors. Data curation: all authors. Supervision: HGW. Funding acquisition: HGW. Writing–original draft: all authors. Writing–review & editing: all authors.

Supplementary materials

Supplementary materials can be found via https://doi.org/10.18700/jnc.230035.

REFERENCES

1. Curry WA. Human nocardiosis: a clinical review with selected case reports. Arch Intern Med 1980;140:818-26.
2. Corti ME, Villafañe-Fioti MF. Nocardiosis: a review. Int J Infect Dis 2003;7:243-50.
3. Lai CC, Lee LN, Teng LJ, Wu MS, Tsai JC, Hsueh PR. Disseminated Nocardia farcinica infection in a uraemia patient with idiopathic thrombocytopenia purpura receiving steroid therapy. J Med Microbiol 2005;54(Pt 11):1107-10.
4. Wang H, Zhu Y, Cui Q, Wu W, Li G, Chen D, et al. Epidemiology and antimicrobial resistance profiles of the Nocardia species in China, 2009 to 2021. Microbiol Spectr 2022;10:e0156021.
5. Malincarne L, Marroni M, Farina C, Camanni G, Valente M, Belfiori B, et al. Primary brain abscess with Nocardia farcinica in an immunocompetent patient. Clin Neurol Neurosurg 2002;104:132-5.
6. de Montmollin E, Corcos O, Noussair L, Leflon-Guibout V, Belmatoug N, Joly F, et al. Retroperitoneal abscesses due to Nocardia farcinica: report of two cases in patients with malnutrition. Infection 2012;40:93-6.
7. Verroken A, Janssens M, Berhin C, Bogaerts P, Huang TD, Wauters G, et al. Evaluation of matrix-assisted laser desorption ionization-time of flight mass spectrometry for identification of nocardia species. J Clin Microbiol 2010;48:4015-21.
8. Khot PD, Bird BA, Durrant RJ, Fisher MA. Identification of Nocardia species by matrix-assisted laser desorption ionization-time of flight mass spectrometry. J Clin Microbiol 2015;53:3366-9.
9. Lerner PI. Nocardiosis. Clin Infect Dis 1996;22:891-903.
10. Wallace RJ Jr, Tsukamura M, Brown BA, Brown J, Steingrube VA, Zhang YS, et al. Cefotaxime-resistant Nocardia asteroides strains are isolates of the controversial species Nocardia farcinica. J Clin Microbiol 1990;28:2726-32.

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):111-114
https://doi.org/10.18700/jnc.230028

Journal of Neurocritical Care

Group B Streptococcus meningitis following subarachnoid hemorrhage suspicions: a case report

Daniel Ratushnyak, BS; Vishal Yajnik, MD, MS

Department Anesthesiology and Perioperative Medicine, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

CASE REPORT

Received: August 21, 2023
Revised: October 15, 2023
Accepted: November 8, 2023

Corresponding Author:
Daniel Ratushnyak
Department Anesthesiology and Perioperative Medicine, Virginia Commonwealth University School of Medicine, 1201 E Marshall St, Richmond, VA 23298, USA
Email: ratushnyakd@vcu.edu

Background: Bacterial meningitis is a life-threatening disease associated with high morbidity and mortality. Subarachnoid hemorrhage (SAH) can accompany bacterial meningitis in adult patients in <1% of cases and significantly worsens the patient's prognosis.
Case Report: A 58-year-old man presented to the emergency department complaining of a 5-day history of progressive abdominal pain, when he suddenly developed "the worst headache of his life" and suffered a 4-minute seizure. Computed tomography head showed SAH. An emergent cerebral angiogram was negative for any bleeding source, and attention shifted to meningoencephalitis. Ultimately, the patient was found to have Group B Streptococcus (GBS) meningitis on cerebrospinal fluid polymerase chain reaction.
Conclusion: To the best of our knowledge, this patient's presentation of GBS meningitis, masked by a classic aneurysmal SAH presentation, represents a rare and acute presentation of an underlying disease complication. Increasing awareness of this presentation can support more rapid diagnosis, earlier treatment, and improved outcomes for affected patients.

Keywords: Group B Streptococcus; Subarachnoid hemorrhage; Neurocritical care; Meningitis; Intensive care

INTRODUCTION

Bacterial meningitis is a life-threatening disease with high mortality and morbidity [1]. Of the potential etiologies of bacterial meningitis, *Streptococcus agalactiae* is most common in neonates and rare in adults [2]. In adult patients (older than 16 years) subarachnoid hemorrhage (SAH) was diagnosed in < 1% of cases in the setting of bacterial meningitis [3]. Unfortunately, SAH in patients with bacterial meningitis is associated with high case fatality and morbidity, with significant complications, including impaired level of consciousness, respiratory failure, circulatory shock, and seizures [3]. Well known risk factors for Group B Streptococcus (GBS) meningitis include previous occurrence, older age (> 65 years), diatetes mellitus, heart disease, obesity, immunodeficiencies, and cancer. In one study, patients with GBS meningitis and concurrent SAH were over three times more likely to die (54% vs. 16%) than patients without SAH [3]. The mechanisms behind the development of SAH secondary to bacterial meningitis are not fully understood but leading theories suggest the inflammatory milieu of the vascular system can lead to breakdown of blood vessels. There have been associations identified between the presence of saccular or mycotic aneurysms and concurrent bacterial meningitis with SAH [3]. There is suspicion that the aneurysms are a risk factor for the development of both bacterial meningitis and the

potential sequelae of SAH [4]. Deliran et al. [3] have produced a nation-wide cohort study in the Netherlands with a sample of 22 patients experiencing concurrent SAH with GBS. Notably, their study found that while only one third of these patients were diagnosed with SAH on admission, none of the patients presented with headache. In addition, the neuroimaging associated with each patient, when available, was unable to significantly correlate to the symptoms each patient presented with. Mook-Kanamori et al. [5] found the increased risk of SAH secondary to any bacterial meningitis increased five-fold when patients were on anticoagulants. Both Deliran et al. [3] and Mook-Kanamori et al. [5] were unable to identify any significantly different clinical presentations when patients had both SAH and GBS meningitis. This is the first published case of GBS meningitis identified following classic SAH presentation.

CASE REPORT

A 58-year-old man presented with a 5-day history of abdominal pain, myalgias, arthralgias, fever, diffuse headache, nausea, vomiting, diarrhea, and poor oral intake. The patient had a medical history of end-stage renal disease requiring hemodialysis, coronary artery disease status post coronary artery bypass grafting and multiple stents (most recently 3 weeks prior), previous stroke with residual blindness bilaterally, diabetes mellitus, and hypertension While in the emergency department (ED), he suddenly developed "the worst headache of his life," followed by a 4-minute tonic-clonic convulsion. His presentation was notable for somnolence without focal neurological deficits, consistent with Hunt Hess grade IV SAH. He was subsequently intubated, and head computed tomography (CT) demonstrated findings consistent with SAH (Fig. 1). Neurosurgery was consulted and he was promptly transported for urgent diagnostic cerebral angiography. Digital subtraction angiography (DSA) was performed and was notable for a normal cerebral angiogram without any evidence of mycotic or saccular aneurysms, dural arteriovenous fistulas, or other etiologies for the patient's SAH (Fig. 2). The patient was subsequently admitted to the neurocritical care unit, and urine culture was positive for GBS bacteriuria.

Lumbar puncture was performed on hospital day 2 (HD 2), and results were suggestive of bacterial meningitis (Table 1). The electroencephalogram was abnormal, with a slow and low amplitude background, but no seizures. Magnetic resonance imaging

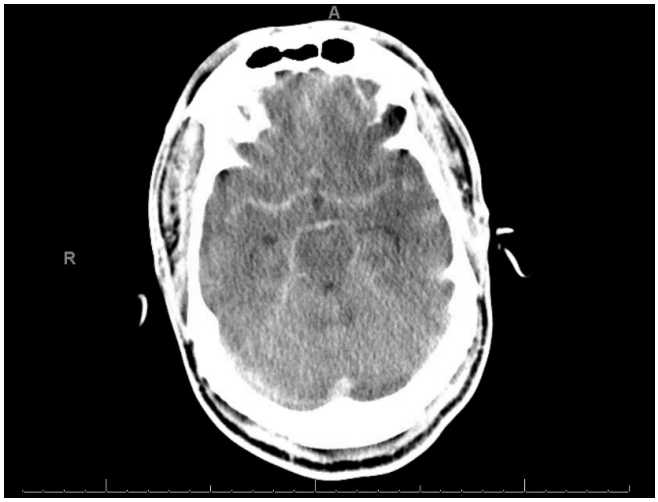

Fig. 1. Non-contrast head computed tomography demonstrating increased enhancement throughout most of the subarachnoid space, suggestive of meningoencephalitis or subarachnoid hemorrhage.

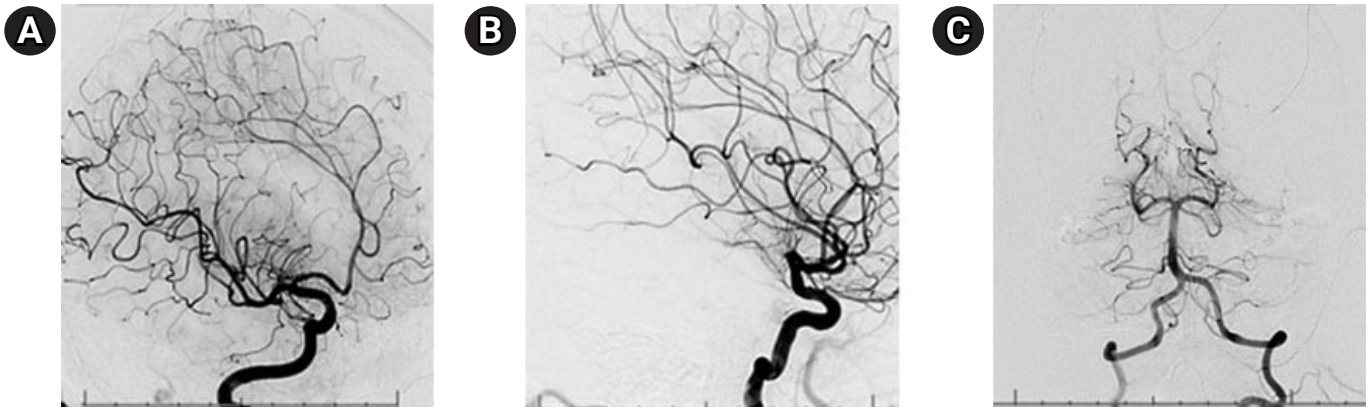

Fig. 2. Digital subtraction angiography performed the day of presentation. (A) Right internal carotid artery shows absence of vascular malformations including aneurysms. (B) Left internal carotid artery shows absence of vascular malformations including aneurysms. (C) Posterior circulation as seen also found to have no vascular malformations including aneurysms.

https://doi.org/10.18700/jnc.230028

Table 1. CSF data sampled during hospitalization

CSF study	HD 2	HD 6
Opening pressure (cm H_2O; normal: 6–25 cm H_2O)	40	53
Cell count with differential RBC (cells/mm^3; normal: 0–5 cells/mm^3)	2,308	92
Cell count with differential PMN (cells/mm^3; normal: 0–2 cells/mm^3)	96	51
Cell count with differential total nucleated count (cells/mm^3; normal: 0–5 cells/mm^3)	6,166	85
Culture results	Gram stain: no microorganisms seen	Gram stain: no microorganisms seen
Glucose (mg/dL; normal: 50–80 mg/dL)	90	129
Lactate (mmol/L; normal: 1.1–2.7 mmol/L)	12.7	3.2
Protein (mg/dL; normal: 15–45 mg/dL)	679	79

CSF, cerebrospinal fluid; HD, hospital day; RBC, red blood cell; PMN, polymorphonuclear cell.

performed on HD 2 provided evidence of scattered areas of increased fluid-attenuated inversion recovery signal with associated enhancement and foci of restriction diffusion in the bilateral cerebral sulci, sylvian fissures and fourth ventricular outflow tract, suggestive of diffuse meningitis with associated encephalitis (Fig. 3). There was additional suspected pus material with restriction effusion layering at the posterior horns of the lateral ventricles. A repeat head CT was performed for slight decline in mental status with imaging negative for worsening bleed and overall was stable with slightly worsening edema. Urine culture was positive for GBS, and the patient continued to have intermittent fevers. Lumbar puncture was repeated on HD 6 and cerebrospinal fluid (CSF) samples continued to not grow any colonies on our in-house laboratory testing. A CSF sample was then sent to Mayo Clinic for further culturing and susceptibility analysis. Their laboratory was able to determine the presence of *S. agalactiae* in the patient's CSF, providing culture-proven evidence of GBS meningitis. The patient was continued on antibiotics and on HD 7 the patient's neurological exam was significantly improved with eyes opening spontaneously, and the patient beginning to follow commands. He was successfully extubated the following day. His transthoracic and transesophageal echocardiograms were negative for the presence of vegetations, and he continued clinical improvement until his hospital discharge on HD 15. As *S. agalactiae* was detected in the CSF by polymerase chain reaction (PCR), our broad workup for potential bacteremia was negative, making bacteremia a less likely diagnosis.

On admission, our patient was started on vancomycin and ampicillin for 7 days, amphotericin B and metronidazole for 3 days, acyclovir for 4 days, and cefepime for 5 days. The final antibiotic plan was to continue ceftriaxone to fulfill a 4-week period of treatment. At the time of discharge, we transitioned his antibiotic regimen to cefazolin with dialysis, to avoid the need for a peripherally-inserted central catheter.

Patient was discharged home HD 15 and received follow-up with neurology 8 months later. The patient was then referred for an outpatient sleep study, with no concerns at that time. The patient is currently doing well and was last seen on December 2, 2022, following up with sleep medicine.

DISCUSSION

Bacterial meningitis in adults is rare, and confers significant morbidity and mortality. Its clinical presentation has been generally well-characterized in the literature. The question of utility emerges when presented with a classical presentation of another condition and the need to reject confirmation bias to explore other possible differentials. Our patient's presentation would most commonly be associated with SAH, that would typically follow with confirmation by DSA and microorganisms seen with CSF samples that appear to be cloudy would have been expected.

In the case we present, our patient described "the worst headache of his life" and had CT findings consistent with SAH. DSA found no obvious source of bleeding and subsequently another differential diagnosis became more likely; meningoencephalitis. No bacteria were identified under microscopy despite repeated attempts with new samples. Fortunately, we were able to contact the Mayo Clinic and through their BioFire Panel PCR, determined the presence of *S. agalactiae*. When our CSF samples were unremarkable for bacteria, we did not pursue culture and antibiotic susceptibility testing. Without having confirmatory PCR evidence, the patient initially continued to receive empiric broad spectrum antibiotic treatment.

There are few case studies exploring the care of patients with *S. agalactiae* bacterial meningitis, and even fewer collections of reported atypical presentations. As such, we felt it was important to illustrate and reiterate the key principles of care when presented with such an uncommon clinical constellation. Improving awareness of this presentation of GBS meningitis, in combination with the negative in-house CSF samples, calls to attention the value of

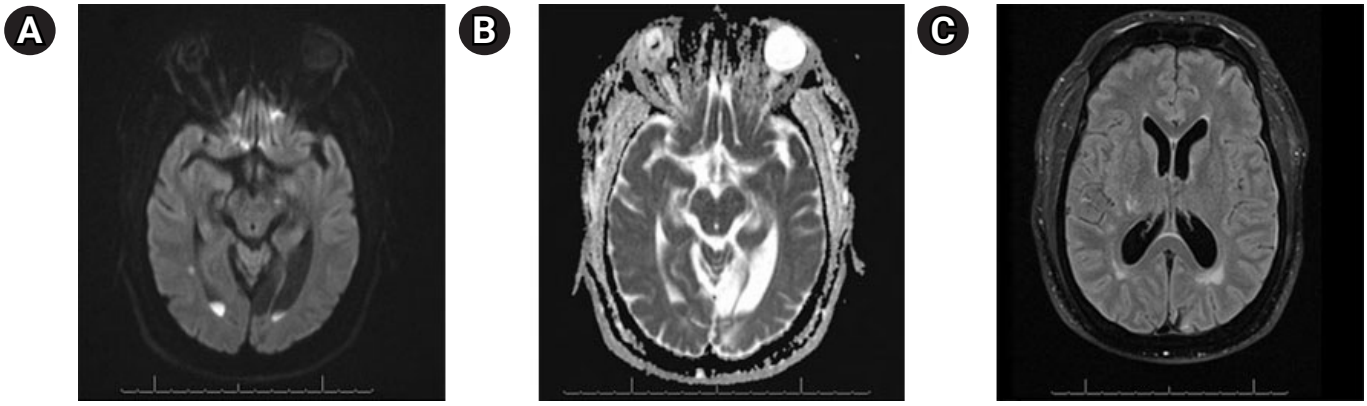

Fig. 3. Magnetic resonance imaging with and without intravenous contrast. (A) Evidence of diffusion restriction indicative of ischemia from EP2D sequence. Additional pus material with restriction effusion layering at the posterior horns of lateral ventricles. (B) Apparent diffusion coefficient (ADC) correlate of the same level as panel (A) demonstrating persistent diffusion restriction from EP2D ADC sequence. (C) Evidence of increased fluid-attenuated inversion recovery signal with association enhancement suggestive of diffuse meningitis.

treating empirically based on clinical suspicion. Furthermore, this raises awareness of the importance of correctly evaluating the resources available for laboratory testing.

With such significant morbidity and mortality associated with this specific presentation of bacterial meningitis, the benefits of earlier diagnosis and treatment are supported in this case report and can contribute to the improvements in outcomes for such patients [2,3]. These clinical interventions can be best practiced, and are more readily apparent, to better informed clinicians.

ARTICLE INFORMATION

Ethics statement

Approval for this study was waived in accordance with our Health System policies because this study is a case report of a single patient and did not include protected health information, data analysis, or testing of a hypothesis, and was de-identified. Written informed consent was obtained from the patient. Authors have obtained a signed consent form that is retained with their records.

Conflict of interest

No potential conflict of interest relevant to this article.

ORCID

Daniel Ratushnyak https://orcid.org/0000-0002-2494-6832
Vishal Yajnik https://orcid.org/0000-0001-9600-9074

Author contributions

Conceptualization: all authors. Writing–original draft: DR. Writing–review & editing: all authors.

REFERENCES

1. van de Beek D, Brouwer MC, Koedel U, Wall EC. Community-acquired bacterial meningitis. Lancet 2021;398:1171-83.
2. Al-Bayati A, Douedi S, Alsaoudi G, Mosseri M, Albustani S, Upadhyaya V, et al. Meningitis from invasive Streptococcus agalactiae in a healthy young adult. IDCases 2020;21:e00907.
3. Deliran SS, Brouwer MC, van de Beek D. Subarachnoid hemorrhage in bacterial meningitis patients. Cerebrovasc Dis 2022;51:118-24.
4. Kannoth S, Iyer R, Thomas SV, Furtado SV, Rajesh BJ, Kesavadas C, et al. Intracranial infectious aneurysm: presentation, management and outcome. J Neurol Sci 2007;256:3-9.
5. Mook-Kanamori BB, Fritz D, Brouwer MC, van der Ende A, van de Beek D. Intracerebral hemorrhages in adults with community associated bacterial meningitis in adults: should we reconsider anticoagulant therapy? PLoS One 2012;7:e45271.

https://doi.org/10.18700/jnc.230028

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):115-118
https://doi.org/10.18700/jnc.230043

Journal of Neurocritical Care

Lateral medullary infarction in a patient with Moyamoya disease associated with RNF213 variants: a case report

Yoo Jeong Roh, MD; Kee Ook Lee, MD, PhD; Hyun Sook Kim, MD, PhD

Department of Neurology, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

CASE REPORT

Received: December 11, 2023
Revised: December 18, 2023
Accepted: December 19, 2023

Corresponding Author:
Hyun Sook Kim, MD, PhD
Department of Neurology, CHA Bundang Medical Center, CHA University School of Medicine, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Korea
Tel: +82-31-780-5486
Fax: +82-31-780-5269
Email: hskim626@cha.ac.kr

Background: Moyamoya disease (MMD) is a rare cerebrovascular disease radiologically characterized by progressive bilateral occlusion of the distal portion of the internal carotid artery and compensating collaterals. Herein, we report a case of medullary infarction in a patient with MMD.

Case Report: We present the case of a 54-year-old male with hypertension, hyperlipidemia, and unstable angina with sudden onset dysarthria and ataxia. Diffusion-weighted and T2-weighted images of magnetic resonance imaging showed a high-signal intensity lesion on the right lateral medulla, suggestive of acute infarction. Transfemoral cerebral angiography also demonstrated bilateral middle cerebral artery (MCA) occlusion. Testing of the ring finger protein 213 (RNF213) gene revealed a homozygous p.R4810K variant that was possibly associated with posterior circulation involvement.

Conclusion: When the MCA is occluded in MMD, there is a possibility that medullary infarction may occur due to the mechanism of increased hemodynamic stress on the anastomotic posterior vessels.

Keywords: Moyamoya disease; Cerebral infarction; Posterior cerebral artery

INTRODUCTION

Moyamoya disease (MMD) is a rare cerebrovascular disease that is radiologically and clinically characterized by slowly progressive occlusion of the supraclinoid internal carotid artery (ICA) and the circle of Willis, with the simultaneous appearance of natural intracranial and extracranial collaterals [1]. Initial presentation of MMD is generally caused by cerebrovascular events such as cerebral infarction, hemorrhage, transient ischemic attack, epileptic seizures, and sometimes cognitive impairment [2].

While typical symptoms are primarily anterior circulation-related problems, the prevalence of posterior cerebral artery (PCA) involvement has been reported to range from 21.2% to 43.4% in adults and tends to be positively correlated with the ipsilateral ICA stage [3,4]. However, cases of brainstem involvement in MMD have rarely been reported. Here, we report a case of lateral medullary infarction with MMD and multiple vascular risk factors.

CASE REPORT

A 54-year-old right-handed male visited the emergency room with the sudden onset of dysarthria and ataxia. He had hypertension, hyperlipidemia, and a history of coronary angioplasty and stent insertion for unstable angina. Because of these underlying diseases, aspirin, clopidogrel, rosuvastatin, ramipril, trimetazidine, carvedilol, and nifedipine were prescribed.

Neurological examination revealed dysarthria and truncal ataxia. He also experienced pain and thermal sensory impairment in the left limbs, trunk, and right side of the face. The initial National Institutes of Health Stroke Scale score was 4. His vital signs were stable, with high blood pressure (blood pressure 167/92 mm Hg, pulse rate 75 beats/min, body temperature 36.8 °C, and respiratory rate 16/min). Electrocardiography revealed a normal sinus rhythm, and chest radiography findings were normal. The fasting blood glucose level was 105 mg/dL, and the HbA1c level was 6.0%. Additional laboratory tests revealed normal cholesterol (155 mg/dL), total triglyceride (127 mg/dL), and low-density lipoprotein cholesterol (95 mg/dL) levels. Laboratory test results for hypercoagulation causes were negative. Other serological parameters, including erythrocyte sedimentation rate and C-reactive protein levels, were within normal limits.

Diffusion-weighted and T2-weighted magnetic resonance imaging (MRI) revealed a high-signal intensity lesion in the right lateral portion of the medulla, suggestive of acute infarction (Fig. 1). Transfemoral cerebral angiography (TFCA) showed bilateral M1 occlusion, and distal middle cerebral artery (MCA) flow was supplied by the collaterals (Fig. 2). The TFCA also showed that the vertebral artery supplied a portion of the right temporal and left temporo-occipital regions (Fig. 3). Transcranial Doppler (TCD) showed increased blood flow velocities in both the anterior cerebral arteries (ACA; 108.8 cm/sec in the left ACA and 93.3 cm/sec in the right ACA) and the right MCA (121.4 cm/sec). MMD was suggested, and subsequent genetic testing for ring finger protein 213 (RNF213) revealed a homozygous p.R4810K variant.

The patient was prescribed cilostazol, clopidogrel, and 40 mg of atorvastatin. At discharge, a maintenance regimen of dual antiplatelet therapy and atorvastatin was prescribed, which was administered upon admission. One month after symptom onset, his condition remained stable except for mild residual dysarthria.

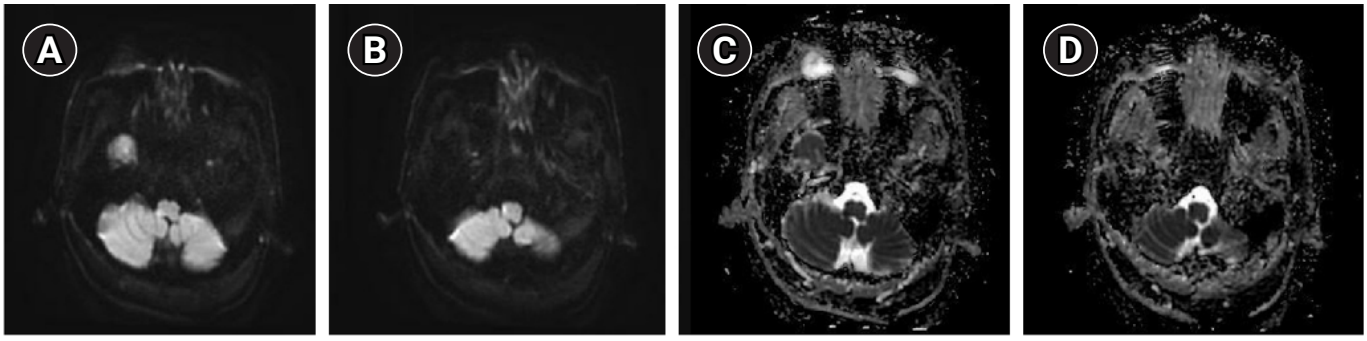

Fig. 1. Magnetic resonance imaging of the brain. (A, B) Diffusion-weighted imaging showed high-signal intensities in the right lateral medulla. (C, D) Apparent diffusion coefficient imaging showed low signal intensities in the corresponding area.

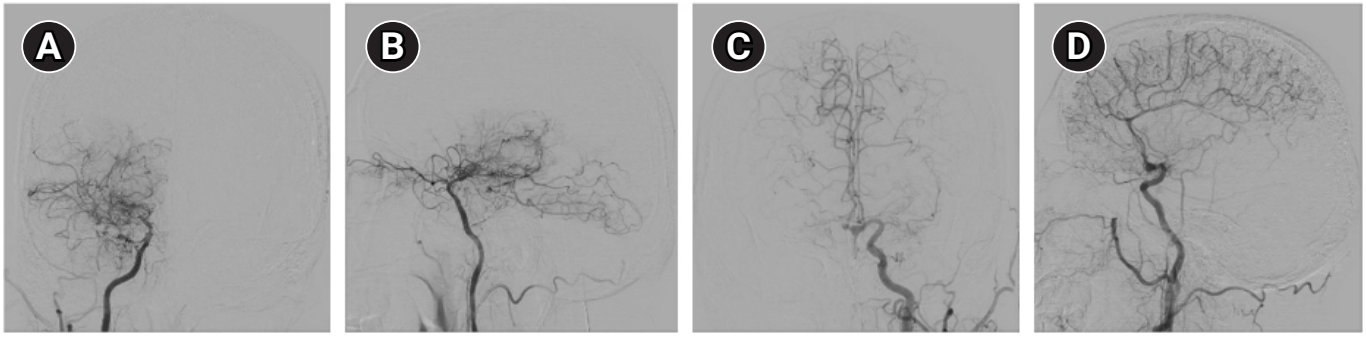

Fig. 2. (A-D) Transfemoral cerebral angiography revealed bilateral middle cerebral artery (MCA) occlusion and distal MCA flow was supplied by collaterals.

https://doi.org/10.18700/jnc.230043

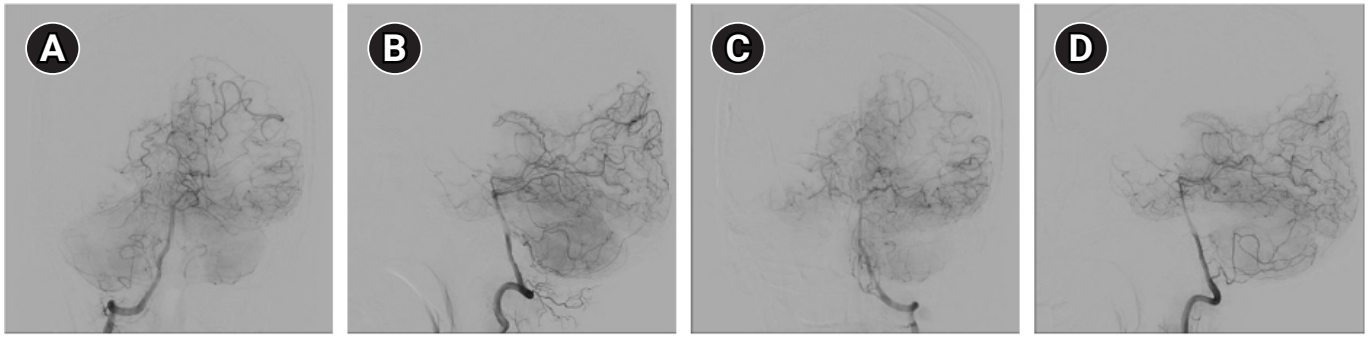

Fig. 3. (A-D) Transfemoral cerebral angiography revealed vertebral artery supplied some portion of right temporal and left temporo-occipital regions.

DISCUSSION

As the distinction and diagnostic criteria between MMD and moyamoya syndrome have been revised, radiological diagnostic criteria have been emphasized [5]. TFCA should demonstrate arterial stenosis or occlusion centered at the distal ends of the bilateral or unilateral intracranial carotid arteries, arterial phase occlusion, or moyamoya vessels near the stenotic lesion, suggesting an abnormal vascular network.

Several monogenic moyamoya syndromes present with the radiological features of MMD and are associated with several pathways involved in the development of moyamoya angiopathy [6]. Among several MMD susceptibility genes, RNF213 14429G→A (rs112735431; resulting in p.R4810K) was identified as a major susceptibility gene for MMD and a major founder variant in East Asian countries, especially in Japan and South Korea [7]. The RNF213 p.R4810K variant is not common in the general Korean population, and these genetic polymorphisms are present in only 0.5% to 2% of the general East Asian population [7,8].

RNF213 may play an important role in the progressive stages of MMD as well as in vascular pathology, such as angiogenesis and collateral vessel development in PCA involvement [9,10]. Furthermore, a study on Korean subjects showed that patients with RNF213 mutations had fewer collateral flow patterns from the PCA to the anterior circulation and more PCA involvement than patients with MMD without RNF213 mutations [9].

MMD-associated lateral medullary infarction and/or vertebral artery occlusion have rarely been reported in the past, and its mechanisms remain unclear [11,12]. As mentioned above, the involvement of the posterior circulation in MMD is relatively rare, and even when involved, it is usually present in PCA. Additionally, although symptoms occur because of the vertebrobasilar artery, most cases are caused by hemorrhage or total vertebrobasilar occlusion, which is different from the present case, which is believed to be caused by hemodynamic stress. From an embryological perspective, because the distal part of the PCA originates from the primitive ICA, most MMD associated with the posterior circulation are considered to be of the primitive ICA system-related type, the primitive vertebrobasilar artery system [13].

Although genetic testing for RNF213 in our patient showed a homozygous p.R4810K variant, he also had multiple vascular risk factors such as hypertension, hyperlipidemia, and smoking. This case did not meet the 2021 criteria for MMD because there was no distal ICA stenosis or occlusion, despite TFCA demonstrating bilateral MCA occlusion. Additionally, atherosclerotic changes related to traditional risk factors may cause lateral medullary infarctions. However, the small, abnormal, and reticular collateral vessels typically observed in MMD, including the posterior collaterals, were observed at multiple sites. TCD also demonstrated increased flow velocity in both the ACA and MCA, consistent with MMD. Furthermore, since the RNF 213 mutation appeared in this case, it is reasonable to consider the possibility that MMD is progressing.

The possibility of occlusion of the MCA, which may increase the hemodynamic stress on the anastomotic posterior vessels due to MMD, may also be considered the cause in this case. Although MMD requires accurate recognition and application of the diagnostic criteria and clinical features, it is necessary to suspect and consider MMD because of its potential to cause various symptoms.

ARTICLE INFORMATION

Ethics statement

This case was reviewed and approved by the Ethics Committee of CHA Bundang Medical Center (No. CHAMC IRB 2023-11-019). The requirement of informed consent was waived. 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.

ORCID

Yoo Jeong Roh https://orcid.org/0000-0001-8966-824X
Kee Ook Lee https://orcid.org/0000-0002-6105-1085
Hyun Sook Kim https://orcid.org/0000-0003-4227-7983

Author contributions

Conceptualization: YJR, HSK. Methodology: all authors. Formal analysis: all authors. Data curation: YJR, HSK. Visualization: all authors. Project administration: YJR, HSK. Writing–original draft: YJR. Writing–review & editing: all authors.

REFERENCES

1. Suzuki J, Kodama N. Moyamoya disease: a review. Stroke 1983;14:104-9.
2. Scott RM, Smith ER. Moyamoya disease and moyamoya syndrome. N Engl J Med 2009;360:1226-37.
3. Mugikura S, Higano S, Shirane R, Fujimura M, Shimanuki Y, Takahashi S. Posterior circulation and high prevalence of ischemic stroke among young pediatric patients with Moyamoya disease: evidence of angiography-based differences by age at diagnosis. AJNR Am J Neuroradiol 2011;32:192-8.
4. Funaki T, Takahashi JC, Takagi Y, Yoshida K, Araki Y, Kikuchi T, et al. Impact of posterior cerebral artery involvement on long-term clinical and social outcome of pediatric moyamoya disease. J Neurosurg Pediatr 2013;12:626-32.
5. Kuroda S, Fujimura M, Takahashi J, Kataoka H, Ogasawara K, Iwama T, et al. Diagnostic criteria for Moyamoya disease: 2021 revised version. Neurol Med Chir (Tokyo) 2022;62:307-12.
6. Ihara M, Yamamoto Y, Hattori Y, Liu W, Kobayashi H, Ishiyama H, et al. Moyamoya disease: diagnosis and interventions. Lancet Neurol 2022;21:747-58.
7. Jang MA, Shin S, Yoon JH, Ki CS. Frequency of the moyamoya-related RNF213 p.Arg4810Lys variant in 1,516 Korean individuals. BMC Med Genet 2015;16:109.
8. Kim JE, Jeon JS. An update on the diagnosis and treatment of adult Moyamoya disease taking into consideration controversial issues. Neurol Res 2014;36:407-16.
9. Kim WH, Kim SD, Nam MH, Jung JM, Jin SW, Ha SK, et al. Posterior circulation involvement and collateral flow pattern in moyamoya disease with the RNF213 polymorphism. Childs Nerv Syst 2019;35:309-14.
10. Miyatake S, Miyake N, Touho H, Nishimura-Tadaki A, Kondo Y, Okada I, et al. Homozygous c.14576G > A variant of RNF213 predicts early-onset and severe form of moyamoya disease. Neurology 2012;78:803-10.
11. Kim JS, Lee JH, Choi CG. Patterns of lateral medullary infarction: vascular lesion-magnetic resonance imaging correlation of 34 cases. Stroke 1998;29:645-52.
12. Kinoshita Y, Kohshi K, Yokota A. Moyamoya disease of adult onset brain stem haemorrhage associated with bilateral occlusion of the vertebral arteries: case report. Acta Neurochir (Wien) 1998;140:181-4.
13. Tan C, Duan R, Ye X, Zhang D, Wang R. Posterior circulation Moyamoya disease versus primitive vertebral-basilar artery system Moyamoya disease: new classification of Moyamoya disease from the perspective of embryology. World Neurosurg 2016;96:222-9.

https://doi.org/10.18700/jnc.230043

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):119-122
https://doi.org/10.18700/jnc.230032

Journal of Neurocritical Care

Extremely elevated international normalized ratio in a patient using dabigatran etexilate: a case report

Jin Kim, MD[1]; Youngchan Jung, MD[1]; Jinyoung Oh, MD[1]; Sang Won Han, MD[1]; Hyun-jeung Yu, MD, PhD[2]

[1]Department of Neurology, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea
[2]Department of Neurology, Bundang Jesaeng General Hospital, Seongnam, Korea

CASE REPORT

Received: September 22, 2023
Revised: October 31, 2023
Accepted: November 1, 2023

Corresponding Author:
Hyun-jeung Yu, MD, PhD
Department of Neurology, Bundang Jesaeng General Hospital, 20 Seohyeon-ro 180beon-gil, Bundang-gu, Seongnam 13590, Korea
Tel: +82-31-779-0216
Fax: +82-31-779-0897
Email: yhj314@dmc.or.kr

Background: We present the case of a patient who was administered dabigatran and showed an extremely elevated prothrombin time-international normalized ratio (PT-INR).
Case Report: A 79-year-old man was referred due to PT-INR 12.6. The patient was taking 110 mg of dabigatran twice daily in capsule form. On admission, blood urea nitrogen level was 23 mg/dL, creatinine was 1.51 mg/dL, and the estimated glomerular filtration rate was 44.8 mL/min/1.73 m^2. Coagulation tests revealed PT 96.8 seconds, PT-INR 12.46, and activated partial thromboplastin time 125.5 seconds. Dabigatran was discontinued, PT-INR on the day after admission was 8.96. PT-INR recovered to 1.61 on the fourth day without any treatment.
Conclusion: The PT-INR was not directly correlated with dabigatran activity. Regular monitoring of coagulation was not necessary in all patients taking dabigatran. However, it may be useful to regularly perform coagulation tests in patients with renal impairment or in those at a high risk of bleeding.

Keywords: Anticoagulants; Blood coagulation; International normalized ratio; Case report

INTRODUCTION

In general, blood coagulation tests are not necessary in patients using non-vitamin K-dependent oral anticoagulants (NOACs) [1,2]. If the patient follows the prescribed indications for NOACs, adjusting the dosage or administration interval of the medication according to the changes in coagulation tests is not necessary [3]. Here, we present the case of a patient with nonvalvular atrial fibrillation (NVAF) who was taking dabigatran and showed an extremely elevated prothrombin time-international normalized ratio (PT-INR).

CASE REPORT

A 79-year-old man living in a nursing home visited the primary hospital with fever and an oxygen saturation level of 70%. Chest computed tomography findings were suggestive of pneumonia, and laboratory findings revealed PT-INR 12.6. The patient was transferred to our hospital with cerebral infarction, persistent NVAF, congestive heart failure, dementia, benign prostatic hyperplasia, and hypothyroidism. At admission, his vital signs were as follows: blood pressure 110/73 mm Hg, heart rate 93/min, oxy-

gen saturation 98%, and body temperature 36.3 °C. The physical examination results were normal. There were no focal neurological abnormalities, except for decreased memory function. The patient was on the following medications: levothyroxine sodium, furosemide, spironolactone, isosorbide dinitrate, atorvastatin, donepezil, tamsulosin, and dabigatran 110 mg twice daily in capsule form without a nasogastric tube.

Blood tests in emergency room revealed a hemoglobin level of 13.3 g/dL, hematocrit 39.7%, white blood cell count 19,680/mm^3, platelet count 161,000/μL and C-reactive protein 2.9 mg/dL (Table 1). Blood urea nitrogen (BUN) was 23 mg/dL (normal range, 7–25 mg/dL), serum creatinine (Cr) was 1.51 mg/dL (normal range, 0.5–1.2 mg/dL), and estimated glomerular filtration rate (eGFR) was 44.8 mL/min/1.73 m^2. Coagulation tests showed that PT was 96.8 seconds (normal range, 11–15 seconds), PT-INR was 12.46 (normal range, 0.8–1.2), and activated partial thromboplastin time (aPTT) was 125.5 seconds (normal range, 28–45 seconds), which were exceptionally increased. Thrombin time (TT) could not be measured because clot formation did not occur, and ecarin clotting time (ECT) could not be performed. Serum albumin levels and liver function test results were normal. Blood tests performed three months prior showed BUN 14.7 mg/dL, Cr 0.93 mg/dL, and eGFR 78.4 mL/min/1.73 m^2. PT and aPTT were not measured at that time. Comparison with the previous laboratory results revealed a rapid decline in renal function during this visit. No signs of sepsis or liver dysfunction were observed, and a patchy opacity was observed in the left lower lobe on chest radiography, suggesting pneumonia. Piperacillin-tazobactam intravenous (IV) injection was initiated.

Although coagulation tests revealed abnormalities, no bleeding-related symptoms or signs were observed. Therefore, vitamin K and fresh frozen plasma were not used, and dabigatran was discontinued. Idarucizumab was not administered because it was unavailable at our hospital. The patient remained clinically stable, and the PT-INR measurement conducted on the day following admission yielded a result of 8.96. PT-INR recovered to 1.61 on the fourth day without any special treatment. The patient was discharged with an oral administration of 100 mg aspirin instead of dabigatran. Fourteen weeks later, blood tests showed PT 17.3 seconds, PT-INR 1.42, aPTT 58.4 seconds, BUN 23.4 mg/dL, Cr 0.99 mg/dL, eGFR 72.2 mL/min/1.73 m^2, and there were no bleeding-related symptoms.

DISCUSSION

NOACs are primarily used to prevent ischemic stroke or transient ischemic attacks in patients with NVAF. Currently, dabigatran, rivaroxaban, apixaban, and edoxaban are available [4]. Among them, dabigatran was the first NOAC approved for stroke prevention in patients with NVAF and acts as a direct thrombin inhibitor. Thrombin is a multifunctional enzyme that converts fibrinogen to fibrin and activates platelets. Dabigatran etexilate is the prodrug of dabigatran, a potent, nonpeptidic small molecule that specifically and reversibly inhibits both free and clot-bound thrombin by binding to the active site of the thrombin molecule [5]. It competitively inhibits thrombin in a concentration-dependent manner.

Dabigatran etexilate has a mean absolute bioavailability of 6.5%, which is independent of the dose and is not influenced by co-administration with food. It is present in capsules containing multiple pellets with a tartaric acid core to facilitate gastrointestinal absorption. This generated an acidic environment that favored drug dissolution and absorption. After oral administration, dabigatran etexilate is rapidly hydrolyzed to its active form by ubiquitous esterases. Given that cytochrome P450 enzymes and other oxidoreductases are not involved in the proteolytic reactions that convert dabigatran etexilate to dabigatran, the risk of drug-drug interactions is low.

Table 1. Serial changes in blood coagulation and kidney function tests during the treatment

Variable	Jul 22, 2022	Jan 10, 2023	Mar 28, 2023[a]	Mar 29, 2023	Mar 30, 2023	Mar 31, 2023	Apr 10, 2023	May 9, 2023	Jul 18, 2023
Hb (g/dL)	12.3	12.4	13.3	13.0	NA	13.0	11.9	11.1	12.6
PLT (1,000/μL)	178	197	161	158	NA	156	201	375	149
PT (sec)	NA	NA	96.8	74.5	36.3	19.1	15	19.6	17.3
PT-INR	NA	NA	12.46	8.96	3.62	1.61	1.19	1.67	1.42
aPTT (sec)	NA	NA	125.5	123.5	95.1	72.7	41.8	41.3	58.4
BUN (mg/dL)	15.5	14.7	23.0	NA	NA	NA	NA	18.8	23.4
Cr (mg/dL)	1.03	0.93	1.51	NA	NA	NA	NA	1.30	0.99
eGFR (mL/min/1.73 m^2)	69.8	78.4	44.8	NA	NA	NA	NA	53.3	72.2

Hb, hemoglobin (normal range, 13–17 g/dL); PLT, platelet (normal range, 150–400 1,000/μL); PT, prothrombin time (normal range, 11–15 sec); PT-INR, PT-international normalized ratio (normal range, 0.8–1.2); aPTT, activated partial thromboplastin time (normal range, 28–45 sec); BUN, blood urea nitrogen (normal range, 7–25 mg/dL); Cr, creatinine (normal range, 0.5–1.2 mg/dL); eGFR, estimated glomerular filtration rate; NA, not available.
[a]Admission date.

https://doi.org/10.18700/jnc.230032

Peak plasma concentrations (Cmax) and anticoagulant effects are achieved within 1.5 to 3 hours after oral dosing. Plasma concentrations show biphasic decline. The first phase is characterized by a rapid distribution phase. This is followed by a prolonged terminal elimination phase, resulting in a mean plasma terminal half-life of 12–14 hours, independent of the dose. Consequently, therapeutic concentrations are maintained for 24-hour periods, while retaining sufficient reversibility. The renal excretion of unchanged dabigatran is the predominant elimination pathway, with approximately 80% of the IV dose excreted unchanged in the urine. The remainder is conjugated with glucuronic acid to form acyl glucuronides, which are predominantly excreted via bile, with only very small amounts of conjugates found in urine.

In our patient, there were no bleeding symptoms during dabigatran administration; however, an exceptional abnormality in the coagulation tests was observed. To date, no laboratory studies are available to confirm dabigatran-induced coagulopathy in a general hospital setting. The most sensitive clotting assays were the TT and ECT, followed by the aPTT and PT-INR. Normally, the PT-INR is not directly correlated with dabigatran activity. Several conditions can induce abnormalities in coagulation test results during dabigatran use. First, kidneys play a major role in NOAC excretion. Approximately 80% of dabigatran is excreted by the kidneys, and dosage adjustments should be considered based on renal function [6,7]. According to the Korean Arrhythmia Society guidelines, for patients with a creatinine clearance rate of 30–50 mL/min, dabigatran administered twice daily at a dose of 110 mg is recommended [8]. In our case, the eGFR value at the time of admission was 44.8 mL/min/1.73 m^2 compared to 78.4 mL/min/1.73 m^2 three months ago, indicating progressive renal failure. However, he was taking 110 mg of dabigatran twice daily before admission and did not overdose. Second, while our patient took all medications without crushing them into powder form, it is not recommended to remove capsules before administration because it increases the bioavailability of dabigatran by more than 75%, and powerful P-glycoprotein inhibitors can increase NOAC plasma concentrations owing to drug interactions related to dabigatran. However, no relevant drugs were administered. Despite extensive literature reviews, the exact mechanisms underlying the extremely elevated coagulation test results in our patient could not be explained. Only a few cases have reported that PT-INR decreased after management with idarucizumab, suggesting a possible relationship between dabigatran use and PT-INR [9,10].

Our patient showed an elevated PT-INR on the 40th day after the discontinuation of dabigatran. Although there are reports that doses of aspirin 2–3 g/day can prolong PT-INR, low-dose aspirin does not usually affect PT-INR [11]. Multiple factors can interfere with PT-INR, such as antibiotics, antifungals, chemotherapeutics, amiodarone, allopurinol, serotonin reuptake inhibitors, acute illness, chronic liver disease, coagulation homeostasis [3]. Even if there was an unidentified coagulopathy in our patient, we believe that the recruitment of similar patients may be essential to determine a safe dose of dabigatran and to monitor drug activity.

In conclusion, regular monitoring of coagulation tests, including PT and aPTT, is not necessary for all patients taking dabigatran. However, it may be useful to regularly perform blood coagulation tests in patients with renal impairment or in those at a high risk of bleeding.

ARTICLE INFORMATION

Ethics statement

This study was approved by the Clinical Trial Review Committee of the Sanggye Paik Hospital (No. SGPAIK 2022-03-011). The requirement for written informed consent was waived, and the study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki.

Conflict of interest

No potential conflict of interest relevant to this article.

ORCID

Jin Kim	https://orcid.org/0000-0001-5623-981X
Youngchan Jung	https://orcid.org/0009-0004-8243-6971
Jinyoung Oh	https://orcid.org/0000-0002-4235-8655
Sang Won Han	https://orcid.org/0000-0002-9503-1883
Hyun-jeung Yu	https://orcid.org/0000-0002-9081-4846

Author contributions

Conceptualization: all authors. Methodology: all authors. Software: SWH, JO. Validation: SWH, HJY. Formal analysis: JK, JO, SWH. Investigation: SWH, YJ, JO. Data curation: all authors. Visualization: JO. Supervision: HJY. Project administration: all authors. Writing–original draft: JK, SWH. Writing–review and editing: all authors.

REFERENCES

1. Blair HA, Keating GM. Dabigatran etexilate: a review in nonvalvular atrial fibrillation. Drugs 2017;77:331-44.
2. Chan NC, Coppens M, Hirsh J, Ginsberg JS, Weitz JI, Vanassche T, et al. Real-world variability in dabigatran levels in patients with atrial fibrillation. J Thromb Haemost 2015;13:353-9.
3. Salem AM, Roh D, Kitagawa R, Choi HA, Chang TR. Assess-

ment and management of coagulopathy in neurocritical care. J Neurocrit Care 2019;12:9-19.
4. Jung KH, Yu KH, Kim YD, Park JM, Hong KS, Rha JH, et al. Focused update of guidelines for antithrombotic management of patients with atrial fibrillation and ischemic stroke or transient ischemic attack. J Korean Neurol Assoc 2016;34:184-92.
5. Duan J, Yang L, Li H, Yamamura N, Harada A. Pharmacokinetics and safety of dabigatran etexilate after single and multiple oral doses in healthy Chinese subjects. Eur J Drug Metab Pharmacokinet 2020;45:601-9.
6. Park H, Yoo J. Use of non-vitamin k dependent oral anticoagulant in ischemic stroke. J Korean Neurol Assoc 2022;40:1-14.
7. Kim J, Yadava M, An IC, Sayeed A, Laird-Fick HS, Gourineni V, et al. Coagulopathy and extremely elevated PT/INR after dabigatran etexilate use in a patient with end-stage renal disease. Case Rep Med 2013;2013:131395.
8. Korean Heart Rhythm Society. 2022 Korean Heart Rhythm Society Guidelines for Non-Vitamin K Antagonist Oral Anticoagulant (NOAC) [Internet]. Korean Heart Rhythm Society; 2022 [cited 2023 Nov 20]. Available from: http://www.k-hrs.org/upload/2022%20Korean%20Arrhythmia%20Society_NOAC_Guidelines.pdf.
9. Vidal J, DePalma R, Forouzan L. Reversal of dabigatran bleeding and coagulopathy using idarucizumab in a patient with acute kidney injury. P T 2018;43:748-9.
10. Memon W, Aamir M, Memon A. Extremely elevated international normalized ratio in a patient with dabigatran etexilate use. Cureus 2019;11:e4906.
11. Cattaneo M, Chahil A, Somers D, Kinlough-Rathbone RL, Packham MA, Mustard JF. Effect of aspirin and sodium salicylate on thrombosis, fibrinolysis, prothrombin time, and platelet survival In rabbits with indwelling aortic catheters. Blood 1983;61:353-61.

https://doi.org/10.18700/jnc.230032

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):123-124
https://doi.org/10.18700/jnc.230024

Journal of Neurocritical Care

Cerebral fat embolism in sickle cell disease

Hortense Le Bourhis, MD[1]; Michel Djibré, MD[1]; Razakamanantsoa, MD[2]; Nina de Montmollin, MD[1]

[1]Service de Médecine Intensive Réanimation, Hôpital Tenon, Assistance Publique – Hôpitaux de Paris, Sorbonne Université, Paris, France
[2]Département de Radiologie, Hôpital Tenon, Assistance Publique – Hôpitaux de Paris, Sorbonne Université, Paris, France

IMAGES IN NEUROCRITICAL CARE

Received: June 21, 2023
Revised: September 9, 2023
Accepted: September 11, 2023

Corresponding Author:
Nina de Montmollin, MD
Service de Médecine Intensive Réanimation, Hôpital Tenon, Assistance Publique – Hôpitaux de Paris, Sorbonne Université, 4 rue de la Chine, 75020 Paris, France
Tel: +33-1-56-01-65- 72,
Fax: +33-1-56-01-60-97
Email: nina.demontmollin@aphp.fr

A 22-year-old man with a history of homozygous sickle cell disease was admitted to the intensive care unit for acute chest syndrome defined with radiodensity on chest imaging, fever, and respiratory symptoms. Within a few hours, the patient developed altered consciousness, necessitating intubation.

Hematological testing revealed pancytopenia (white blood cell count, 2×10^9/L; hemoglobin, 8 g/dL; platelet count, 40×10^9/L; reticulocyte count, $< 100 \times 10^9$/L), likely caused by bone marrow necrosis. Cerebral magnetic resonance imaging (MRI) performed on day 1 of admission revealed bilateral punctate foci of restricted diffusion in the supratentorial white matter on diffusion-weighted imaging without vascular systematization or evidence of collateral flow on fluid- attenuated inversion recovery sequence (Fig. 1A-C). Computed tomography and MR angiography of the supra-aortic trunk and intracranial vessels yielded normal findings. Without an alternative diagnosis, cerebral fat embo-

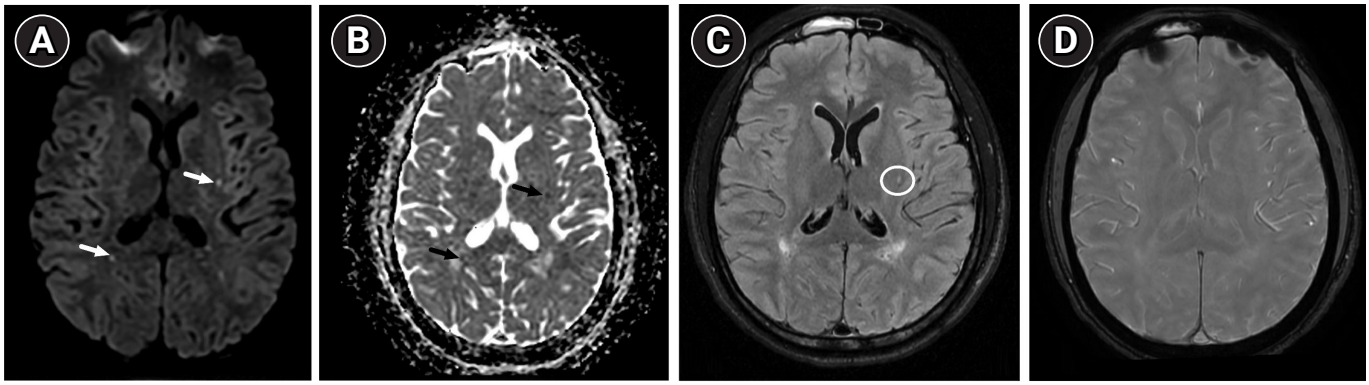

Fig. 1. Initial axial brain magnetic resonance imaging performed 24 hours after admission. (A) Diffusion-weighted imaging (b=1,000 sec/mm^2) and (B) the corresponding apparent diffusion coefficient map revealing bilateral scattered punctate foci of restricted diffusion of the supratentorial white matter (arrows). (C) Fluid-attenuated inversion recovery sequence showing hyperintensity of a left putamenal lesion without evidence of collateral flow (circle). (D) Susceptibility-weighted imaging sequence showing no hypointense area in the brain.

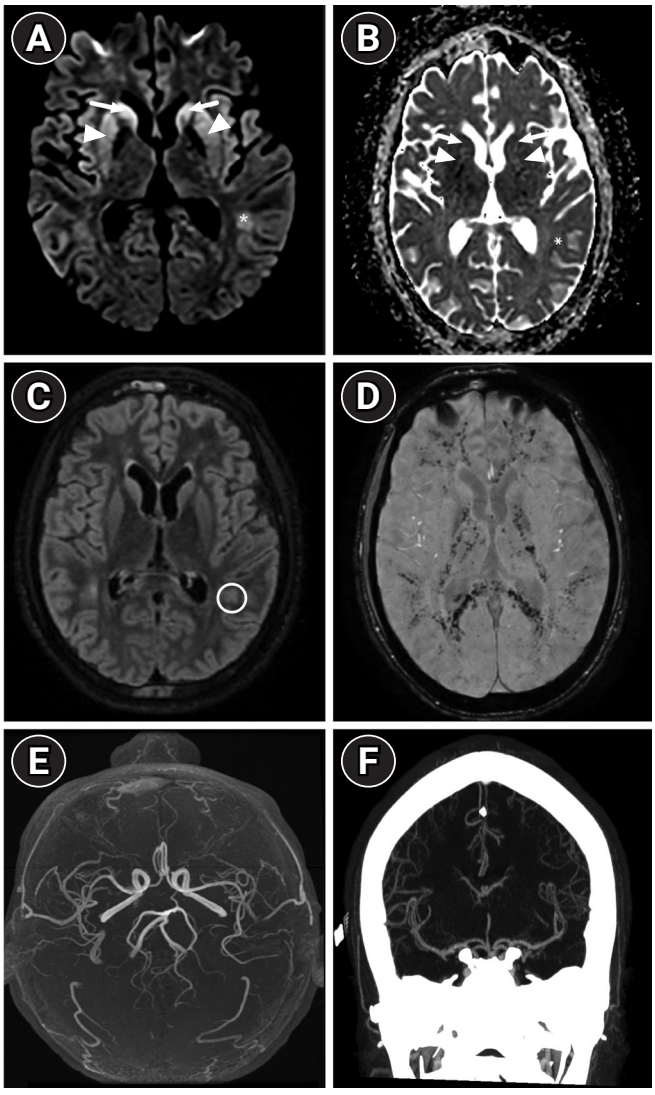

Fig. 2. Second axial brain magnetic resonance imaging performed 26 days after admission. (A) Diffusion-weighted imaging and (B) the corresponding apparent diffusion coefficient map showing bilateral hyperintensity with restricted diffusion of the head of caudate (arrows) and putamen (arrowheads), and left occipital subcortical white matter (asterisks) suggesting additional hypoxic-ischemic encephalopathy. (C) Fluid-attenuated inversion recovery sequence showing hyperintensity of a left occipital white matter lesion (circle) without evidence of collateral flow. (D) The susceptibility-weighted Imaging sequence reveals widespread and consistent pinpoint susceptibilities within the gray matter, gray-white junction, posterior arms of the internal capsules, the splenium of the corpus callosum, basal ganglia, and thalami. This presentation is characteristic of the "walnut kernel microbleed pattern," which strongly indicates cerebral fat embolism. (E, F) The corresponding three-dimensional time-of-flight angiography and computed tomography angiography revealing no abnormalities of intracranial vessels.

lism syndrome (CFES) following bone marrow necrosis was suspected despite the absence of hyperintensity on susceptibility-weighted imaging (Fig. 1D).

A second MRI performed on day 26 due to persistent coma revealed countless microbleeds of the entire white matter displaying a "walnut kernel microbleed pattern" predominant in the posterior arms of the internal capsules, and in the splenium of the corpus callosum, suggestive of an extensive CFES. Moreover, bilateral hyperintensity with restricted diffusion in the head of the caudate and putamen suggested secondary hypoxic-ischemic encephalopathy (Fig. 2A-D) due to fat embolism in the absence of a cardiac origin.

Echocardiography revealed normal findings, and the cardiac rhythm remained sinus on multiple electrocardiograms. MRI and computed tomography angiography revealed no abnormalities (Fig. 2E and F). Although rare, CFES should be considered in SCD patients with altered consciousness [1-3].

ARTICLE INFORMATION

Ethics statement

The French law does not require an institutional review board's approval for the diffusion of a medical image, or other clinical data collected in the context of the medical care provided during a patient stay in the department, as long as it is confidential. The patient's next of care have been informed, and signed a consent form for publication.

Conflict of interest

No potential conflict of interest relevant to this article.

ORCID

Michel Djibré https://orcid.org/0000-0002-9306-4550
Nina de Montmollin https://orcid.org/0000-0001-7496-3350

Author contributions

Writing–original draft: all authors. Writing–review & editing: all authors.

REFERENCES

1. Dhakal LP, Bourgeois K, Barrett KM, Freeman WD. The "starfield" pattern of cerebral fat embolism from bone marrow necrosis in sickle cell crisis. Neurohospitalist 2015;5:74-6.
2. Gendreau S, Scholer M, Cecchini J, Habibi A, Razazi K, De Prost N, et al. Cerebral fat embolism in sickle cell disease. Am J Hematol 2020;95:E41-5.
3. Tsitsikas DA, Vize J, Abukar J. Fat embolism syndrome in sickle cell disease. J Clin Med 2020;9:3601.

https://doi.org/10.18700/jnc.230024

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2023;16(2):125-126
https://doi.org/10.18700/jnc.230027

Journal of Neurocritical Care

Detection of neck hematoma after carotid endarterectomy by chest X-ray

Min Joon Seo, MD[1]; Jin-Heon Jeong, MD[2]

[1]Department of Emergency Medicine, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Korea
[2]Department of Intensive Care Medicine and Neurology, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Korea

IMAGES IN NEUROCRITICAL CARE

Received: August 12, 2023
Revised: September 21, 2023
Accepted: September 26, 2023

Corresponding Author:
Jin-Heon Jeong, MD
Department of Intensive Care Medicine and Neurology, Dong-A University Hospital, Dong-A University College of Medicine, 26 Daesingongwon-ro, Seo-gu, Busan 49201, Korea
Tel: +82-51-240-5266
Fax: +82-51-244-8338
Email: jhjeong@dau.ac.kr

A 61-year-old man presented to the emergency room with left hemiparesis and dysarthria. Brain magnetic resonance imaging showed right middle cerebral artery territory infarction with proximal internal carotid artery stenosis. Carotid endarterectomy (CEA) was performed on the 8th day of admission. After 3 hours of CEA, the patient complained of dyspnea, and stridor was developed. Chest X-ray was performed immediately (Fig. 1), and emergent endotracheal intubation was performed under suspicion of airway obstruction due to hematoma. Neck computed tomography (CT) confirmed hematoma formation around the carotid vessels (Fig. 2). Blood pressure was strictly controlled without discontinuation of clopidogrel, and hematoma was noted to

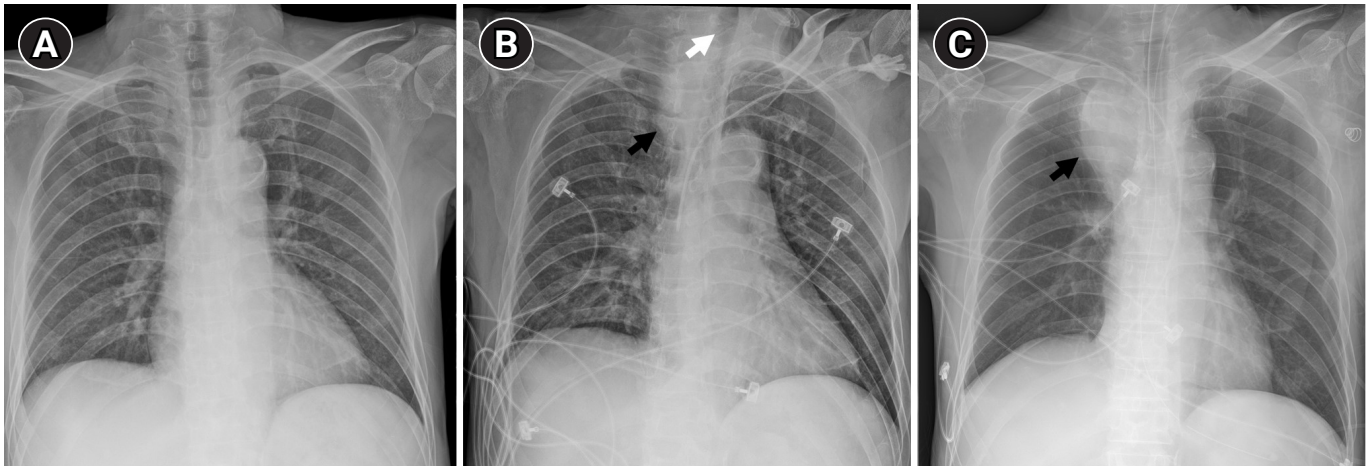

Fig. 1. (A) Chest X-ray taken before carotid endarterectomy (CEA) shows normal findings. (B) Chest X-ray taken during dyspnea after CEA shows soft tissue swelling (black arrow) with tracheal deviation (white arrow). (C) Chest X-ray taken the day after intubation shows aggravation of soft tissue swelling (black arrow).

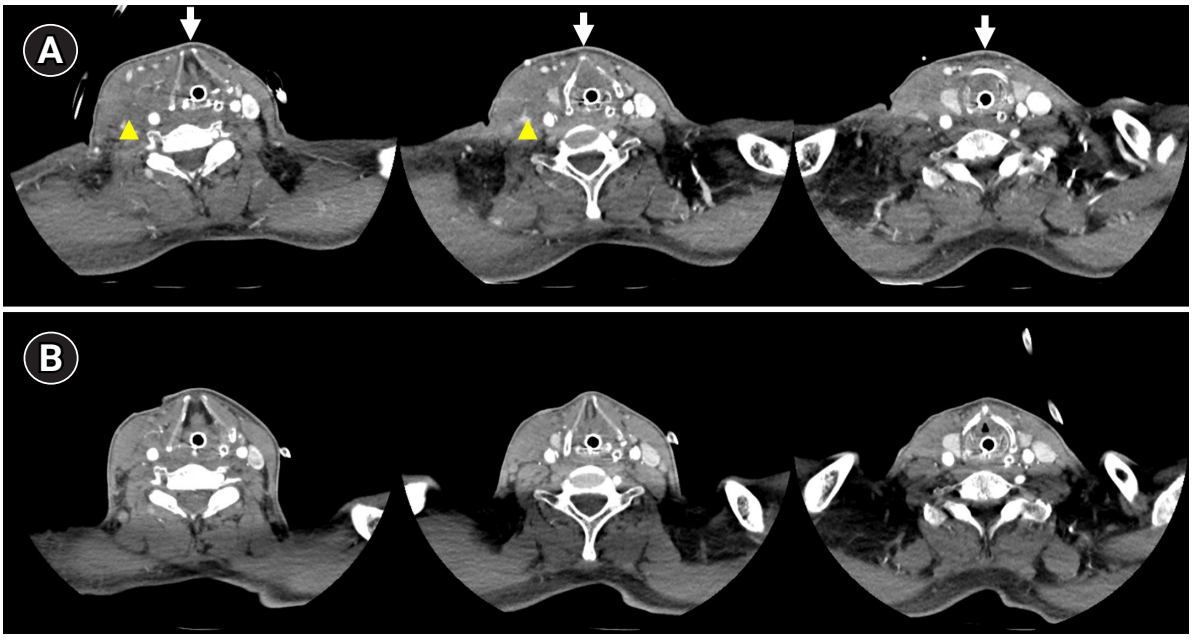

Fig. 2. (A) Neck computed tomography (CT) taken after intubation shows tracheal deviation (white arrows) due to hematoma formation (yellow arrowheads) around the carotid vessels. (B) Neck CT taken 10 days later shows resorption of hematoma and improvement in tracheal deviation.

be reduced on a CT scan 10 days after intubation. The patient was extubated without airway problems.

CEA is the standard treatment for symptomatic carotid stenosis [1,2]. A previous study reported that perioperative hematoma occurred in 7.1% of patients after CEA and was associated with increased perioperative stroke and mortality [3]. Neck hematoma is potentially life-threatening because it can cause respiratory failure and often requires airway management [2]. Suspicion of neck hematoma is crucial if the patient complains of respiratory discomfort after CEA, and airway management should be performed immediately [2]. Checking the chest X-ray can provide guidance in the differential diagnosis of respiratory discomfort after CEA.

ARTICLE INFORMATION

Ethics statement

This study was reviewed and approved by the Institutional Review Board of Dong-A University Hospital (No. DAUHIRB-23-159). The need for informed consent from the patient was waived by the board.

Conflict of interest

Jin-Heon Jeong 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 conflict of interest relevant to this article was reported.

ORCID

Min Joon Seo https://orcid.org/0000-0001-7626-8909
Jin-Heon Jeong https://orcid.org/0000-0002-5878-9206

Author contributions

Conceptualization: JJH. Methodology: all authors. Formal analysis: all authors. Data curation: all authors. Visualization: all authors. Project administration: all authors. Writing–original draft: all authors. Writing–review & editing: all authors.

REFERENCES

1. Brott TG, Hobson RW 2nd, Howard G, Roubin GS, Clark WM, Brooks W, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. N Engl J Med 2010;363:11-23.
2. Shakespeare WA, Lanier WL, Perkins WJ, Pasternak JJ. Airway management in patients who develop neck hematomas after carotid endarterectomy. Anesth Analg 2010;110:588-93.
3. Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, et al. The North American symptomatic carotid endarterectomy trial: surgical results in 1415 patients. Stroke 1999;30:1751-8.

https://doi.org/10.18700/jnc.230027

Instructions to Authors

Journal of Neurocritical Care

Enacted April 1, 2008
Last revised Marh 1, 2023

The *Journal of Neurocritical Care* (J Neurocrit Care, JNC) is the official publication of the Korean Neurocritical Care Society. *JNC* is a peer-reviewed, open-access journal dealing with broad aspects 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 readers—neurointensivists, critical care physicians, neurologists, neurosurgeons, anesthesiologists, emergency physicians, critical care nurses, and clinical pharmacists. 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. *JNC* is published online twice a year: at the end of June and of December. The official website of *JNC* is https://www.e-jnc.org.

Manuscripts submitted to *JNC* should be prepared according to the instructions below. For issues not addressed in these instructions, the author should refer to the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/recommendations) from the International Committee of Medical Journal Editors (ICMJE).

CONTACT US

Editor-in-Chief: Tae Jung Kim, MD, PhD
Department of Neurology and Critical Care, Seoul National University Hospital, 101, Daehak-ro, Jongno-gu, Seoul, 03080 Korea
Tel:+82-2-2072-1810, Fax: +82-2-3672-7553
E-mail: editor@e-jnc.org

Editorial Office: The Korean Neurocritical Care Society
1412, 359 Gangnam-daero, Seocho-gu, Seoul 06621, Korea
Tel: +82-2-521-1412, Fax: +82-2-598-1413
E-mail: office@neurocriticalcare.or.kr

ARTICLE PROCESSING CHARGES

There is no author's submission fee or other publication-related fees as all publication costs are shouldered by the publisher.

RESEARCH AND PUBLICATION ETHICS

The journal adheres to the guidelines and best practices published by professional organizations, including ICMJE Recommendations and the Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by the Committee on Publication Ethics [COPE, https://publicationethics.org], Directory of Open Access Journals [DOAJ, https://doaj.org], World Association of Medical Editors [WAME, https://www.wame.org], and Open Access Scholarly Publishers Association [OASPA, https://oaspa.org]; https://doaj.org/bestpractice). Further, all processes of handling research and publication misconduct shall follow the applicable COPE flowchart (https://publicationethics.org/resources/flowcharts).

Institutional and Ethical Approval

Clinical research should be conducted in accordance with the World Medical Association's Declaration of Helsinki (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/). Clinical studies that are not in accordance with the Helsinki Declaration will not be considered for publication. For human subjects, identifiable information, such as patient names, initials, hospital numbers, dates of birth, and other confidential health care information should not be disclosed. Details regarding the Institutional Review Board (IRB) approval for clinical research should be included in the Methods section of the manuscript. For animal subjects, the authors should adhere to the local or national requirements for the care and use of laboratory animals in research. All animal experiments should be reviewed by the Institutional Animal Care and Use Committee (IACUC) of the organization where the experiments are performed. The Methods section of the manuscript must include a statement regarding IACUC compliance. If necessary, the editor or reviewers may request a copy of the document for clarifications about IRB/IACUC approval and related issues. JNC retains the right to reject any manuscript on the basis of

unethical methodology or misconduct of research.

Patient Privacy and Consent

Some article types (such as clinical research or case reports) may contain descriptions of individual patients. In such cases, a signed consent form must be obtained from each patient described in the manuscript and retained by the authors. The same rule applies to images of patients appearing (in part or whole) in a photograph or video. It is preferable to provide patients with the opportunity to read the manuscript and/or view the images or videos containing their images. A signed informed consent must also be obtained from non-patients (e.g., a physician or nurse) who are exposed to photographs or videos included in the manuscript. Authors should state in the cover letter submitted along with the manuscript that they have obtained a signed consent form and that this form will be retained with their records. This must also be stated in the Methods section. If the need for an informed consent is waived by the IRB for a study, this should be stated in the manuscript.

Conflict of Interest Statement

The author is responsible for disclosing any financial support or benefit that might affect the content of the manuscript or might cause a conflict of interest. When submitting the manuscript, the author must attach the letter of conflict of interest statement (https://www.e-jnc.org/authors/copyright_transfer_COI_statement.php). Examples of potential conflicts of interest are financial support from or connections to companies, political pressure from interest groups, and academically related issues. In particular, all sources of funding applicable to the study should be explicitly stated.

Originality, Plagiarism, and Duplicate Publication

Redundant or duplicate publication refers to the publication of a paper that overlaps substantially with one already published. Upon receipt, submitted manuscripts are screened for possible plagiarism or duplicate publication using Crossref Similarity Check. If a paper that might be regarded as duplicate or redundant had already been published in another journal or submitted for publication, the author should notify the fact in advance at the time of submission. Under these conditions, any such work should be referred to and referenced in the new paper. The new manuscript should be submitted together with copies of the duplicate or redundant material to the editorial committee. If redundant or duplicate publication is attempted or occurs without such notification, the submitted manuscript will be rejected immediately. If the editor was not aware of the violations and of the fact that the article had already been published, the editor will announce in the journal that the submitted manuscript had already been published in a duplicate or redundant manner, without seeking the author's explanation or approval.

Secondary Publication

It is possible to republish manuscripts if the manuscripts satisfy the conditions for secondary publication of the ICMJE Recommendations (http://www.icmje.org/recommendations).

Authorship and Author's Responsibility

Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these four conditions.

- A list of each author's role should accompany the submitted paper.
- Correction of authorship: Any requests for such changes in authorship (adding author(s), removing author(s), or re-arranging the order of authors) after the initial manuscript submission and before publication should be explained in writing to the editor in a letter or e-mail from all authors. This letter must be signed by all authors of the paper. A copyright assignment must be completed by every author.
- Role of corresponding author: The corresponding author takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process. The corresponding author typically ensures that all of the journal's administrative requirements, such as providing the details of authorship, ethics committee approval, clinical trial registration documentation, and conflict of interest forms and statements, are properly completed, although these duties may be delegated to one or more coauthors. The corresponding author should be available throughout the submission and peer review process to respond to editorial queries in a timely manner, and after publication, should be available to respond to critiques of the work and cooperate with any requests from the journal for data or additional information or questions about the article.
- Contributors: Any researcher who does not meet all four ICMJE criteria for authorship discussed above but contribute substantively to the study in terms of idea development, manuscript writing, conducting research, data analysis, and financial support should have their contributions listed in the Acknowledgments section of the article.

Process for Managing Research and Publication Misconduct

When the journal faces suspected cases of research and publication misconduct, such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, undisclosed conflict of interest, ethical problems with a submitted manuscript, appropriation by a reviewer of an author's idea or data, and complaints against editors, the resolution process will follow the flowchart provided by COPE (http://publicationethics.org/resources/flowcharts). The discussion and decision on the suspected cases are carried out by the Editorial Board.

Editorial Responsibilities

The Editorial Board will continuously work to monitor and safeguard publication ethics: guidelines for retracting articles; maintenance of the integrity of academic records; preclusion of business needs from compromising intellectual and ethical standards; publishing corrections, clarifications, retractions, and apologies when needed; and excluding plagiarized and fraudulent data. The editors maintain the following responsibilities: responsibility and authority to reject and accept articles; avoid any conflict of interest with respect to articles they reject or accept; promote the publication of corrections or retractions when errors are found; and preserve the anonymity of reviewers.

EDITORIAL POLICY

Copyright

Copyright in all published material is owned by the Korean Neurocritical Care Society. Authors must agree to transfer copyright (https://www.e-jnc.org/authors/copyright_transfer_COI_statement.php) during the submission process. The corresponding author is responsible for submitting the copyright transfer agreement to the publisher.

Open Access Policy

JNC is an open-access journal. Articles are distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. Author(s) do not need to permission to use tables or figures published in *JNC* in other journals, books, or media for scholarly and educational purposes. This policy is in accordance with the Budapest Open Access Initiative definition of open access.

For any commercial use of material from this open-access journal, permission must be obtained from Korean Neurocritical Care Society (E-mail: office@e-jnc.org).

Article Sharing (Author Self-Archiving) Policy

JNC is an open-access journal, and authors who submit manuscripts to JNC can share their research in several ways, including on preprint servers, social media platforms, at conferences, and in educational materials, in accordance with our open-access policy. However, it should be noted that submitting the same manuscript to multiple journals is strictly prohibited.

Registration of Clinical Trial Research

It is recommended that any research that deals with a clinical trial be registered with a clinical trial registration site, such as http://cris.nih.go.kr, http://www.who.int/ictrp, and http://clinicaltria.gov.

Data Sharing

JNC encourages data sharing wherever possible, unless this is prevented by ethical, privacy, or confidentiality matters. Authors wishing to do so may deposit their data in a publicly accessible repository and include a link to the DOI within the text of the manuscript.

- Clinical Trials: *JNC* accepts the ICMJE Recommendations for data sharing statement policy. Authors may refer to the editorial, "Data Sharing statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in the Journal of Korean Medical Science (https://dx.doi.org/10.3346/jkms.2017.32.7.1051).

Archiving Policy

JNC provides electronic archiving and preservation of access to the journal content in the event the journal is no longer published, by archiving in the National Library of Korea (https://www.nl.go.kr).

Preprint Policy

A preprint can be defined as a version of a scholarly paper that precedes formal peer review and publication in a peer-reviewed scholarly journal. *JNC* allows authors to submit the preprint to the journal. It is not treated as duplicate submission or duplicate publication. *JNC* recommend authors to disclose it with DOI in the letter to the editor during the submission process. Otherwise, it may be screened from the plagiarism check program — Similarity Check (Crosscheck) or Copy Killer. Preprint submission will be processed through the same peer-review process with a usual submission. If the preprint is accepted for publication, authors are recommended to update the info at the preprint with a link to the published article in *JNC*, including DOI at *JNC* It is strongly recommended that authors cite the article in *JNC* instead of the preprint at their next submission to journals.

SUBMISSION AND PEER-REVIEW PROCESS

Submission

All manuscripts should be submitted online via the journal's website (https://submit.e-jnc.org) by the corresponding author. Once you have logged into your account, the online system will lead you through the submission process in a stepwise orderly process. Submission instructions are available at the website. All articles submitted to the journal must comply with these instructions. Failure to do so will result in the return of the manuscript and possible delay in publication.

Peer-Review Process

- A submitted manuscript will be evaluated by editors and reviewers. All manuscripts submitted to *JNC* undergo screening by the Editorial Board, who then determines whether a manuscript undergoes external review. Peer review is conducted by at least two reviewers with relevant expertise.
- The journal uses a **double-blind** peer review process: the reviewers do not know the identity of the authors, and vice versa.
- Reviewers can request authors to revise the content. The corresponding author must indicate the modifications made in their item-by-item response to the reviewers' comments. Failure to resubmit the revised manuscript within **2 months** of the editorial decision is regarded as a withdrawal.
- The editorial committee has the right to revise the manuscript without the authors' consent, unless the revision substantially affects the original content.
- After review, the editorial board determines whether the manuscript is accepted for publication or not. Once rejected, the manuscript does not undergo another round of review.
- After a manuscript is received by the editorial committee, an e-mail confirmation thereof will be sent to the author within 7 days. The author will be notified of any possible delay that is due to evaluation difficulty. The authors can make an inquiry to the editorial committee on the current evaluation phase of the manuscript. The Board will notify the author on the status of the board review process.

Submission by Editors

Final decisions regarding manuscript publication are made by the editor-in-chief or a designated editor who does not have any relevant conflicts of interest. In the event that an editor has a conflict of interest with a submitted manuscript or with the authors, the manuscript will be handled by one of the other editors who does not have a conflict with the review and who is not at the same institution as the submitting editor. In such circumstances, full masking of the process will be ensured so that the anonymity of the peer reviewers is maintained.

Appeals of Decisions

Any appeal against an editorial decision must be made within 2 weeks of the date of the decision letter. Authors who wish to appeal a decision should contact the Editor-in-Chief, explaining in detail the reasons for the appeal. All appeals will be discussed with at least one other associate editor. If consensus cannot be reached thereby, an appeal will be discussed at a full editorial meeting. The process of handling complaints and appeals follows the guidelines of COPE available from (https://publicationethics.org/appeals). *JNC* does not consider second appeals.

MANUSCRIPT PREPARATION

JNC focuses on clinical and experimental studies, reviews, case reports, and images in neurocritical care. Any researcher throughout the world can submit a manuscript if the scope of the manuscript is appropriate. Manuscripts should be submitted in English.

General Requirements

- The manuscript must be written using Microsoft Word and saved as ".doc" or ".docx" file format. Authors should search for reporting guidelines relevant to their study design and submit the completed checklist as part of the initial submission.
- The page numbers must be indicated in Arabic numerals in the middle of the bottom margin, starting from the title page.
- Neither the authors' names nor their affiliations should appear on the manuscript pages.
- Use only standard abbreviations; the use of non-standard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The full form of a term followed by the abbreviation in parentheses should be used at the first mention, unless the abbreviation is a standard (e.g., DNA).
- The names of manufacturers of equipment and non-generic drugs should be given.
- Authors should express all measurements in conventional units using International System (SI) units.

Reporting Guidelines for Specific Study Designs

For specific study designs, such as randomized controlled trials, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, we strongly recommend that authors follow and adhere to the reporting guidelines relevant to their specific research design. For case reports, authors should follow the **CARE guidelines** (https://www.care-statement.org). Authors

should **upload** a completed **checklist** for the appropriate reporting guidelines during initial submission. Some reliable sources of reporting guidelines are **EQUATOR Network** (https://www.equator-network.org/) and NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

Composition of Manuscripts

- The manuscript types are divided into Original Article, Review Article, Case Report, and Images in Neurocritical Care. There is no limit to the length of each manuscript; however, if unnecessarily long, the author may be penalized during the review process.
- Original Articles should be written in the following order: title page, abstract, keywords, main body (introduction, methods, results, discussion), acknowledgments (if necessary), references, tables, figure legends, and figures. The number of references is limited to 45. Authors should select their study design of the reporting guidelines on the submission system and complete the checklist accordingly. The checklist should be submitted as part of the initial submission. The examples of the study designs are as follows: Randomized trials, Observational studies, Systematic reviews, Study protocols, Diagnostic/prognostic studies, Clinical practice guidelines, Qualitative research, Animal pre-clinical studies, Quality improvement studies, Economic evaluations, and others.
- Review Articles should be written in the following order: title page, abstract, keywords, and main body (introduction, main text, and conclusion), acknowledgments (if necessary), references, tables, figure legends, and figures. There is no limit to the length of the main text as well as the number of references.
- Case Reports should be written in the following order: title page, abstract, keywords, main body (introduction, case report, and discussion), acknowledgments (if necessary), references, tables, figure legends, and figures. The total number of references is limited to 15. We recommend the use of the template provided at https://www.e-jnc.org/authors/authors.php for formatting the manuscript.
- Images in Neurocritical Care should be written in the following order and should not include an abstract and keywords: title page, main body, acknowledgments (if necessary), references, figure legends, and figures. The main body can be written freely without any constraints but should be within 200 words. The total number of references is limited to 4. A maximum of four authors is permitted.
- The requirements for the number of references and length of the main text can be consulted with the Editorial Office.

Title Page

- The title page must include a title, the authors' names and academic degrees (include ORCID*), affiliations, and corresponding authors' names and contact information. In addition, a running title must be written within up to 50 characters including spaces. The corresponding authors' contact information must include a name, addresses, e-mails, telephone numbers, and fax numbers.

* ORCID: We recommend that the open researcher and contributor ID (ORCID) of all authors be provided. To have an ORCID, authors should register in the ORCID website: http://orcid.org/. Registration is free to every researcher in the world.

- The contributions of all authors must be described using the CRediT (https://credit.niso.org) Taxonomy of author roles.
- All persons who have made substantial contributions, but who have not met the criteria for authorship, are acknowledged here. All sources of funding applicable to the study should be stated here explicitly.

Abstract and Keywords

- For Original Articles, the abstract must be written by dividing it into background, methods, results, and conclusion; the abstract should be within 250 words. For Case Reports, the abstract must be written by dividing it into background, case report, and conclusion, and should be within 150 words. For Review Articles, the main body as well as the abstract can be written freely without any constraints.
- At the end of the abstract, three to six keywords should be listed. For the selection of keywords, refer to Medical Subject Heading (MeSH, http://www.ncbi.nlm.nih.gov/mesh).

Main Body

- For abbreviations, when first introduced, they should be fully explained and then inserted within parentheses. Thereafter, only the abbreviations should be used.
- In the abstract and main body, authors should use an italicized capital letter "*P*" for "*P* value" or the significance probability.
- All articles using clinical samples or data and those involving animals must include information on the IRB/IACUC approval and waiver or informed consent. An example is shown below. "We conducted this study in compliance with the principles of the Declaration of Helsinki. The study's protocol was reviewed and approved by the Institutional Review Board of OO (IRB no. OO). Written informed consent was obtained / Informed consent was waived."
- Description of participants: Ensure the correct use of the terms "sex" (when reporting biological factors) and "gender" (identity,

psychosocial, or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example, in only one sex, authors should justify why, except in obvious cases (e.g., ovarian cancer). Authors should define how they determined race or ethnicity and justify their relevance.

- References must be numbered according to their quotation order. When more than two quotations of the same authors are indicated in the main body, a comma must be placed between a discontinuous set of numbers, whereas a dash must be placed between the first and last numerals of a continuous set of numbers: "Kim et al. [2,8,9] insisted…" and "However, Park et al. [11–14] showed opposing research results."
- Figures and tables used in the main body must be indicated as "Fig." and "Table." For example, "Magnetic resonance imaging of the brain revealed… (Figs. 1-3).

Figure

- Figures must be prepared in digital image files, and each figure must be submitted as a separate file.
- If one figure includes more than two pictures, they must be distinguished by adding alphabet labeling in capital letters, such as A, B, and C (e.g., Fig. 1A).
- Patterns are used instead of or in addition to colors for conveying information (colorblind users would then be able to distinguish the visual elements).
- Digital images
  - Each figure has to be prepared as a separate file and should not be inserted in the main body.
  - Remove the margins as much as possible when preparing pictures (especially CT or MRI images). Moreover, medical history reference numbers and names or other personal information must not be included.
  - When submitting photos of patients, the patients should not be recognizable. In case that the face of a patient is visibly recognizable, the patient's consent must be obtained.
  - The name of each file must correspond to its respective figure number.
  - If one figure contains more than two pictures (for example, A, B, and C), the figure must be prepared to be printed as a single image and submitted as a single file.
- File size and resolution
  - The digital image file of each figure must be of an adequate size and resolution so as not to compromise the quality of the printed output.
  - Line art (e.g., graphs, charts, family trees) must not exceed 800 dpi, whereas halftone (CT, MRI) or color pictures must be prepared in no less than 300 dpi.
  - When determining the size of a digital image file, the photo or image size must be greater than the print size, even when downscaled for insertion in the main body.
- File types
  - All file types (tiff, gif, jpeg, and ppt) may be submitted for evaluation by reviewers. However, if an article receives approval for publication, files must be submitted as .tiff or .pdf.
  - In the case of color photos, they must be saved and submitted in CMYK formats. Black-and-white pictures, such as CT and MRI images, must be submitted in grayscale mode.
- Figure legends
  - Figure legends must be precise and written in English on a separate page.
  - All abbreviations introduced in the figure legends must be defined as their first use.
  - If a figure contains more than two pictures, they must be labeled as A, B, C, and so on. The description of the entire figure as well as the individual explanation of A, B, and C must be included.

Table

- Tables must be embedded in the main body of the Microsoft Word file and include their respective title.
- One page must not include more than two tables.
- Footnotes are followed by the source notes, other general notes, abbreviation, notes on specific parts of the table (a), b), c), d)…), and notes on level of probability (*, **, *** for *P*-values).
- A single unified decimal point must be applied in the same table.

References

- All references must be indicated in English.
- Every reference in the Reference section should be cited in the text. The number assigned to the reference citation is according to the first appearance in the manuscript. References in tables or figures are also numbered according to the appearance order. Reference number in the text, tables, and figures should in a bracket ([ ]).
- If there are more than six authors, the names of the first six authors must be specified, followed by "et al."
- The journals should be abbreviated according to the style used in the list of journals indexed in the NLM Journal Catalog (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals).
- The overlapped numerals between the first page and the last page must be omitted (e.g., 2025-6).

- References to unpublished material, such as personal communications and unpublished data, should be noted within the text and not cited in the References. Personal communications and unpublished data must include the individual's name, location, and date of communication.
- Other types of references not described below should follow ICMJE Recommendations (https://www.nlm.nih.gov/bsd/uniform_requirements.html).
- We recommend using the EndNote or Papers citation style available on the journal homepage.

  Please refer to the following examples.

  - Articles in academic journals

  1. Kang J, Kang CH, Roh J, Yeom JA, Shim DH, Kim YS, et al. Feasibility, safety, and follow-up angiographic results of endovascular treatment for non-selected ruptured intracranial aneurysms under local anesthesia with conscious sedation. J Neurocrit Care 2018;11:93-101.
  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, Mohney 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

Supplemental Data

Additional data, including Methods, Results, References, Tables, Figures, and video, that are difficult to be inserted in the main body can be submitted in the form of Supplemental Data. Supplemental Data submitted by the author will be published online together with the main body without going through a separate editing procedure. All supplemental data, except video materials, are to be submitted in a single file, and the manuscript title, authors' title, organization, and corresponding author's contact information must be specified in the first page.

FINAL PREPARATION FOR PUBLICATION

Final Version

After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked, and if the originally submitted image files were of poor resolution, higher resolution image files should be submitted at this time. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All symbols must be defined in the figure caption. If references, tables, or figures are moved, added, or deleted during the revision process, renumber them to reflect such changes so that all tables, references, and figures are cited in numeric order.

Manuscript Corrections

Before publication, the manuscript editor will correct the manuscript such that it meets the standard publication format. The author(s) must respond within 2 days when the manuscript editor contacts the corresponding author for revisions. If the response is delayed, the manuscript's publication may be postponed to the next issue.

Galley Proof

The author(s) will receive the final version of the manuscript as a PDF file. Upon receipt, the author(s) must notify the editorial office (or printing office) of any errors found in the file within 2 days. Any errors found after this time are the responsibility of the author(s) and will have to be corrected as an erratum.

Errata and Corrigenda

To correct errors in published articles, the corresponding author should contact the journal's Editorial Office with a detailed description of the proposed correction. Corrections that profoundly affect the interpretation or conclusions of the article will be reviewed by the editors. Corrections will be published as corrigenda (corrections of the author's errors) or errata (corrections of the publisher's errors) in a later issue of the journal.

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.

Copyright Transfer Agreement

Journal of Neurocritical Care

Manuscript ID: _____

Title of Manuscript: _____

_____

The manuscript is to be submitted as an original article to be published in the Journal of Neurocritical Care. If the manuscript is published in the Journal of Neurocritical Care, the copyrights of the manuscript will be transferred to the Korean Academy of Neurocritical Care. The authors possess all rights excluding copyrights, or in other words, the right to use the entirety or parts of this manuscript for patent application and paper publication in the future. As all authors have made detailed and substantial contributions to the contents of this manuscript, they share common responsibilities for the contents of the original manuscript.

The manuscript abides by the Research and Publication Ethics of the Korean Neurological Association and the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/icmje-recommendations.pdf) from the International Committee of Medical Journal Editors. Additionally, this manuscript should not have previously been published, and at present should not be submitted to other academic journals, nor should there be any plans to do so in the future.

Author	Date	Signature

※ This agreement requires the signatures of all authors and those whose names are included in the acknowledgments.

Conflict of Interest Statement

Journal of Neurocritical Care

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

Examples of conflicts of interest include the following: source of funding, paid consultant to sponsor, study investigator funded by sponsor, employee of sponsor, board membership with sponsor, stockholder for mentioned product, any financial relationship to competitors of mentioned product, and others (please specify).

Author	No conflict involved	Conflict (specify)

I accept the responsibility for the completion of this document and attest to its validity on behalf of all co-authors.

Corresponding author (name/signature) :_____

Date: _____

Checklist for Authors

Journal of Neurocritical Care

☐ Authors have written the manuscript in compliance with Instructions to Authors and Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/icmje-recommendations.pdf) from the International Committee of Medical Journal Editors, and the Guideline of Committee on Publication Ethics (https://publicationethics.org).

☐ Authors have omitted names and organizations in the manuscript submitted for review.

☐ The title page should include a title, authors' names and academic degrees, affiliations, and corresponding author(s)' name(s), contact information, ORCID, and author contributions.

☐ A running title should be given in 50 characters or shorter including spaces.

☐ The abstract should be divided into Background, Methods, Results, and Conclusion; it is within 250 words for Original Articles. For Case Reports, the abstract should be written by dividing it into Background, Case report, and Conclusion, and be within 150 words.

☐ The abstract should be included in the manuscript, regardless of whether it is included in the submission system.

☐ Three to six keywords should be included (those recommended in MeSH (http://www.ncbi.nlm.nih.gov/mesh)).

☐ Information regarding approval of an institutional review board and obtaining informed consent should be mentioned in the Method section.

☐ The number of references is limited to 45 (for original articles), 15 (for case reports) or 4 (for images).

☐ Each figure should be uploaded as a separate file and should not be included in the main text. The file name of each figure should be the figure number.

☐ Line art (e.g., graphs, charts, family trees) must not exceed 800 dpi, whereas halftone (CT, MRI) or color pictures must be prepared in no less than 300 dpi.

☐ All authors have completed the Copyright Transfer Agreement and COI Statement.

☐ The authors are responsible for obtaining permission from the copyright holder to reprint any previously published material in JNC.

☐ A checklist for the appropriate reporting guidelines, as available on the EQUATOR website (http://www.equator-network.org/), should be uploaded along with the manuscript.

☐ For a case report, authors should follow the CARE guidelines (https://www.care-statement.org).