Journal of Neurocritical Care

pISSN 2005-0348
eISSN 2508-1349

Journal of Neurocritical Care Vol. 15 No. 2 December 2022

pages 79-154

www.e-jnc.org

THE KOREAN NEUROCRITICAL CARE SOCIETY

pISSN 2005-0348
eISSN 2508-1349

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Vol. 15
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www.e-jnc.org

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pISSN 2005-0348
eISSN 2508-1349

# Journal of Neurocritical Care

Vol. 15, No. 2, December 31, 2022

## Aims and Scope

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

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Publisher
The Korean Neurocritical Care Society

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Published on December 31, 2022



This paper meets the requirements of KS X ISO 9706, ISO 9706-1994 and ANSI/NISO Z39. 48-1992 (Permanence of paper).

# Editorial Board

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pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):79-87
https://doi.org/10.18700/jnc.220085

Journal of Neurocritical Care

# Quantitative assessments of pupillary light reflexes in neurocritically ill patients

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REVIEW ARTICLE

Received: October 28, 2022
Revised: November 28, 2022
Accepted: November 21, 2022

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The pupillary light reflex is a component of bedside neurological examinations in neurological intensive care units (neuroICUs). A quantitative pupillometer provides a non-invasive and objective pupil reactivity parameter clinically significant for changes in the pupillary light reflex in neuroICUs. This article reviews the physiology and importance of the pupillary light reflex and the parameters of quantitative pupillometers. Moreover, this review discusses the clinical applications of quantitative pupillometers for post-cardiac arrest prognostication and monitoring of elevated intracranial pressure and neurological worsening in stroke, seizures, and other neurological diseases in the neuroICU. Quantitative pupillometry is a routine part of neurological examinations and an important monitoring tool for neurological diseases in neuroICUs.

**Keywords:** Abnormal pupillary function; Neurological examination; Assessment; Outcomes; Critical care

## INTRODUCTION

Intensive neurological examination is the most relevant diagnostic evaluation of neurological status at the bedside in patients with brain injury due to multiple etiologies and conditions predisposing them to neurological deterioration in the neurological intensive care unit (neuroICU). Monitoring of the pupillary light reflex (PLR) is a standard examination for detecting changes in cerebral dysfunction in patients with known brain injuries [1-4]. Quantitative pupillometry is an important noninvasive monitoring method of PLR that provides an objective measure of pupil diameter and pupillary reactivity [2-5]. Therefore, quantitative pupillometer monitoring has become a fundamental element of neurological assessment to quantify and standardize this aspect of neurological evaluation in neurological care. This article aims to review a quantitative pupillometer's clinical applications and impacts on neurological diseases in the neuroICU.

## IMPORTANCE OF PUPILLARY LIGHT REFLEX MONITORING IN THE NEUROLOGICAL INTENSIVE CARE UNITS

Neuromonitoring of the PLR is important to detect changes in brain lesions, identify newly developed pathologies, and prevent

impending secondary brain injury. In addition, changes in PLR could strongly predict neurological worsening after acute brain injury [2,3,6,7]. Under normal conditions of pupillary reactive responses, the stimulant signal of retinal cells is carried through the synapse between the optic nerve and the optic tract in the pretectum of the midbrain, which projects to the Edinger-Westphal nucleus in the dorsal midbrain [2,4,8,9]. After stimulation of the Edinger-Westphal nucleus, the parasympathetic signal is delivered by the oculomotor nerve to the superior orbital fissure of the eye and ciliary ganglion. The parasympathetic pupillary efferent signal stimulates the short posterior ciliary nerves that innervate the iris for pupil constriction [2,4,8,9]. Parasympathetic input for pupil constriction is balanced and controlled by sympathetic signals from the superior cervical ganglion for pupil dilatation. When the afferent and efferent pathways for pupil reactivity are intact in functional and structural processes, both pupils show equal sizes and brisk constriction responses when stimulated with bright light [2,4,8,9].

In neurocritically ill patients, changes and differences in both PLRs often provide early information about aggravated intracranial problems, such as increased intracranial pressure (ICP) and critical pathologies, including brainstem lesions and transtentorial herniation [10-12]. In particular, the sudden onset of a unilaterally dilated pupil, a neurological emergency condition, has been attributed to compression of the oculomotor nerve or horizontal displacement of the midbrain by increasing mass effects, leading to transtentorial herniation [10-12]. Additionally, damage to the Edinger-Westphal nuclei in the midbrain caused by ischemia, hemorrhage, or demyelinating diseases can induce abnormal PLRs bilaterally [10-12].

When performing manual pupil examinations, we usually describe the clinical features of pupil diameter and PLRs based on subjective terms as follows: unilateral (anisocoria), bilateral (isocoria), fixed, dilated, brisk, sluggish, and nonreactive [2-6]. Moreover, manual examination of the PLR has a limited inter-rater reliability of approximately 60%, as the examiners have different skills based on training levels and are allowed to use various non-standardized penlights and other light sources [13-15]. Therefore, there is a potential for compound inaccuracies and discrepancies in PLR for evaluating neurological dysfunction using manual pupil examinations [2-6,13,15].

## ADVANTAGES OF A QUANTITATIVE PUPILLOMETER FOR MONITORING THE PUPILLARY LIGHT REFLEX

A quantitative pupillometer is a noninvasive portable device with a light-emitting diode light source, liquid crystal display screen, and digital video camera based on infrared that measures and analyzes both PLRs. The dynamics of PLR measured by a quantitative pupillometer consisted of four phases, which were based on changes in pupil diameter over time by light stimuli (Fig. 1) [16]. A quantitative pupillometer, especially Neuroptics neurological pupil index (NPi), which measures constriction response to light, provides measured objective parameters during four phases: pupil diameter, latency, constriction velocity (CV), and dilation velocity (DV) (Fig. 2, Table 1) [4,8,17,18]. Latency (ms) is the delay time in pupil constriction following the light stimulus, which is affected by the intensity of the light and the iris smooth muscle. After the latency period, the pupil starts constricting, and the CV is analyzed and reported using changes in the pupil diameter (mm) per second (mm/sec) as well as the maximum CV (MCV). MCV is usually observed during the initial constriction phase before reaching the minimum pupil diameter. Following peak constriction, the pupil quickly starts dilating from its constricted state to its initial size. During these phases, DV was calculated using the changes in diameter over time. In addition, the percentage change (%CH) in pupil constriction was analyzed using the difference between the maximum and minimum pupil diameters. The NPi is calculated by a proprietary algorithm using multiple parameters, including latency, CVs, pupil diameter at baseline, percentage of change, and DVs (Table 1) [2-15,17,18]. In %CH, %CH ≥ 15% is considered a normal and brisk response, %CH < 15% is a sluggish response, and 0%CH indicates a fixed pupil response. NPis of 3–5 are considered normal, NPi < 3.0 is considered abnormal, and an NPi of 0 is considered a fixed pupil response (Table 1) [2-4,6-8,13,17-19]. Another quantitative pupillometer, NeuroLight-Algiscan, which measures the dilatation response of the pupil to pain, provides the PLR to gradually increase pain stimuli (Fig. 2) [4,20-22]. After baseline measurement of PLR, both PLR were assessed with electrical stimulation with gradual stepwise increasing intensity from 10 to a maximum of 60 mA applied on the left forearm connecting two electrodes to the pupillometer, with pupil diameter (mm), pupillary reflex dilation (PRD) to pain (%), and the pupillary pain index (PPI). These parameters were measured based on pupil dilation in response to increasing electrical stimulation from 10 to 60 mA with incremental steps of 10 mA for 1 second and a pulse width of 200 μs [22-24]. PPI was calculated after stopping electrical stimulation when the PRD was over 13% during stimulation. PPI of 1, the PRD is below 5% during maximal stimulation intensity (60 mA), and a PPI of 9 indicates that PRD is above 13% during the stimulation of 10 mA. In addition, a PPI score < 4 is usually considered adequate for pain control [22-25]. Quantitative pupillometers provide more reliable,


https://doi.org/10.18700/jnc.220085

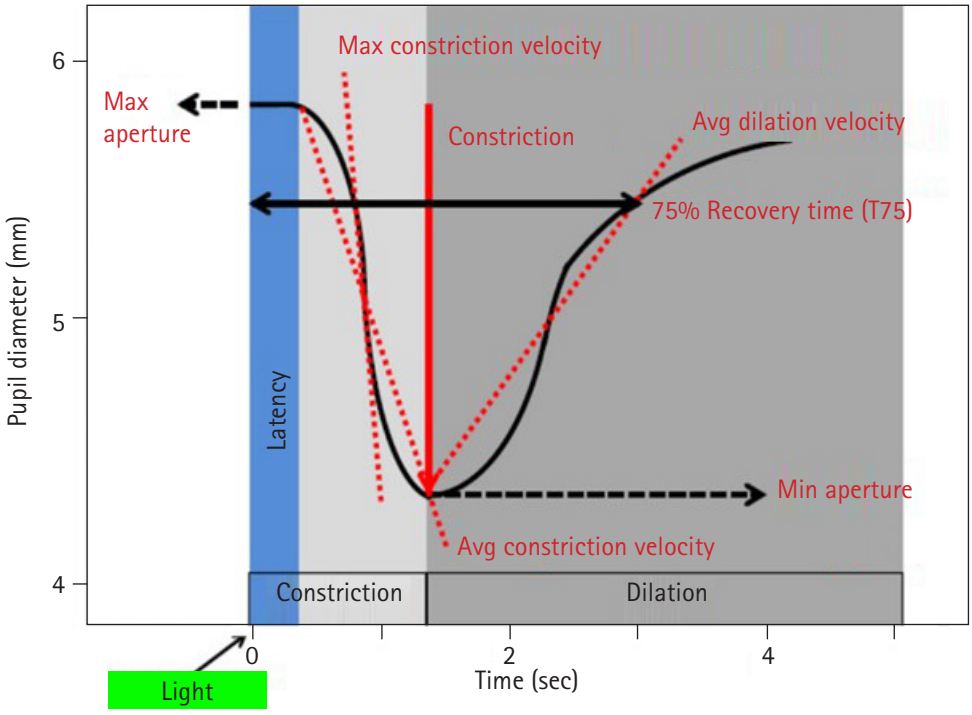


**Fig. 1.** Phases of the pupillary light reflex measured by a quantitative pupillometer. Latency is the time of onset of constriction following a light stimulus. The constriction velocity and maximum constriction velocity were calculated using the slope and maximal slope, respectively, during the constriction phase. During the dilation phase, dilation velocity was evaluated using the slope of the dilation phase. Max, maximum; Avg, average. Reproduced from Packiasabapathy et al. Can J Anaesth 2021;68:566-78 with permission of Springer Nature [16].

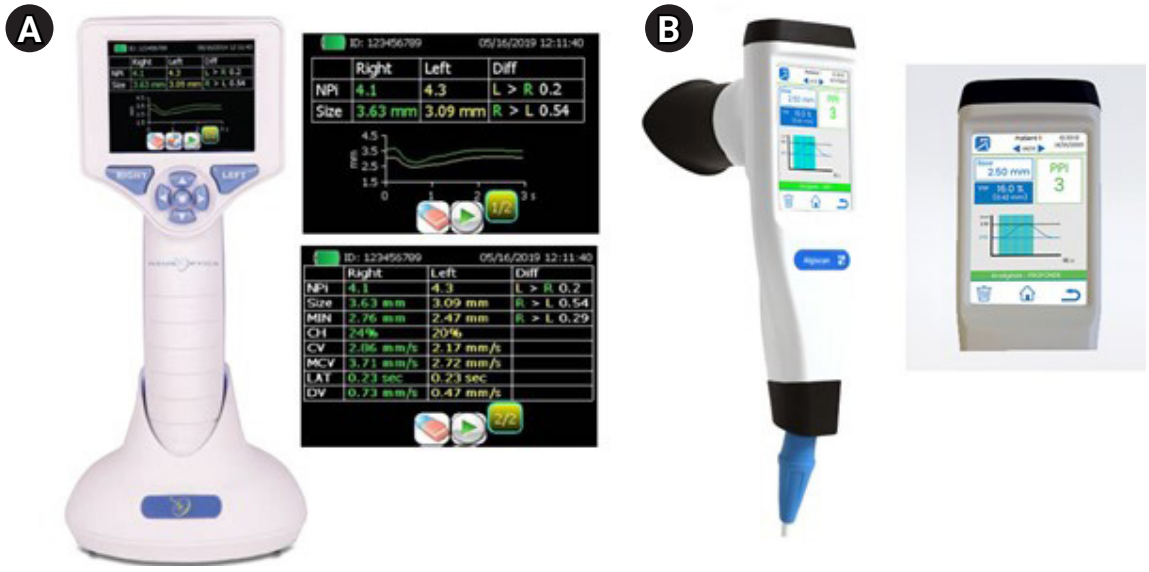


**Fig. 2.** Quantitative pupillometers devices and parameters. (A) Neuroptics NPiTM-200 and result screens. (B) NeuroLight-Algiscan and result screen. Reproduced from NeuroOptics (https://neuroptics.com/npi-200-pupillometer) and IDMED (https://www.idmed.fr/en/analgesia) with permission.

**Table 1.** Parameters measured by a quantitative pupillometer [4,8,17,18]

| Parameter | Definition | Normal value |
|---|---|---|
| Max | Pupil diameter at rest (before constriction, mm) | Asymmetry <0.5 mm |
| Min | Pupil diameter at peak constriction (mm) | Asymmetry <0.5 mm |
| %CH | % Of change (max–min)/size as max (%) | ≥15%: Brisk (normal) |
| | | 1%–14%: Sluggish |
| | | 0%: Non-reactivity |
| LAT | Time of onset of constriction following initiation of the light stimulus (sec) | 0.24–0.28 sec |
| CV | Average measure of how fast the pupil diameter is constricting (mm/sec) | ≥1.0–1.5 mm/sec |
| MCV | Maximum velocity of pupil constriction of the pupil diameter responding to the flash of light measured (mm/sec) | - |
| DV | Distance of redilation divided by the duration of redilation (mm/sec) | Up to 2.83 mm/sec |
| NPi | Proprietary algorithm using all parameters to determine pupillary reactivity | Npi 3.0–4.9: Normal, brisk |
| | | Npi <3.0: Abnormal, sluggish |
| | | NPi 0: Non-reactivity |

Max, maximum; min, minimum; %CH, percentage change; LAT, latency; CV, constriction velocity; MCV, maximum CV; DV, dilation velocity; NPi, neurological pupillary index.

accurate, and objective measurements and have higher inter-rater reliability than manual pupil examinations [9,13-15,17,18].

## CLINICAL APPLICATIONS OF QUANTITATIVE PUPILLOMETER IN NEUROLOGICAL INTENSIVE CARE UNITS

### Prognosis in patients with post-cardiac arrest

Assessment of PLR has been recognized as an essential part of neurological examinations for prognostication performed after hypoxic-ischemic brain injury following cardiac arrest (CA). In particular, evaluating PLR ≥72 hours after the return of spontaneous circulation (ROSC) using a quantitative pupillometer is emerging as a helpful examination to evaluate brainstem function in post-CA patients [26,27]. Several studies have evaluated the relationship between pupillometer parameters and prognostication following CA (Table 2) [1,11,12,28-35]. A prospective study of out-of-hospital cardiac arrest (OHCA) patients treated with targeted temperature management (TTM) at 33°C with sedation and neuromuscular blocking agents reported that the quantitative %CH on days 1 and 2 were associated with poor outcomes at 90 days (cerebral performance categories [CPCs] 3–5). The day-1 quantitative %CH <13% had a sensitivity of 66.7% and a specificity of 91.3% for predicting 90-day poor neurological outcome, and the day-2 quantitative %CH <13% had a sensitivity of 63% and a specificity of 100% for predicting poor outcome at 90 days [28]. Moreover, a prospective study of 55 patients with CA treated with TTM reported that early PLR values, such as the 6-hour NPi after ROSC, predicted poor outcomes at discharge (CPCs 3–5) with an area under the curve (AUC) of 0.72 (cut-off value, 3.7) with a specificity of 82%, sensitivity of 60%, and false positive rate of 0.17. Additionally, patients with poor outcomes had lower 6-hour CVs (median value: poor outcome, 0.36 mm/sec vs. good outcome, 0.65 mm/sec) and %PLRs (%CHs) (median value: poor outcome, 8% vs. good outcome, 14%) [29]. In a prospective multicenter study of 50 patients with OHCA, 0-hour %CH ≥3% predicted 90-day survival (AUC=0.82, sensitivity=0.87, specificity=0.80) and 0-hour %CH ≥6% predicted favorable outcomes (CPCs 1–2) (AUC=0.84, sensitivity=0.92, specificity=0.74) at 90 days after CA [30]. In a prospective multicenter study of patients with CA (n=477), the predictive value of NPi for 3-month outcomes after CA was evaluated. The authors showed that an NPi ≤2 at any time between days 1 and 3 predicted poor outcomes (CPCs 3–5) 3 months after CA with 100% specificity, 32% sensitivity, 51% negative predictive value (NPV), and 100% positive predictive value (PPV). Moreover, an NPi ≤2 with bilaterally absent somatosensory evoked potentials had a higher predictive power for poor outcomes at three months after CA than an NPi ≤2 [31]. NPi also had good prognostic performance in 100 patients who received venoarterial extracorporeal membrane oxygenation therapy after refractory cardiogenic shock or CA. An abnormal NPi (<3) between 24 and 72 hours showed a predictive value of 100% specificity, 53% sensitivity, 100% PPV, and 61% NPV for 90-day mortality [36]. Regarding PPI as a prognostic value, PPI=1 at day 2 after CA predicted poor outcomes with a specificity of 100% and sensitivity of 26% in a single-center retrospective study [37]. Therefore, lower PLR parameters such as NPi, CV, and %CH were associated with poor outcomes after CA, with good predictive performance in predicting poor outcomes in patients with CA.


https://doi.org/10.18700/jnc.220085

**Table 2.** Summary of studies on neurological diseases based on quantitative pupillometer

| Study | Description | Main finding |
|---|---|---|
| Post-cardiac arrest | | |
| Suys et al. [28] | A prospective study of patients with OHCA (n=50) treated with TTM on sedative drugs and NM-blocking agents | Days 1 and 2 quantitative PLRs (%) <13% are associated with poor outcomes (CPCs 3–5) at 90 days after CA. |
| Riker et al. [29] | A prospective study of patients with CA (n=55) treated with TTM | A lower 6-hr CV <0.23 mm/sec and PLR (%) <5% are associated with poor outcomes (CPCs 3–5) at discharge. |
| Tamura et al. [30] | A prospective multi-center study of patients with OHCA (n=50) | The 0-hr PLR (%) <3% is associated with mortality, and a 0-hr PLR (%) >6% is associated with favorable outcomes (CPCs 1–2) at 90 days. |
| Oddo et al. [31] | A prospective multi-center study of patients with CA (n=477) | An NPi ≤2 at any time between days 1 and 3 is associated with poor outcomes (CPCs 3–5) at 90 days. |
| Stroke | | |
| Osman et al. [11] | A retrospective study of patients with stroke (n=134) | A lower NPi and lower CV are associated with aggravated midline shift on brain imaging. |
| Kim et al. [12] | A retrospective study of large hemispheric stroke (n=30) | A decrease of 30% in the NPi is associated with neurological worsening, and the cut-off value of the NPi for detecting neurological worsening is 2.8. |
| Dowlati et al. [1] | A retrospective study of patients with ischemic stroke after mechanical thrombectomy (n=284) | An abnormal NPi (<3.0) within 72 hr after mechanical thrombectomy is associated with malignant cerebral edema. |
| NCSE | | |
| Godau et al. [32] | A prospective cross-sectional observational study of patients with clinical seizure and without recovery (n=103) | The lowest NPis of both sides <4.0 and the absolute difference of NPi on both sides >0.2 are associated with NCSE. |
| Godau et al. [33] | A prospective observational study of patients with NCSE (n=68) | The lowest NPis of both sides is improved after anti-seizure medication therapy. |
| Other neurological diseases | | |
| Yan et al. [34] | An observational study of recipients of liver transplantation (n=183) | A prolonged latency phase and reduced constrictive ratio (the value of the resting diameter minus the MAX constriction diameter/resting diameter) are associated with unconscious patients with grade 4 hepatic encephalopathy. After transplantation, PLRs were improved. |
| Favre et al. [35] | An observational cohort study of medical-surgical ICU patients on mechanical ventilation on sedation (n=100) | A lower %CH and CV in the early stage of ICU care are associated with the development of delirium. |

OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management; NM, neuromuscular; PLR, pupillary light reflex; CPC, cerebral performance category; CA, cardiac arrest; CV, constriction velocity; NPi, neurological pupil index; NCSE, nonconvulsive status epilepticus; ICU, intensive care unit.

**Monitoring in patients with increased ICP and stroke**

Changes in PLR are often recognized as signs of neurological worsening due to secondary brain injury, cerebral edema, and increased ICP related to hemispheric stroke. Serial monitoring of PLRs using a quantitative pupillometer is important for the early detection of aggravation of stroke lesions and the decision of therapy to control cerebral edema and increased ICP (Table 2). In a retrospective study of 134 patients with stroke (ischemic stroke and intracerebral hemorrhage), there was a significant negative correlation between midline shift measured by the septum pellucidum and NPi, CV, and pupil asymmetry. A lower NPi is related to an aggravated midline shift on brain computed tomography or magnetic resonance imaging [11]. A study of large hemispheric stroke (n=30) reported that a sudden decrease in the NPi value, approximately 30% of the baseline NPi value, was a surrogate marker of neurological worsening and the cut-off value of the NPi for detecting neurological deterioration was 2.8 after stroke [38]. In addition, abnormal NPi values (<3.0) on the ipsilateral side of stroke lesions within 72 hours after mechanical thrombectomy had a strong independent association with malignant cerebral edema in patients with large vessel occlusion (odds ratio, 21.80; 95% confidence interval [CI], 3.32–286.4) [1].

Regarding the role of the pupillometer in increased ICP with brain herniation syndrome, several studies have shown that lower NPi values <3.0 were associated with increased ICP (mean ICP: normal NPi group, 19.6 mmHg; abnormal NPi group, 30.5 mmHg) [36] and that lower NPi values (<1.6) were associated with brain herniation syndrome with a specificity of 91% and sen-

sitivity of 49% [39]. Moreover, repeated quantitative pupillary measurements could be a useful monitoring method of treatment in addition to early diagnostic tools for neurological deterioration in patients with acute brain injury. A study of critically ill neurologic patients with stroke or brain tumors showed that pupillary parameters such as the NPi and %CH were improved after the administration of osmotic therapy such as mannitol and hypertonic, which demonstrated the possibility of using a quantitative pupillometer as a useful monitoring method for the treatment effect in reducing brain edema [40].

### Monitoring in nonconvulsive status epilepticus

Few studies have evaluated the usefulness of quantitative pupillometers for seizures (Table 2). A prospective cross-sectional observational study of 103 patients with clinical seizures without recovery to prior function examined the ability of a quantitative pupillometer to diagnose nonconvulsive status epilepticus (NCSE). The diagnosis of NCSE was established based on clinical features and electroencephalography (EEG) results, and a pupillometer was used before EEG. The NCSE groups (possible NCSE and confirmed NCSE) had the lowest NPi values on both sides (minNPi), with an optimal cut-off value of 4.0 (AUC, 0.93; 95% CI, 0.86–0.99) and a higher absolute difference of both sides (diffNPi) of 0.2 (AUC, 0.89; 95% CI, 0.80– 0.99) [32]. In a prospective observational study of 68 patients with NCSE, the authors examined the changes in minNPi and diffNPi according to treatment response during anti-seizure medication (ASM) therapy. At baseline, a minNPi ≤4.0 was found in 85.3% of patients with NCSE. After ASM therapy, 77.6% of the minNPi values were normalized in the treatment responder group among the NCSE-terminated patients (n=66). Moreover, the improvement in minNPi was significant according to the responsiveness of each ASM in responder groups [33]. Therefore, a quantitative pupillometer could be a useful non-invasive neuromonitoring tool for the diagnosis and treatment responsiveness of NCSE.

### Other neurological diseases

Quantitative pupillometry could be a useful neurological monitoring tool for patients with cortical dysfunction for several medical reasons. In an observational study of liver transplantation (n=183), unconscious patients with grade 4 hepatic encephalopathy before liver transplantation had a prolonged latency phase and reduced constrictive ratio (the value of the resting diameter minus the maximum constriction diameter/resting diameter). In addition, the recovery of pupillometer parameters was slower in patients with grade 4 hepatic encephalopathy after liver transplantation, in which the recovery time of grade 4 hepatic encephalopathy was delayed to 36 hours. In contrast, other groups recovered within 24 hours of transplantation [34]. Moreover, lower %CH and CV in the early stages of intensive care unit (ICU) care were associated with the development of delirium irrespective of the baseline severity, analgesia, and sedation dose in sedated, mechanically ventilated ICU patients without brain injuries [35]. A prospective observational study based on ICU patients reported that a lower DV was independently related to unreactive EEG findings, indicating no EEG change in response to external stimuli in patients with brain injuries, such as stroke, traumatic brain injury, infection, and other medical diseases [41].

## FACTORS AFFECTING THE PUPILLOMETER PARAMETERS IN THE NEUROLOGICAL INTENSIVE CARE UNITS

Several factors related to treatments and environments in the neuroICU are associated with pupillometer parameters. Many medications that affect the PLR are frequently used in neuroICUs. The most used medications are opioids, which usually induce miosis by activating parasympathetic activity. In healthy volunteers who received remifentanil, the drug reduced pupil diameters (5.6 mm to 2.5 mm) related to hypercarbia and hypoxia and decreased NPi values (4.6 to 4.3), but the values were within the normal range. Therefore, PLR examination during opioid administration may be useful for neurological assessment [42]. In the neuroICU, sedative drugs, such as benzodiazepine, propofol, and dexmedetomidine, are commonly used for treatment and sedation in neurocritically ill patients. In a prospective study of 15 male volunteers, pupillary function, including pupil diameter and light reflex function, was examined under darkness and at three luminance levels after oral administration of diazepam (10 mg), and pupil diameter and light reflex function did not change during monitoring [43]. Regarding the effect of propofol on PLR, a cross-sectional study of 19 volunteers treated with propofol reported that propofol sedation decreased pupil diameter and CV [44]. In patients with acute intracranial pathology, dexmedetomidine induced an increase in NPi (3.77 to 4.14) and smaller pupil diameters (3.41 to 3.13) despite the values being within the normal range [7]. PLR changes in the neuroICU could be affected by ambient light and circadian rhythms in the neuroICU. The circadian rhythm is changed by external stimuli such as abnormal lighting, nocturnal light exposure, noise, and altered feeding schedules. Therefore, pupil dynamics in the neuroICU may be altered by the circadian phases and environment of the neuroICU [45-47]. Additionally, age, iris color, and sex may affect PLR [48]. Although several factors, including medications and the environment, could affect PLR


https://doi.org/10.18700/jnc.220085

changes in the neuroICU, serial monitoring of PLR using a quantitative pupillometer is a helpful neuromonitoring method because the variability of PLR is within the normal range.

## CONCLUSIONS

PLR has long been an important neurological examination for evaluating various neurological conditions. A quantitative pupillometer provides objective and reliable parameters for assessing changes in PLRs compared to manual pupil examinations. Quantitative pupillometry has many potential benefits in detecting intracranial pathology, treatment effects, and monitoring increased ICP in the neuroICU. Moreover, the parameters of the quantitative pupillometer have prognostic value when assessing outcomes after CA. Although PLR is affected by several factors, such as medications and environments, quantitative pupillometry could be an important clinical monitoring tool to evaluate changes in neurological conditions for determining treatment effects and outcomes in the neuroICU.

## ARTICLE INFORMATION

**Ethics statement**
Not applicable.

**Conflict of interest**
Tae Jung Kim 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 conflicts of interest relevant to this article were reported.

**Acknowledgments**
This study was funded by Seoul National University Hospital (No. 0320210350).

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https://doi.org/10.18700/jnc.220085

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pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):88-95
https://doi.org/10.18700/jnc.220063

Journal of Neurocritical Care

# In-hospital mortality of atrial fibrillation-associated acute ischemic stroke in the intensive care unit

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ORIGINAL ARTICLE

Received: June 27, 2022
Revised: July 8, 2022
Accepted: July 9, 2022

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**Background:** Although atrial fibrillation (AF)-associated acute ischemic stroke (AIS) is on the rise, is devastating, and life-threatening, there is limited data on the clinical course and in-hospital mortality of patients treated in the intensive care unit (ICU). This study aimed to describe the clinical course and factors associated with in-hospital mortality in AF-associated AIS patients admitted to the ICU.

**Methods:** This study was a retrospective analysis of a prospective nationwide multicenter cohort including non-valvular AF-AIS patients receiving ICU care admitted to 14 stroke centers in South Korea from 2017 to 2020. In-hospital outcomes, including in-hospital mortality and neurological deterioration (ND) have been described.

**Results:** Amongst 2,487 AF-associated AIS patients, 259 (10.4%) were treated in the ICU. In-hospital mortality and ND occurred in 8.5% and 17.0% of the patients, respectively. Higher rates of initial National Institute for Health Stroke Scale scores, symptomatic steno-occlusive lesions, and $CHA_2DS_2$-VASc (Congestive Heart Failure, Hypertension, Age ≥75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65–74, Female) scores were found in those with in-hospital mortality. The $CHA_2DS_2$-VASc score after admission increased the risk of in-hospital mortality (odds ratio [OR], 1.48; 95% confidence interval [CI], 1.00–2.18) were associated with in-hospital mortality. Antithrombotic use within 48 hours was related to decreased in-hospital mortality (OR, 0.26; 95% CI, 0.10–0.67).

**Conclusion:** ICU care in AF-associated AIS is common, and the establishment of optimal treatment strategies in the ICU may be needed.

**Keywords:** Stroke; Atrial fibrillation; Cerebral infarction; Critical care; Intensive care units

## INTRODUCTION

Atrial fibrillation (AF) is a major risk factor for ischemic stroke, contributing to an incremental risk of more than five times [1]. Furthermore, AF was associated with more severe symptoms and a greater than 30-day mortality risk among acute ischemic stroke (AIS) patients as per the Framingham sub-study [2]. As AF prevalence increases with age from 0.1% in those aged < 55 years to 9.0% in those aged 80 years or older [3], the number of AF-related embolic events is estimated to triple by 2050 with an increasing average life span [4]. Therefore, discussions on treatment strategies for this devastating, life-threatening, and increasing AF-associated AIS is essential to improve patient care [5].

Proper management in the intensive care unit (ICU) is known to improve outcomes in neurological diseases [6]. For AIS, ICU care is focused on post-reperfusion management, cerebral edema/increased intracranial pressure (IICP) treatment, determination of surgical options, prevention of stroke progression and recurrence, and airway/respiratory support [7,8]. If AF-AIS patients have greater infarct size, infarct growth, and hemorrhagic transformation rates [9], dedicated ICU care for the indicated AF-AIS patients is essential, and the role of ICU care should especially be highlighted in them. However, data regarding AF-AIS patients treated in the ICU are scarce.

Understanding individual profiles and clinical courses may be required to establish optimal treatment strategies to enhance outcomes in AF-AIS patients in the ICU. In this study, we aimed to describe baseline characteristics and stroke information in AF-associated AIS patients treated in the ICU, compared to those who did not; further, the clinical parameters associated with in-hospital mortality using clinical data from a prospective nationwide multicenter AF cohort study were investigated.

## METHODS

### Study subjects

Among AIS patients admitted to 14 stroke centers in Korea, the East Asian Ischemic Stroke Patients with Atrial Fibrillation Study (EAST-AF) Part II was used to provide risk stratification tools for assessing the risk of stroke recurrence by collecting clinical and neuroimaging characteristics potentially associated with clinical outcomes. The EAST-AF Part II prospectively enrolled patients with nonvalvular AF. These patients included those with priorly known AF and AF diagnosed after stroke upon routine electrocardiography, automatic electrocardiography monitoring or 24-hour Holter monitoring during their hospital stay. Clinical information and outcome data were derived from the Clinical Research Collaboration for Stroke in Korea (CRCS-K) registry [10].

A total of 15,353 patients admitted to the EAST-AF-Part II participating centers between October 26, 2017, and March 31, 2020, were screened. Amongst 2,690 non-valvular AF patients who provided informed consent, we included 2,489 patients who completed clinical and neuroimaging data from the prospective registry in this study (Fig. 1). After excluding two patients with essential clinical information, 2,487 patients were included in the analysis. In total, 259 ICU patients were enrolled in the current study. ICU admission was determined by neurological (malignant middle cerebral artery infarction, stroke causing decreased consciousness, in need of treatment for increased intracranial cerebral pressure or monitoring, etc.), cardiopulmonary (cardiac arrest, heart failure, pneumonia, pulmonary embolism, acute respiratory distress syndrome requiring intubation and ventilator support), and other clinical conditions. Physicians determined the need for ICU care [6,11].

### Data collection and outcome assessment

Clinical data were obtained from the CRCS-K database, including records of intensive care during hospital stay. Information on sex, age, vascular risk factors including hypertension, diabetes, dyslipidemia, smoking status, history of stroke and coronary heart disease, and heart failure was further collected. Data on prior antithrombotic and premorbid functional statuses were also collected. Stroke information such as systolic and diastolic blood pressure, initial glucose level, initial National Institute for Health Stroke Scale (NIHSS) score, symptomatic steno-occlusive lesion ( > 50% stenosis or occlusion) [12], emergent revascularization therapy (intravenous thrombolysis and endovascular treatment [EVT]),

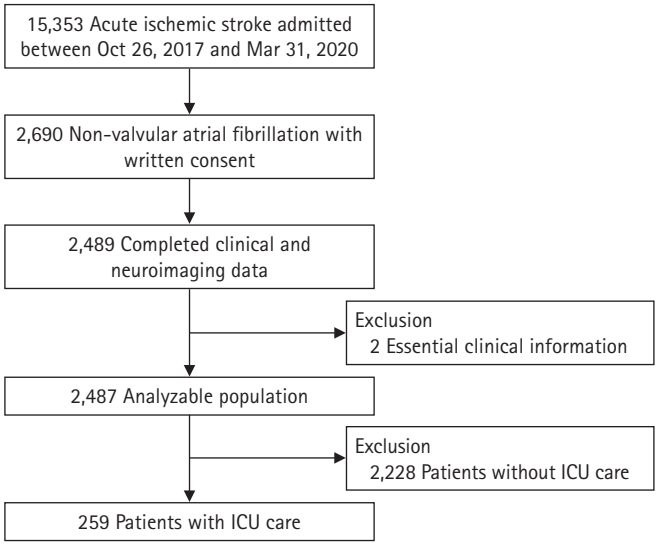


**Fig. 1.** Study population. ICU, intensive care unit.

and acute antithrombotic treatment including antiplatelet and anticoagulant therapy within 48 hours of admission were evaluated. Door-to-needle time was defined in 89 patients who underwent intravenous thrombolysis and an onset-to-arrival of < 24 hours. Door-to-puncture time was defined in 99 patients who underwent EVT and an onset-to-arrival of < 24 hours, and onset-to-reperfusion time was defined in 79 patients who underwent EVT, ≥ 2a thrombolysis in cerebral infarction, and an onset-to-arrival of < 24 hours.

The primary outcome was in-hospital mortality rate. Among the three discharge states, in-hospital mortality, transfer to other departments, and discharge, the occurrence of in-hospital mortality was analyzed. In-hospital mortality included patients with hopeless discharge. The occurrence of neurological deterioration (ND) was also assessed. ND was defined as any new neurological symptoms or signs worsening among patients with a total NIHSS score ≥ 2 or an increase in the NIHSS subscore of ≥ 1 for consciousness or motor function level, occurring during the hospital stay within 3 weeks of onset [13]. Stroke recurrence, stroke progression, symptomatic hemorrhagic transformation, and other causes including myocardial infarction, pulmonary embolism, deep vein thrombosis, or unknown etiologies constituted ND. Stroke recurrence was determined as having new discrete lesions on brain imaging. Stroke progression was defined as neurologic deterioration lasting more than 24 hours due to progressive ischemia, swelling, or perilesional edema of the infarcted area, distinguished from stroke recurrence with brain imaging, which is caused by new discrete lesions [14]. Amongst stroke progression, brain swelling/IICP was defined as ND caused by swelling of infarcted tissue or perilesional edema that was confirmed by a physician with brain imaging. Symptomatic hemorrhagic transformation was diagnosed as per European Cooperative Acute Stroke Study (ECASS) criteria, defined as any hemorrhage site found on brain imaging that caused a decrease in the NIHSS score of ≥ 4 [15,16]. The modified Rankin scale scores at discharge and number of admission days were also obtained. The change in NIHSS score from the initial NIHSS score to the discharge NIHSS score was calculated.

### Statistical analysis

Baseline characteristics and stroke information of patients in the ICU were described as mean ± standard deviation or median (interquartile range [IQR]), as appropriate. The discharge status and proportion of ND were described. Patients who received ICU care were further distinguished based on the occurrence of in-hospital mortality. We compared the baseline characteristics and stroke information between patients with and without in-hospital mortality. Clinical parameters that differed between the two groups were determined using the chi-square test or Fisher's exact test for categorical variables and Student *t*-test or Mann Whitney *U*-test for continuous variables, as appropriate. Among variables of $P < 0.05$ in difference between the two groups, the relationship between in-hospital mortality and clinical parameters in difference was analyzed by binary logistic regression model. We established multivariable models as follows: (1) unadjusted model and (2) adjusted model with the initial NIHSS score. With substantial validated predictability, the initial NIHSS score was chosen as a variable for adjustment [17]. Due to the limited number of outcomes, the variables were adjusted with the initial NIHSS score. If the $CHA_2DS_2$-VASc (Congestive Heart Failure, Hypertension, Age ≥ 75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65–74, Female) score was related to the outcome, variables that were components of the $CHA_2DS_2$-VASc score were not included in the multivariable model, considering potential multicollinearity. Multicollinearity between the initial NIHSS score and the variables was evaluated using the variance inflation factor, and no significant relationship was found. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated. Data were analyzed using R 4.1.3, and a *P*-value of < 0.05 was considered statistically significant.

## RESULTS

Demographics and stroke information were described for patients receiving ICU care (Table 1). The median age was 78 (IQR, 69–83) and the median $CHA_2DS_2$-VASc score was 5.5 ± 1.3. Antithrombotics prior to the index stroke were used in 43.2% of patients. The median NIHSS score was 14 (IQR, 8–19) and 53.7% of the patients underwent emergent revascularization therapy. Among the AF-associated AIS patients treated in the ICU, in-hospital mortality occurred in 22 patients (8.5%) (Table 2). Two-thirds of the patients were discharged. ND occurred in 17.0% of patients. Stroke progression occurred in 10.4% of the patients and was the most frequent subtype of ND, which included 5.8% of the patients whose ND was caused by brain swelling or increased intracranial cerebral pressure. Symptomatic hemorrhagic transformation was observed in 2.3% of patients. After admission, the median decrease in the NIHSS score was 3.

Comparing patients without in-hospital mortality among AF-associated stroke in the ICU, patients with in-hospital mortality were older, had higher $CHA_2DS_2$-VASc score, initial NIHSS score, proportion of symptomatic steno-occlusive lesions, and lower acute antithrombotic treatment within 48 hours (Table 3).


https://doi.org/10.18700/jnc.220063

**Table 1.** Baseline characteristics of atrial fibrillation-associated acute ischemic stroke patients with intensive care management

| Variable | Value (n=259) |
|---|---|
| Sex | |
| Female | 128 (49.4) |
| Male | 131 (50.6) |
| Age (yr) | 78 (69–83) |
| Onset to arrival | 87.0 (43.5–290.5) |
| Vascular risk factor | |
| Hypertension | 182 (70.3) |
| Diabetes | 88 (34.0) |
| Dyslipidemia | 72 (27.8) |
| Current smoking | 36 (13.9) |
| History of stroke | 56 (21.6) |
| History of coronary heart disease | 42 (16.2) |
| Heart failure | 35 (13.5) |
| $CHA_2DS_2$-VASc score | 5.5±1.3 |
| Prior antithrombotics | 112 (43.2) |
| Premorbid mRS | 0 (0–1) |
| Stroke information | |
| Systolic BP (mmHg) | 151.3±27.9 |
| Diastolic BP (mmHg) | 87.7± 19.0 |
| Initial glucose (mg/dL) | 152.3±79.5 |
| Initial NIHSS score | 14 (8–19) |
| Symptomatic steno-occlusive lesion | 168 (64.9) |
| Emergent revascularization therapy | 139 (53.7) |
| Door to needle time (min)[a] | 40.0 (27.0–53.0) |
| Door to punture time (min)[b] | 107.0 (76.0–142.5) |
| Onset-to-reperfusion time (min)[c] | 229.0 (187.5–295.0) |
| Antithrombotics within 48 hours | 210 (81.1) |

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
mRS, modified Rankin scale; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale.
[a]Defined in 89 patients who underwent intravenous thrombolysis and an onset-to-arrival of <24 hours; [b]Defined in 99 patients who underwent endovascular treatment and an onset-to-arrival of <24 hours; [c]Defined in 79 patients who underwent endovascular treatment, with thrombolysis in cerebral infarction of ≥2a, and an onset-to-arrival of <24 hours.

**Table 2.** In-hospital outcomes of atrial fibrillation-associated acute ischemic stroke patients treated in the intensive care unit

| Outcome | Study population (n=259) |
|---|---|
| Discharge state | |
| In-hospital mortality[a] | 22 (8.5) |
| Transfer to other departments | 59 (22.8) |
| Discharge | 178 (68.7) |
| Early neurological deterioration | 44 (17.0) |
| Stroke recurrence | 6 (2.3) |
| Ischemic recurrence | 5 (1.9) |
| Hemorrhagic recurrence | 1 (0.4) |
| Stroke progression | 27 (10.4) |
| Brain swelling/IICP | 15 (5.8) |
| Symptomatic hemorrhagic transformation | 6 (2.3) |
| Others | 5 (1.9) |
| mRS at discharge | 4 (2–5) |
| Admission day | 15.4±19.0 |
| Discharge NIHSS score | 6 (2–16) |
| NIHSS score change | 3 (0–9) |

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
IICP, increased intracranial pressure; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale.
[a]In-hospital mortality includes hopeless discharge.

In the logistic regression model, the initial NIHSS score increased the odds of in-hospital mortality in the unadjusted model (OR, 1.11; 95% CI, 1.05–1.19) (Table 4). When adjusted for the initial NIHSS score, $CHA_2DS_2$-VASc score (OR, 1.48; 95% CI, 1.00–2.18]) increased the risk of in-hospital mortality, while symptomatic steno-occlusive disease (OR, 2.72; 95% CI, 0.76–9.68) did not. Antithrombotic use 48 hours after admission was associated with a low mortality risk (OR, 0.26; 95% CI, 0.10–0.67).

## DISCUSSION

In this retrospective analysis of a multicenter prospective cohort of AF-associated AIS patients, approximately one-tenth of the patients were managed in the ICU. The $CHA_2DS_2$-VASc score was associated with increased in-hospital mortality, whereas antithrombotic treatment within 48 h was related to low in-hospital mortality. ND and stroke progression, including brain swelling, were frequently observed in these patients. A decrease in the NIHSS score from admission to discharge was observed.

Several studies on AIS patients receiving ICU care have reported variable hospital mortality and functional outcomes [11,18]. Compared with previous literatures (25%–40%), the in-hospital mortality rate was quite low (8.5%). This finding might be attributable to the variable indications of ICU admission according to hospital policy or physicians' decisions. An observational study of neurological and neurosurgical ICU in Korea reported similar in-hospital mortality (7.3% for ICU and 4.7% for neurosurgical ICU), comparable to the current study [6]. This study also suggests the potential benefit of ICU care with the improvement of NIHSS score of 3 points at discharge, and the rates of patients with an indication of neurological treatment. As neurological aspects of ICU care in AIS patients concentrate on post-reperfusion therapy and ND [7,8,19,20], this study reported that emergent revascularization therapy reported in 53.7% of ICU-treated patients could be a potential target population for the neurological

**Table 3.** Comparison of baseline characteristics and outcomes in atrial fibrillation-associated acute ischemic stroke patients treated in the intensive care unit according to in-hospital mortality

| Variable | In-hospital mortality (+) (n=22) | In-hospital mortality (–) (n=237) | *P*-value |
|---|---|---|---|
| Sex | | | 0.163[a] |
| Female | 14 (63.6) | 114 (48.1) | |
| Male | 8 (36.4) | 123 (51.9) | |
| Age (yr) | 81 (76–86) | 78 (68–83) | 0.029[f] |
| Onset to arrival | 101.0 (41.0–391.0) | 87.0 (44.0–277.0) | 0.810 |
| Vascular risk factor | | | |
| Hypertension | 13 (59.1) | 169 (71.3) | 0.230[a] |
| Diabetes | 11 (50.0) | 77 (32.5) | 0.097[a] |
| Dyslipidemia | 4 (18.2) | 68 (28.7) | 0.455[b] |
| Current smoking | 3 (13.6) | 33 (13.9) | 1.000[b] |
| History of stroke | 4 (18.2) | 52 (21.9) | 0.793[b] |
| History of coronary heart disease | 6 (27.3) | 36 (15.2) | 0.141[a] |
| Heart failure | 1 (4.5) | 34 (14.3) | 0.328[b] |
| $CHA_2DS_2$-VASc score | 6.1±1.3 | 5.4±1.3 | 0.022 |
| Prior antithrombotics | 9 (47.4) | 103 (42.9) | 0.706[b] |
| Premorbid mRS | 0 (0–2) | 0 (0–1) | 0.125 |
| Stroke information | | | |
| Systolic BP (mmHg) | 155.5±29.8 | 150.9±27.8 | 0.462 |
| Diastolic BP (mmHg) | 95.8±29.2 | 86.9±17.7 | 0.175 |
| Initial glucose (mg/dL) | 170.5±62.0 | 150.6±80.8 | 0.264 |
| Initial NIHSS score | 19 (14–24) | 14 (7–18) | 0.002[f] |
| Symptomatic steno-occlusive lesion | 19 (86.4) | 149 (62.9) | 0.027[a,f] |
| Emergent revascularization therapy | 10 (45.5) | 129 (54.4) | 0.419[a] |
| Door to needle time (min)[c] | 37.0 (35.0–45.5) | 40.5 (26.0–53.0) | 0.790 |
| Door to punture time (min)[d] | 108.0 (92.0–160.0) | 107.0 (75.0–142.0) | 0.484 |
| Onset to reperfusion time (min)[e] | 367.0 (269.5–423.0) | 226.0 (184.0–285.0) | 0.164 |
| Antithrombotics within 48 hours | 11 (50.0) | 199 (84.0) | <0.001[a,f] |

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
mRS, modified Rankin scale; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale.
[a]Chi-square test; [b]Fisher's exact test; [c]Defined in 89 patients who underwent intravenous thrombolysis and an onset-to-arrival of <24 hours; [d]Defined in 99 patients who underwent endovascular treatment and an onset-to-arrival of <24 hours; [e]Defined in 79 patients who underwent endovascular treatment, with thrombolysis in cerebral infarction of ≥2a, and an onset-to-arrival of <24 hours; [f]Indicates $P<0.05$.

**Table 4.** Odds ratio of variables for associating in-hospital mortality in atrial fibrillation-associated acute ischemic stroke patients treated in the intensive care unit

| Variable | Model | OR of variables | | OR of initial NIHSS score | |
|---|---|---|---|---|---|
| | | OR (95% CI) | *P*-value | OR (95% CI) | *P*-value |
| $CHA_2DS_2$-VASc score (per 1 point increment) | Unadjusted | 1.52 (1.06–2.19) | 0.024 | | |
| | Adjusted with NIHSS | 1.48 (1.00–2.18) | 0.049 | 1.11 (1.04–1.18) | 0.002 |
| Symptomatic steno-occlusive lesion | Unadjusted | 3.74 (1.08–13.00) | 0.038 | | |
| | Adjusted with NIHSS | 2.72 (0.76–9.68) | 0.123 | 1.11 (1.04–1.18) | 0.003 |
| Antithrombotics within 48 hours | Unadjusted | 0.19 (0.08–0.47) | <0.001 | | |
| | Adjusted with NIHSS | 0.26 (0.10–0.67) | 0.005 | 1.10 (1.03–1.17) | 0.007 |
| Initial NIHSS score (per 1 point increment) | Unadjusted | 1.11 (1.05–1.19) | <0.001 | | |

OR, odds ratio; NIHSS, National Institute of Health Stroke Scale; CI, confidence interval.


https://doi.org/10.18700/jnc.220063

management in the ICU.

Several clinical parameters have been associated with in-hospital mortality in patients with ICU-treated AF-associated AIS. The $CHA_2DS_2$-VASc score is a well-established risk stratification tool for stroke and thromboembolism in AF [21]. $CHA_2DS_2$-VASc score has been reported as an independent value to predict long-term mortality in AF patients [22]. The current study suggests that the $CHA_2DS_2$-VASc score could be utilized for predicting the in-hospital mortality of ICU-treated AF-associated AIS patients, and a meticulous inspection of adverse events in patients with high scores might be needed to enhance in-hospital outcomes. Symptomatic steno-occlusive lesions showed a tendency to increase mortality risk without statistical significance in the current study. In the previous literature, symptomatic steno-occlusive lesions were associated with unfavorable functional outcomes in AIS patients [22]. In the era of EVT for AIS patients [23], treatment strategies for the failed recanalization cases might be developed in neurocritical care, which constituted 86% of the expired patients in the current study. Furthermore, although EVT was performed in the indicated patients, a treatment plan for obtained recanalization with a large infarct core is also needed, as AF is one of the risk factor for futile recanalization following EVT [24].

The lower risk of mortality in patients receiving acute antithrombotic treatment might be attributable to the preventive effect as well as selection bias. Acute antithrombotic therapy has been proven to reduce the risk of stroke recurrence and has been applied to AIS patients in current practice [25,26]. However, a discrepancy in stroke severity (median initial NIHSS score of 19 vs. 14 in patients who died and survived, respectively) infers a difference in neurologic and medical conditions between the two groups. Therefore, a cautious interpretation is needed for acute antithrombotic treatment in patients with ICU-treated AF-associated AIS. In the acute phase of AF-associated ischemic stroke, physicians often face a great dilemma in initiating anticoagulation and optimal timing of commencement due to the risk of hemorrhagic transformation [27]. As a larger infarction is a strong predictor of hemorrhagic transformation in AF-associated stroke [28], guidelines on starting anticoagulation therapy recognize a distinction in their recommendations according to stroke severity [29,30]. Ongoing trials on anticoagulation timing are expected to provide high-level of evidence with safety and efficacy profiles [31,32]. A thoughtful risk-benefit balance in initiating anticoagulation therapy based on individual clinical situations is required for severe AF-associated AIS patients.

This study has several strengths. To our knowledge, this is the largest prospective AF cohort study in Asia, consisting of 14 nationwide stroke centers. This cohort represents the current clinical status and real-life practice of AF stroke management in Korea. As we collected data from a nationwide multicenter prospective cohort, we also attempted to reduce bias in the enrollment of participants. This cohort had a high outcome capture rate (3-month capture rate, 99%), on which this study could provide relatively accurate outcome information.

However, this study has several limitations. First, as decisions of ICU admission vary according to the centers' policy in the indication, medical resources, and physicians' opinions, the variable effect of the center or physician might be present. Detailed information on the indication for ICU admission and the time from onset to ICU admission were not available. Second, some patients with irreversible neurological damage with very severe stroke or underlying incurable progressive diseases, including malignancy, could have rejected ICU care, but resulted in in-hospital mortality and might not have been included in this study. Third, specific echocardiographic findings, such as left atrium diameter or cardiac markers, including brain natriuretic peptide or cardiac enzymes, were not included in the analysis. Further studies involving specific cardiac markers are warranted in the future.

In conclusion, ICU care is common in patients with AF-associated ischemic stroke. Initial stroke severity and $CHA_2DS_2$-VASc score increased the risk of in-hospital mortality whereas antithrombotic treatment was associated with decreased risk. To improve patient outcomes in AF-associated AIS, establishing optimal treatment strategies with upcoming high-level evidence may be required.

## ARTICLE INFORMATION

### Ethics statement

The study was reviewed and approved by the Institutional Review Boards of the participating centers (No. B-1705/396-306). Written informed consent was obtained from all patients.

### Conflict of interest

No potential conflict of interest relevant to this article.

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**Additional contributions**

We would like to express our gratitude to the institutions that provided us with the opportunity to analyze the East Asian Ischemic Stroke Patients with Atrial Fibrillation Study (EAST-AF) and Clinical Research Collaboration for Stroke in Korea (CRCS-K) databases for this study.

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pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):96-103
https://doi.org/10.18700/jnc.220061

Journal of Neurocritical Care

# Prevalence and prediction of augmented renal clearance in the neurocritical care population

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ORIGINAL ARTICLE

Received: May 18, 2022
Revised: July 27, 2022
Accepted: August 8, 2022

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**Background:** Augmented renal clearance (ARC; creatinine clearance [CrCl] >130 mL/min/1.73 $m^2$) is prevalent in patients with neurological injuries and may influence their exposure to important pharmacological therapies. Little is known about the relationship between estimated and measured CrCl in this population.
**Methods:** This single-center, prospective, observational cohort study aimed to describe the association between ARC and estimated CrCl and neurological outcomes in a broad neurocritical care population. Prospective patient screening criteria included adults aged 18–85 years, with critical illness due to neurologic causes (such as ischemic stroke or subarachnoid hemorrhage) and lack of renal dysfunction on admission. Patients who had at least one urine CrCl measurement performed within the first 7 days of hospitalization were included. Two cohorts were evaluated: those with ARC and those without ARC.
**Results:** Fifty-seven patients were included, of whom 49 (86%) exhibited ARC. Subjects with ARC were more likely to be male and had a significantly higher median measured CrCl (201.7 mL/min/1.73 $m^2$) than those without ARC (109.8 mL/min/ 1.73 $m^2$). The Augmented Renal Clearance in Trauma Intensive Care (ARCTIC) score displayed the strongest association (vs. CrCl equations) with ARC development (area under the receiver operating characteristic curve, 0.648).
**Conclusion:** The prevalence of ARC in the present study of a broad neurocritical care population appeared to be high (86%). The ARCTIC score had higher sensitivity and specificity for diagnosing ARC than the common serum creatinine-based estimation.

**Keywords:** Stroke; Aneurysmal subarachnoid hemorrhage; Pharmacokinetics; Traumatic brain injury

## INTRODUCTION

Neurologically injured patients are at high risk of developing augmented renal clearance (ARC) due to hemodynamic alterations, aggressive fluid resuscitation, vasopressors usage, osmotherapy agents, and increased cardiac output from sympathetic nervous system responses to critical illness [1-5]. ARC is defined in critically ill patients as a measured creatinine clearance (CrCl) ≥130 mL/min/1.73 $m^2$ [6]. Previous studies have noted ARC in as many as 85%–100% of patients with severe neurological injury [2,3]. This is notable when dosing patients on renally-eliminated medications, particularly those with unavailable

routine serum concentration monitoring. Most medications have specific dosing recommendations for patients who exhibit reduced renal function, but recommendations for patients with so-called normal renal function (typically an estimated CrCl >60 mL/min/1.73 $m^2$) do not address patients with ARC. Patients admitted with neurological critical illness have extensive pharmacotherapy needs pertaining to the management of infection, intracranial pressure, seizures, hemodynamics, and thromboembolic events, of which the expected pharmacokinetic/pharmacodynamic relationship is impacted by ARC. Thus, the presence of ARC may be more than a curious observation but a factor that may influence the response to important therapies and could substantially impact the optimization of pharmacotherapy [7,8].

Despite previous studies demonstrating a significant prevalence of ARC in critically ill patients, its diagnosis remains challenging due to difficulties in directly measuring renal function. If a direct assessment of CrCl is not available, serum creatinine-based CrCl estimation equations can assist in the diagnosis; however, these equations have performed poorly in identifying ARC [9,10]. Simple, bedside diagnostic tools have been developed, including the Augmented Renal Clearance in Trauma Intensive Care (ARCTIC) score, which considers easily retrievable patient factors like age and serum creatinine; however, the ARCTIC score has not been extensively validated in the neurocritical care population [11].

This study aimed to describe the association between measured CrCl values and commonly used CrCl estimation equations in neurocritical care patients with ARC [11-17]. In addition, this study evaluated the association between ARC and neurological outcomes at discharge. The primary study hypothesis was that commonly used CrCl estimation equations lack the ability to accurately predict actual CrCl in neurocritical care patients with ARC.

## METHODS

This single-center, prospective, observational cohort study was conducted at an 865-bed tertiary academic medical center, which is also a Joint Commission accredited Comprehensive Stroke Center and level 1 trauma center. The center is a regional hub for the care of patients with complex neurological illnesses. Adult patients (aged 18–85 years) admitted to the neuroscience intensive care unit with a diagnosis of subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), acute ischemic stroke (AIS), and intracerebral hemorrhage (ICH), and had an indwelling urinary catheter in place at the time of screening were included. Study participants were excluded for incarceration, pregnancy, anticipated intensive care unit length of stay <72 hours, or serum creatinine >1.5 mg/dL at the time of screening. The study population included patients treated from May 2017 to April 2019. The management of SAH, TBI, AIS, and ICH was generally consistent with the published guidelines [18-21].

The study timeframe included the first 7 days of ICU stay for CrCl measurement and the time from admission to discharge for neurologic outcome. The unit protocol for 8-hour urine creatinine collection was performed to measure the CrCl level within the first few days of admission. Up to three 8-hour urine collections were performed during this 7-day period. The standard sampling procedure for an 8-hour urine creatinine collection included documentation of collection time, urine volume, and storage on ice throughout the duration of urine collection. The clinical laboratory measured urine volume and performed the urine and serum creatinine assays by colorimetric assay using the Jaffe method [22]. Pertinent clinical and demographic data were collected to describe study outcomes. The severity of illness measures varies based on the admission diagnosis. An etiology-specific severity measure was recorded for each patient: Hunt-Hess score (SAH), admission GCS score (TBI), National Institutes of Health (NIH) Stroke Scale (AIS), and ICH score [23-26]. While consecutive patients were screened for the need to measure urine CrCl, factors such as moribund state, long-standing or severe pre-existing disease that may affect renal function (such as diabetes mellitus), or other clinically relevant issues may have led investigators to forego CrCl measurement in specific patients. This resulted in the non-consecutive inclusion of patients in the overall cohort.

Cohorts for comparison were derived from patients with and without ARC, defined as at least one instance of a measured CrCl of ≥130 mL/min/1.73 $m^2$ by an 8-hour urine creatinine collection. The measured CrCl was calculated based on the urine creatine clearance equation standardized to the body surface area (Fig. 1). The primary study outcome was the predictive ability

**Urine creatinine clearance equation utilized for measured CrCl**

$$\text{CrCl} = \frac{\text{Urine creatinine} \times \text{urine volume} \times 1.73}{\text{SCr} \times 480 \times \text{BSA}}$$

**Cockcroft-Gault equation utilized for estimated CrCl**

$$\frac{(140 - \text{Age}) \times \text{weight} \times 1.73}{\text{SCr} \times 72 \times \text{BSA}} \quad (\times 0.85 \text{ if female})$$

**Fig. 1.** Creatinine clearance calculations. CrCl, creatinine clearance; SCr, serum creatinine (mg/dl); BSA, body surface area ($m^2$).

and diagnostic accuracy of the estimation equations compared with the measured CrCl [11-17]. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each diagnostic test (ARCTIC score and the various estimated CrCl) in the whole cohort and according to subgroup (SAH, TBI, AIS, ICH) were calculated. The secondary outcomes were the overall prevalence of ARC in the study population and the neurological outcome at discharge (measured using the discharge modified Rankin Scale [mRS]). The mRS was derived from comments regarding patient functional status from the physical therapist and the provided notes at discharge. Poor outcome was defined as an mRS score of 4–6 (moderate disability to death), whereas an mRS of 1–3 was considered a good outcome.

Continuous variables were tested for distribution using histogram visualization and the Shapiro-Wilk test. Continuous variables with a normal distribution are presented as mean (standard deviation), and non-normally distributed continuous variables are presented as median (interquartile range [IQR]). These were analyzed using the Student *t*-test or Wilcoxon rank-sum test, respectively. Categorical variables were presented as frequencies and proportions and analyzed using the Pearson's chi-square or Fisher's exact test, as appropriate. The diagnostic test performance for ARC, comparing the measured CrCl (gold standard) to the ARCTIC score and serum creatinine-based CrCl equations, was performed using 2 × 2 tables with calculations of sensitivity, specificity, PPV, and NPV, and visualization of receiver operating characteristic (ROC) curves. ROC curves were constructed using multiple CrCl equations, and the areas were compared using the DeLong test. Percent agreement between the measured CrCl and ARCTIC score was assessed with the Kappa statistic [27]. Missing data were omitted from specific calculations and noted when appropriate. All statistical tests were performed using Stata/IC 14.2 (StataCorp., College Station, TX, USA).

## RESULTS

A total of 57 patients were included, of which 49 of 57 (86%) exhibited ARC via measured CrCl on at least one study day. All patients had at least one 8-hour urine collection. The demographic data of the cohort are presented in Table 1. The mean age in those with ARC was 49.7 years (13.5) versus 56 years (13.74) in those without ARC, $P = 0.231$. Patients with ARC were more likely to be male (51% vs. 12.5%, $P = 0.043$). Overall, admission diagnoses included 63.2% SAH, 14% ICH, 14% TBI, and 8.8% AIS. No differences were identified in the primary neurological diagnoses between patients with and without ARC ($P = 0.981$) (Table 1). Between the two cohorts, however, with the number of patients in the study, the balance based on the severity of illness is difficult to assess. Overall, patients with SAH had a median Hunt and Hess score of 3 (IQR, 2–3), patients with ICH had a median ICH score of 2 (IQR, 2–3), and patients with TBI had a median admission Glasgow Coma Scale score of 7 (IQR, 5–10). Patients with AIS had a median NIH Stroke score of 15 (IQR, 13–18). These metrics suggest high severity of illness across the spectrum of diagnoses.

Patients with ARC had a significantly higher median measured CrCl of 201.7 mL/min/1.73 $m^2$ (IQR, 172.1–250.8) compared to those without ARC, 109.8 mL/min/1.73 $m^2$ (IQR, 100.6–123.3) ($P < 0.0001$). Overall, male patients exhibited a higher median measured CrCl compared to female patients, 213.5 mL/min/1.73 $m^2$ (IQR, 158–273) versus 175.6 mL/min/1.73 $m^2$ (IQR, 138.9–200.1), respectively ($P = 0.006$). The creatinine-based estimation equations routinely underestimated the measured CrCl (Tables 1 and 2). For example, the CrCl estimated by Cockcroft-Gault underestimated the measured CrCl in each of the four disease states (Fig. 2). The diagnostic performances of the creatinine-clearance-based equations are presented in Table 2. Overall, each equation was performed with a high sensitivity and PPV (> 80%) and a low specificity and NPV (< 25%), with the ARCTIC score displaying the strongest association with measured CrCl. Using the standard pre-defined cutoff of ARCTIC score ≥ 6, 79.6% (45/49) of patients in the ARC group were at high risk for ARC, and 50% (4/8) of the non-ARC group were at high risk for ARC ($P = 0.071$). The PPV and NPV for the ARCTIC score were 91% and 71%, respectively. The Kappa statistic for percent agreement between ARCTIC score and estimated CrCl was 0.31 (31% agreement), denoting a fair strength of agreement outside of chance between the two assessments. There was no difference among the areas under the ROC curve for all equations and the ARCTIC score ($P = 0.74$) (Fig. 3).

There was no difference in neurologic outcome, as determined by the discharge mRS score (Table 1). The median mRS in the ARC group was 4 (IQR, 4–5) compared with that in those without ARC 4 (IQR, 4–6) ($P = 0.428$). A poor outcome was observed in 47 of 49 (95.9%) subjects in the ARC group and 8 of 8 (100%) subjects in those without ARC ($P = 1.000$).

## DISCUSSION

The prevalence of ARC in our broad neurocritical care population was 86%, which is similar to previous reports in both general critical care populations and other specific neurocritical care cohorts, such as TBI, ICH, and SAH [2,3,5]. The severity of illness was high in the current study at baseline and the discharge mRS in this


https://doi.org/10.18700/jnc.220061

**Table 1.** Baseline characteristics

| Variable | ARC (n=49) | Non-ARC (n=8) | Total (n=57) | *P*-value |
|---|---|---|---|---|
| Age (yr) | 49.7±13.5 | 56±13.74 | 50.59±13.62 | 0.231 |
| Male | 25 (51.02) | 1 (12.5) | 26 (45.61) | 0.043 |
| Weight (kg) | 85.2 (76.0–113.6) | 81.6 (25.0–104.75) | 85.0 (75.6–112.5) | 0.291 |
| Height (cm) | 177.8 (162.5–182.8) | 158.7 (151.1–168.9) | 172.7 (160.0–182.8) | 0.012 |
| Diagnosis | | | | 0.981 |
| ICH | 7 (14.29) | 1 (12.5) | 8 (14.04) | |
| SAH | 31 (63.27) | 5 (62.5) | 36 (63.16) | |
| TBI | 7 (14.29) | 1 (12.5) | 8 (14.04) | |
| AIS | 4 (8.16) | 1 (12.5) | 5 (8.77) | |
| Severity score | | | | |
| ICH score (ICH only) | 2.16±0.75 (n=7) | 2 (n=1) | 2.14±0.69 (n=8) | - |
| Hunt and Hess score (SAH only) | 2.5 (2–3) (n=31) | 3 (3–3) (n=5) | 3 (2–3) (n=36) | 0.412 |
| GCS (TBI only) | 7 (5–9) (n=7) | 11 (n=1) | 7 (5–9.5) (n=8) | 0.122 |
| NIHSS (AIS only) | 15 (13–18) (n=4) | 18 (n=1) | 17 (14–23) (n=5) | - |
| Renal function | | | | |
| 24-Hour fluid balance (mL) | 4,180±4,012.3 | 5,239±3,934.1 | 4,328.74±3,983.9 | 0.491 |
| Serum creatinine (mg/dL) | 0.69±0.21 | 0.66±0.14 | 0.68±0.20 | 0.775 |
| Total collections | | | | 0.209 |
| 1 | 7 (87.50) | 42/57 (85.71) | 49 (85.86) | |
| 2 | 0 | 6/57 (12.24) | 6 (10.53) | |
| 3 | 1 (12.55) | 1/49 (2.04) | 2 (3.51) | |
| Measured CrCl | 201.7 (172.1–250.8) | 109.8 (100.6–123.3) | 187.8 (144.7–226.5) | <0.001 |
| ARTIC score | 6 (6–7) | 5.5 (3.5–7) | 6 (6–7) | 0.125 |
| ARTIC score ≥6 | 39 (79.59) | 4 (50.00) | 43 (75.44) | 0.071 |
| Outcome | | | | |
| mRS score | 4 (4–5) | 4 (4–6) | 4 (4–5) | 0.428 |
| mRS poor (4–6) | 47 (95.92) | 8 (100) | 55 (96.49) | 1.000 |

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
ARC, augmented renal clearance; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; AIS, acute ischemic stroke; GCS, Glasgow Coma Score; NIHSS, National Institutes of Health Stroke Score; AIS, acute ischemic stroke; CrCl, creatinine clearance; ARTIC, Augmented Renal Clearance in Trauma Intensive Care; mRS, modified Rankin Scale.

**Table 2.** Test diagnostics of various creatinine clearance equations

| Equation | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| ARCTIC score ≥6 | 80 | 50 | 91 | 71 |
| C-G | 80 | 25 | 87 | 17 |
| MDRD | 35 | 75 | 89 | 16 |
| Jelliffe | 24 | 75 | 92 | 16 |
| Hull | 84 | 25 | 87 | 20 |
| CKD-EPI | 12 | 100 | 100 | 16 |
| Davis | 53 | 63 | 90 | 18 |

PPV, positive predictive value; NPV, negative predictive value; ARCTIC, Augmented Renal Clearance in Trauma Intensive Care; C-G, Cockcroft-Gault; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

study was not different in patients with or without ARC. The high incidence of poor outcome is commensurate with the relatively high admission severity of illness for the current study population, as well as the screening criteria favoring patients with an anticipated prolonged ICU stay. Patients with neurological critical illness appear to be at a high risk for developing ARC early in the course of illness, as suggested by the high prevalence in the current study.

The gold standard for identifying ARC is the prospective collection of urine samples for creatinine analysis. Although feasible at most institutions, limitations exist, including inconvenience due to collection time, specimen processing and storage requirements, and reduced reliability in patients who do not have an in-dwelling catheter. Therefore, in most clinical settings, there is a reliance on serum creatinine-based CrCl equations to provide insights into a patient's renal function. However, these equations consistently fail to fully characterize glomerular filtration in patients with ARC, as illustrated in the current study and others [2,10]. For example, the current study demonstrated an overall sensitivity of 79.6% and specificity of only 25% for the Cockcroft-Gault equation to predict the presence of ARC (the Cockcroft-Gault equation is the equation used in nearly all package in-

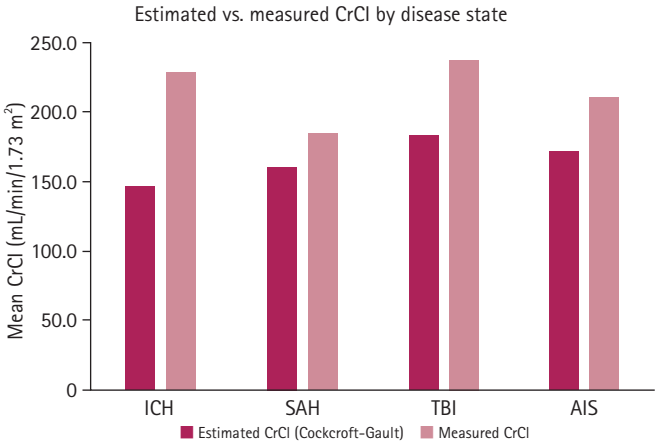


**Fig. 2.** Estimated versus measured creatinine clearance (CrCl) by disease state. Comparison of creatinine clearance values (estimated and measured) by disease state. This graph depicts the creatinine clearance values of all patients with or without augmented renal clearance. ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; AIS, acute ischemic stroke. *P*>0.05 for all comparisons between estimated and measured CrCl.

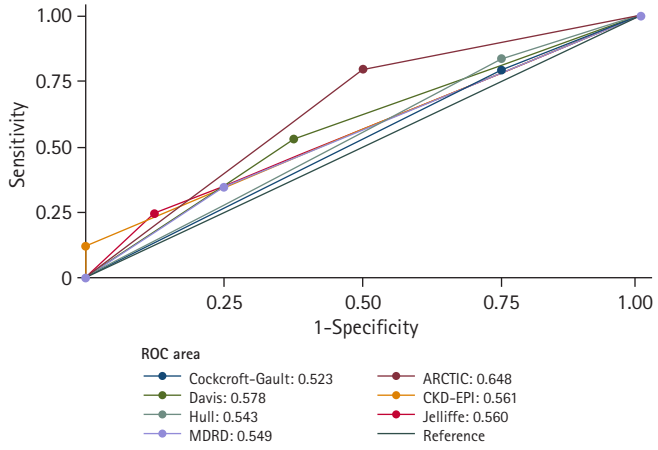


**Fig. 3.** Receiver operating characteristic (ROC) curves of various creatinine clearance equations (≥130 mL/min/m$^2$) and Augmented Renal Clearance in Trauma Intensive Care (ARCTIC) score (≥6) (*P*-value for comparison, 0.74). MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

sert dosing recommendations).

The ARCTIC score, validated to identify ARC in trauma patients, is a tool that uses readily available patient-specific data, which may be useful in the neurocritical care population [11]. The performance of ARCTIC in this neurocritical care population is comparable to the original findings by Barletta et al. [11], where the ARCTIC score demonstrated acceptable sensitivity (0.843), specificity (0.682), PPV (0.843), and NPV (0.682). In the current study, the ARCTIC score had a numerically higher area under the ROC than the Cockcroft-Gault, Modification of Diet in Renal Disease [MDRD], Jelliffe, Hull, CKD-EPI, and Davis-Chandler equations for predicting ARC occurrence; however, this difference was not statistically significant. The relative inaccuracy of the CrCl equations in the critical care population is a known limitation. The current analysis corroborates prior work that also assessed the discrepancies found in estimating CrCl using equations versus measuring the urine CrCl in ARC and high CrCl settings [10]. More research using the ARCTIC score is needed in a broader neurocritical care population to validate the usefulness of this predictor for the risk of ARC. A different approach that would likely require additional patients to be studied would be the development of an adjustment to the Cockcroft-Gault equation (or creation of a new equation) to estimate renal clearance more accurately in this population. A larger and more diverse dataset is necessary to accomplish this. Until a reliable approach is determined, however, institutions may opt to directly measure renal clearance via urine collection as the most accurate method in high-risk patients, despite the associated difficulties.

While ARC has been described consistently in the critical care population, it is not well known whether the severity of illness is a differentiating factor for exhibiting ARC or whether ARC influences outcomes. Many iatrogenic factors that contribute to the ARC, such as the need for fluid resuscitation, vasopressors, and osmotherapy agents, are more extensively used in patients with increasing severity of illness [28]. Therefore, it may be that the presence of ARC is a marker of the severity of illness and possibly a harbinger of poor outcomes. Hypermetabolic and catabolic states such as TBI, polytrauma, sepsis, and burns are all associated with ARC, perhaps as a physiological response to handling the solute load in a hypercatabolic state [29-33].

ARC may result in suboptimal exposure to many integral therapies used in neurocritical patents such as antiepileptic agents and antimicrobials (renally eliminated solutes) [8,34-36]. This may lead to complications such as breakthrough seizures and infection persistence or recurrence [8,34]. Evaluating outcomes in neurocritical care patients with more diversity in severity and etiology of illness may help to better define any relationship with ARC and outcome. Future studies should also evaluate outcomes specific to medication that might be affected by ARC (for example, renally eliminated medications such as levetiracetam, and the incidence of seizures.

As previously noted, the incidence of ARC in neurocritical care patients with TBI, SAH, and ICH has been considerably described in the literature [2,3,5]. However, ARC has not yet been reported in patients with AIS, which is notable in this study. The


https://doi.org/10.18700/jnc.220061

majority of patients with AIS in the current study had large middle cerebral artery strokes, with one patient presenting with venous sinus thrombosis and concomitant ICH. This represents a subset of ischemic stroke that may exhibit elevated intracranial pressure, a pronounced swelling period early after ictus, increased intensive care unit needs, and an increased risk of complications such as seizures. While aspects of critical care such as fluid resuscitation or use of vasopressors are usually not necessary after a large AIS, we hypothesize that the vigorous swelling pattern typical of middle cerebral artery stroke, the common use of permissive hypertension early in care, and the use of hypertonic solutions to prevent or treat hyponatremia and cerebral edema may have contributed to the presence of ARC in these patients. Although AIS patients comprise a small percentage of the total population, reporting this group's susceptibility to ARC is valuable. However, further research in this population is necessary to better describe the physiological and iatrogenic factors that may promote ARC after AIS.

One important limitation of this study is that the sample size was too small to compare the outcomes in patients with and without ARC. The small sample size also limits the use of more sophisticated statistical tests. Continued evaluation of ARC and clinical outcomes is needed to better define any association between the two variables. In addition, not all patients underwent multiple urine CrCl measurements. Future studies using serial collections of the same patient would provide more insight into the clinical progression of ARC throughout a patient's critical illness. Additionally, future studies that collect data on a wider breadth of neurological diagnoses, such as AIS or status epilepticus, would be valuable to expand these conclusions. The degree of illness in this study's patient population was also particularly severe; therefore, further studies with a broader range of severity would be worthwhile. Finally, further pharmacokinetic studies in patients with ARC could precisely describe how the aforementioned renally cleared medications are affected throughout the course of a patient's critical illness. Underexposure to vital therapies, such as agents for seizure prevention or treatment (for example, levetiracetam), or antimicrobials for hospital-acquired infections (for example, beta-lactams) can adversely affect patient responses [34-36].

In the present study, the prevalence of ARC in a broad neurocritical care population appeared to be high, at 86%. The ARC-TIC score had improved sensitivity and specificity for diagnosing ARC when compared to common serum creatinine-based estimation equations, but did not exhibit a strong performance in predicting measured CrCl. If feasible, prospective urine collection and creatinine measurements remain accurate in directly detecting the presence of ARC. In this study, ARC was not associated with inferior outcomes compared with those who did not have ARC. Given the high likelihood of ARC in the neurocritical care population and the potential that it may affect common pharmacotherapy options, clinicians should consider prospective monitoring of ARC in at-risk patients.

## ARTICLE INFORMATION

### Ethics statement

The study protocol was approved by the local Institutional Review Board of University of Kentucky (No. 45285) with a waiver of written informed consent because of the observational study design and minimal risk to the participants.

### Conflict of interest

No potential conflict of interest relevant to this article.

### Acknowledgments

REDCap was supported by an institutional NIH CTSA grant (UL1TR000117).

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https://doi.org/10.18700/jnc.220061

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pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):104-112
https://doi.org/10.18700/jnc.220054

Journal of Neurocritical Care

# Failed recanalization mediates the association of women with poor outcomes after thrombectomy: a single-center experience

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ORIGINAL ARTICLE

Received: April 19, 2022
Revised: June 6, 2022
Accepted: June 30, 2022

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**Background:** Whether thrombectomy benefits differ according to sex remains debatable. We aimed to investigate whether there was a difference in stroke outcomes between men and women treated with thrombectomy.
**Methods:** We studied 173 patients with anterior circulation strokes. Failed recanalization was defined as thrombolysis in cerebral infarction grade 0-2a. Scores >2 on the modified Rankin Scale at 3 months were regarded as poor outcomes. To prove that failed recanalization mediated the association between sex differences and functional outcome, the four steps of the reasoning process adapted from Baron and Kenny's causal-steps approach were tested. The adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were calculated.
**Results:** This study included 76 women and 97 men. Women were older and presented with atrial fibrillation more frequently than men. Female sex was independently associated with failed recanalization (aOR, 2.729; 95% CI, 1.334–5.582), which was an independent predictor of poor outcomes (aOR, 4.630; 95% CI, 1.882–11.389). Women were associated with poor outcomes in the analysis adjusted for confounders, except for failed recanalization (aOR, 2.285; 95% CI, 1.064–4.906). However, the association became insignificant in the additional analysis adjusted for failed recanalization (aOR, 1.670; 95% CI, 0.738–3.784). The indirect effect between female sex and poor outcomes via failed recanalization was statistically significant (aOR, 1.038; 95% CI, 1.010–1.127).
**Conclusion:** Our study showed that failed recanalization mediated the association between women and poor outcomes after thrombectomy. Nonetheless, this might be explained by chance given our limited study population.

**Keywords:** Sex; Stroke; Outcome; Thrombectomy

## INTRODUCTION

Mechanical thrombectomy has recently been established as an essential treatment modality for emergent large vessel occlusion within 8–24 hours of symptom onset, as multiple randomized clinical trials (RCTs) have demonstrated its dramatic efficacy in the improvement of patient outcomes [1-5]. Using the data from the RCTs, some studies reported that the benefit of thrombectomy was equal in both sexes [6,7], while other studies showed differences in the outcomes between men and women treated with

thrombectomy [8,9]. On the other hand, several studies using nonclinical trial data investigated whether the benefit of thrombectomy differed by sex. However, the results are conflicting among such studies [10-12], and thus this topic is still debatable. In addition, real-world nonclinical trial data to date are insufficient in the literature. Thus, in this study, using single-center nonclinical trial data, we aimed to investigate whether there is a significant difference in clinical outcomes between men and women treated with thrombectomy.

## METHODS

### Patient recruitment

We retrospectively reviewed the medical records of 216 patients who were prospectively enrolled in the patient registry for endovascular thrombectomy at Soonchunhyang University Bucheon Hospital from January 2012 to November 2020. Among them, we excluded 20 patients with posterior circulation stroke, 16 patients without collateral score data (no computed tomography [CT] angiography performed), four patients without outcome data, and three patients who proved to have cancer-related strokes. Finally, 173 patients with anterior circulation stroke were included in this study.

### Patient treatment process

For all the included patients, non-contrast-enhanced CT and CT angiography were performed before treatment. Using a 128-detector high-definition CT scanner (Discovery CT750 HD; GE Healthcare, Milwaukee, WI, USA), CT angiography images were obtained from the aortic arch to the vertex in series (section thickness, 0.625 mm; tube voltage, 100 kV; tube current, 200 mA) after a single bolus injection of 100 mL nonionic contrast agent into the antecubital vein. Candidates for intravenous thrombolysis (IVT) and thrombectomy were selected in accordance with previously published guidelines [13,14]. Notably, from November 2019, patients with stroke within 6 to 24 hours of the last known normal were also considered to be treated by thrombectomy if a mismatch between the infarct core and penumbra—the presence of a significant salvageable tissue—was confirmed on CT perfusion images [4,5].

Catheter angiography for thrombectomy was performed via the femoral artery under local anesthesia. If necessary, conscious sedation was used at the discretion of the treating interventionists. An 8-Fr flow-gate balloon guide catheter was placed in the proximal internal carotid artery to approach the target artery. Thrombectomy was performed using a stent retriever (Solitaire, Medtronic, Dublin, Ireland or Trevo, Stryker, Kalamazoo, MI, USA) or an aspiration device (Penumbra system; Penumbra Inc., Alameda, CA, USA). Non-contrast-enhanced CT and magnetic resonance diffusion-weighted imaging (DWI) were performed immediately and 24 hours after the procedure, respectively. Additional CT or DWI was performed on the basis of the decision of the treating physician.

### Clinical data and imaging analysis

The following clinical information was obtained: age, sex, hypertension, diabetes mellitus, hyperlipidemia, history of prior stroke, ischemic heart disease, atrial fibrillation, current smoking habits, premorbid independence (pre-stroke modified Rankin Scale [mRS] ≤2), history of antithrombotic and statin medication use, initial blood pressure, blood glucose level, National Institutes of Health Stroke Scale (NIHSS) score, time interval from stroke onset to arrival at the emergency department and from arrival to groin puncture, thrombectomy procedure time, location of symptomatic occlusion, clot burden score [15], use of IVT, and stroke classification [16].

The Alberta Stroke Program Early CT score (ASPECTS) was rated based on pretreatment CT angiography source images (CTA-SI). All images were adjusted to have maximum contrast between the normal and abnormal sides. Diminished contrast enhancement in each region of ASPECTS compared with the healthy hemisphere was considered abnormal [17]. In addition, collateral status was dichotomized as poor (≤50% filling of the occluded territory) or good (>50% filling) status [18]. The final recanalization state was assessed using catheter angiography based on the thrombolysis in cerebral infarction (TICI) perfusion scale after the thrombectomy procedure was finished [19]. Failed recanalization was defined as a TICI grade of 0-2a. Hemorrhagic transformation and infarct size were determined on the basis of follow-up gradient-echo images and DWIs. Symptomatic intracranial hemorrhage [20], hemorrhagic infarct, and parenchymal hemorrhage [21] were defined according to the previously published criteria. All images were analyzed independently by two investigators (SJL and TKL) blinded to the clinical data. The final decision was made by consensus. The 3-month mRS score was documented in the follow-up clinic note by a neurologist or neurosurgeon. Scores of ≤2 (>2) on the mRS at 3 months were regarded as good (poor) functional outcomes.

### Statistical analysis

Statistical analyses were performed using IBM SPSS version 21.0 (IBM Corp., Armonk, NY, USA) and R software, version 4.0.5 (The R Foundation for Statistical Computing, Vienna, Austria). Univariate group comparisons were performed using the inde-

pendent two-sample *t*-test (or Mann-Whitney *U*-test for non-normally distributed continuous variables) and the chi-square test (or Fisher's exact test). The assumptions of normality and equivalent variance were assessed using the Shapiro-Wilk test and Levene's test, respectively. Age and variables with $P < 0.1$ in the univariate comparison were included in the multivariable logistic regression analysis for failed recanalization and poor functional outcomes. Procedural time was excluded from the multivariable logistic analysis for functional outcomes because it was associated with failed recanalization ($P = 0.006$ by independent *t*-test). To prove that failed recanalization mediated the association between sex differences and functional outcome, we tested the four steps of the reasoning process adapted from Baron and Kenny's causal-steps approach [22,23]. Specifically, using adjusted logistic regression, we attempted to prove the following steps: (1) the significant association of women (predictor) with failed recanalization (dependent variable), (2) the significant association of failed recanalization (predictor) with poor outcomes (dependent variable), (3) the significant association of women (predictor) with poor outcomes (dependent variable) (total effect), and (4) the insignificant association of women (predictor) with poor outcomes (dependent variable) when additionally adjusted for failed recanalization (direct effect).

Then, using 5,000 bootstrap samples, the significance of the indirect effect was assessed as recommended for small sample sizes [24]. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were obtained. All statistical tests were two-tailed, and *P*-values $< 0.05$ were considered statistically significant.

## RESULTS

Among 173 patients, 76 were women and 97 were men. Compared to men, women were older and tended to have less premorbid independence and more frequent antiplatelet medication use. Women more frequently presented with atrial fibrillation and were more likely to have a cardioembolic or undetermined stroke than men. Men were more likely to be current smokers and tended to have higher pretreatment CTA-SI ASPECTS scores than women (Table 1). Women differed from men in terms of some clinical outcomes. In women, failed recanalization was more common, and there was a statistical trend toward a larger final infarct size. Above all, women were more likely to have poor outcomes (mRS $\geq 3$) than men, although there was no significant difference in intracranial hemorrhage between sexes (Table 2).

Women were associated with poor functional outcomes in the univariate analysis (Table 3). However, when age and all variables with $P < 0.1$ in the univariate comparison were included in the multivariable logistic regression analysis, sex was no longer associated with functional outcome (result C' in Fig. 1). Mediation analysis using Baron and Kenny's causal steps approach was performed to test if failed recanalization mediated the association between sex and functional outcome. All analyses were adjusted for age and variables with $P < 0.1$ in the univariate analysis for each dependent variable. Therefore, in the analysis wherein poor outcomes were the dependent variable, age, premorbid independence, previous anticoagulant use, NIHSS score at admission, M2 occlusion (vs. internal carotid artery or M1 occlusion), CTA-SI ASPECTS, and poor collateral status were adjusted (Table 3). In addition, in the analysis wherein failed recanalization was the dependent variable, age, systolic blood pressure at admission, NIHSS score at admission, CTA-SI ASPECTS, and poor collateral status were adjusted (Supplementary Table 1). These four steps are listed in Fig. 1. (1) The effect of female sex on failed recanalization was significant (A). (2) The effect of failed recanalization on poor functional outcomes adjusted for female sex was significant (B). (3) The total effect of female sex on poor outcomes was significant (C). (4) The direct effect of female sex on poor outcomes adjusted for failed recanalization was non-significant (C'). Moreover, the indirect effect between female sex and poor outcomes via failed recanalization was statistically significant ($A \times B$).

## DISCUSSION

### Failed recanalization as a mediator of poor outcomes in women

Similar to previous studies [7,11], women were older and presented with atrial fibrillation more frequently than men. Notably, women were more likely than men to have poor functional outcomes at 3 months. The association remained significant even after adjusting for several confounders, but became statistically insignificant when the recanalization outcome was additionally adjusted. However, it is incorrect to conclude that there was no association between sex and functional outcomes in our study. Instead, as proven by the mediation analysis, it is reasonable to conclude that women were associated with failed recanalization, which mediated the association between sex and poor outcomes.

### Sex differences in thrombectomy outcomes: a short literature review

There are many reports in the literature regarding sex differences in thrombectomy outcomes. However, the results of these studies have been conflicting. Several results were obtained from clinical trials that tested thrombectomy. An analysis of 500 patients from an RCT of thrombectomy in the Netherlands (Multicenter Ran-


https://doi.org/10.18700/jnc.220054

**Table 1.** Comparison of basic characteristics between women and men

| Variable | Women (n=76) | Men (n=97) | *P*-value |
|---|---|---|---|
| Age (yr) | 72.0±13.3 | 65.1±12.3 | 0.001[a] |
| Hypertension | 50 (65.8) | 64 (66.0) | 0.979[b] |
| Diabetes | 17 (22.4) | 31 (32.0) | 0.162[b] |
| Hyperlipidemia | 24 (31.6) | 32 (33.0) | 0.844[b] |
| Prior stroke | 16 (21.1) | 19 (19.6) | 0.812[b] |
| Ischemic heart disease | 12 (15.8) | 14 (14.4) | 0.804[b] |
| Atrial fibrillation | 50 (65.8) | 46 (47.4) | 0.016[b] |
| Current smoking | 1 (1.3) | 27 (27.8) | <0.001[c] |
| Premorbid independence (pre-stroke mRS ≤2) | 71 (93.4) | 96 (99.0) | 0.088[c] |
| Previous medication | | | |
| Antiplatelet | 25 (32.9) | 20 (20.6) | 0.068[b] |
| Anticoagulant | 12 (15.8) | 11 (11.3) | 0.392[b] |
| Statin | 18 (23.7) | 14 (14.4) | 0.120[b] |
| Initial systolic BP (mmHg) | 145.4±25.1 | 148.4±27.4 | 0.459[a] |
| Initial diastolic BP (mmHg) | 84.4±15.0 | 87.4±17.1 | 0.239[a] |
| Initial blood glucose (mg/dL) | 147.3±48.8 | 159.3±66.6 | 0.194[a] |
| Initial NIHSS | 16 (12–19) | 16 (10–19) | 0.378[d] |
| Onset to ER time (min) | 84 (37–173) | 71 (36–188) | 0.685[d] |
| ER to groin time (min) | 146 (120–182) | 144 (117–189) | 0.999[d] |
| Procedure time (min) | 53.4±33.6 | 60.6±38.9 | 0.208[a] |
| Left-side infarct | 39 (51.3) | 52 (53.6) | 0.764[b] |
| Location of symptomatic occlusion | | | 0.274[b] |
| Internal carotid artery | 25 (32.9) | 43 (44.3) | |
| M1 | 39 (51.3) | 39 (40.2) | |
| M2 | 12 (15.8) | 15 (15.5) | |
| CTA-SI ASPECTS | 5 (3–8) | 7 (3–9) | 0.063[d] |
| Clot burden score on CTA | 6 (4–7) | 6 (4–8) | 0.963[d] |
| Use of IVT | 36 (47.4) | 48 (49.5) | 0.782[b] |
| Stroke classification | | | 0.005[b] |
| Large artery atherosclerosis | 15 (19.7) | 40 (41.2) | |
| Cardioembolism | 46 (60.5) | 48 (49.5) | |
| Undetermined | 15 (19.7) | 9 (9.3) | |
| Large artery atherosclerosis (vs. others) | 15 (19.7) | 40 (41.2) | 0.003[b] |
| Poor collaterals | 32 (42.1) | 37 (38.1) | 0.597[b] |

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
mRS, modified Rankin Scale; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; ER, emergency room; CTA-SI ASPECTS, CT (computed tomography) angiography source image Alberta Stroke Program Early CT Score; IVT, intravenous thrombolysis.
Variables were analyzed using [a]Independent *t*-test, [b]Chi-square test, [c]Fisher exact test, or [d]Mann-Whitney *U*-test.

domized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands) showed a significant interaction between sex and thrombectomy treatment ($P=0.016$) with higher mortality in women than in men [8]. Secondary analysis of 182 patients from the multicenter randomized controlled trial of endovascular therapy following imaging evaluation for ischemic stroke (DEFUSE 3) trial data also demonstrated a statistical trend for a lower 90-day functional independence in women than in men within the thrombectomy arm (35% vs. 54%, $P=0.059$) [9]. However, no difference in outcome between sexes was reported in the analyses based on a larger number of clinical trial patients. The pooled analyses of 1,762 patients from seven RCTs within the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration reported no difference in functional independence (mRS 0-2) at 90 days between men and women (48% vs. 48%) treated with thrombectomy [6]. An analysis of 389 patients from the three clinical trials (SWIFT, STAR, and SWIFT PRIME) also showed a similar rate of func-

**Table 2.** Comparison of outcomes between women and men

| Variable | Women (n=76) | Men (n=97) | *P*-value[a] |
|---|---|---|---|
| Failed recanalization | 34 (44.7) | 25 (25.8) | 0.009 |
| Final infarct size | | | 0.230 |
| <1/3 MCA territory | 30 (39.5) | 51 (52.6) | |
| 1/3–2/3 MCA territory | 22 (28.9) | 22 (22.7) | |
| >2/3 MCA territory | 24 (31.6) | 24 (24.7) | |
| <1/3 MCA territory (vs. others) | 30 (39.5) | 51 (52.6) | 0.086 |
| Any intracranial hemorrhage | 44 (57.9) | 63 (64.9) | 0.343 |
| HT1 | 12 (16.0) | 16 (16.5) | |
| HT2 | 6 (8.0) | 12 (12.4) | |
| PH1 | 3 (4.0) | 12 (12.4) | |
| PH2 | 23 (30.7) | 23 (23.7) | |
| sICH | 13 (17.1) | 13 (13.4) | 0.499 |
| Poor outcome (mRS ≥3) | 54 (71.1) | 50 (51.5) | 0.009 |
| mRS 0 | 7 (9.2) | 13 (13.4) | |
| mRS 1 | 9 (11.8) | 13 (13.4) | |
| mRS 2 | 6 (7.9) | 21 (21.6) | |
| mRS 3 | 11 (14.5) | 14 (14.4) | |
| mRS 4 | 11 (14.5) | 11 (11.3) | |
| mRS 5 | 16 (21.1) | 9 (9.3) | |
| mRS 6 | 16 (21.1) | 16 (16.5) | |

Values are presented as number (%).
MCA, middle cerebral artery; HT, hemorrhagic transformation; PH, parenchymal hemorrhage; sICH, symptomatic intracranial hemorrhage; mRS, modified Rankin Scale.
[a]Variables were analyzed using chi-square test.

tional independence at 90 days between sexes (aOR, 1.01; 95% CI, 0.64–1.59) despite older ages and a higher rate of atrial fibrillation for women [7]. Uniquely, a recent study of 198 patients from a multi-center prospective cohort study data (CRISP) reported a favorable shift in the mRS score (aOR, 1.79; 95% CI, 1.04–3.08) with better collaterals and less ischemic core growth (median, 15 mL vs. 29 mL; $P < 0.01$) in women [25].

Meanwhile, most studies based on nonclinical trial data have suggested worse thrombectomy outcomes in women than in men, which is similar to our study. A study of 2,420 patients with large vessel occlusion from a Japanese multi-center registry showed a tendency for poor outcomes among women in both groups who underwent thrombectomy (aOR, 0.83; 95% CI, 0.63–1.09) and who did not undergo thrombectomy (aOR, 0.73; 95% CI, 0.52–1.04) [26]. A single-center study of 279 patients reported lower 90-day functional independence in women (aOR, 0.37; 95% CI, 0.16–0.87) even after adjustment for confounders [12]. Similarly, a study of 2,316 patients from the German registry revealed higher mortality (30.7% vs. 26.4%) with less functional independence (33.2% vs. 40.6%) at 90 days in women. However, this association disappeared after adjusting for confounders [11]. Apart from the above studies, a single-center study of 145 patients reported no significant difference in 3-month functional independence between men and women (60.9% vs. 66.7%) [10].

### Possible reasons for more failure of recanalization in women

To sum up the aforementioned studies, there appears to be a trend toward poor functional outcomes in women after thrombectomy under certain circumstances. However, most of the studies described no sex difference in recanalization outcome during thrombectomy [6-11,25]. In this regard, their results are different from ours, indicating poorer outcomes in women mediated by failed recanalization. In fact, only a few reports to date have shown a more frequent failure of recanalization in women during thrombectomy [27,28]. The exact reason for the higher rate of failed recanalization among women in our study is presently unknown. Instead, there is only a speculative presumption. That is to say, sex disparities in arterial diameter might be responsible for the sex difference in recanalization outcome [27,29]. Reportedly, the mean diameters of the terminal internal carotid artery and M1 were smaller in women than in men [29,30]. As the flow rate is proportional to the vessel radius to the fourth power according to the Hagen-Poiseuille equation, the diameter


https://doi.org/10.18700/jnc.220054

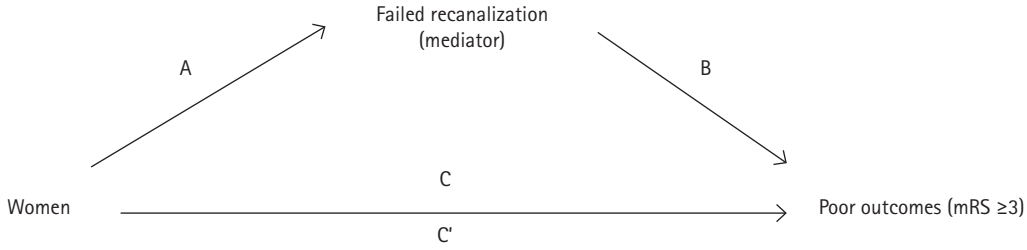
**Table 3.** Comparison between patients with good and poor outcomes

| Variable | Good outcome (n=69) | Poor outcome (n=104) | *P*-value |
|---|---|---|---|
| Age (yr) | 67.3±13.0 | 68.7±13.3 | 0.488[a] |
| Women | 22 (31.9) | 54 (51.9) | 0.009[b] |
| Hypertension | 44 (63.8) | 70 (67.3) | 0.631[b] |
| Diabetes | 15 (21.7) | 33 (31.7) | 0.151[b] |
| Hyperlipidemia | 22 (31.9) | 34 (32.7) | 0.911[b] |
| Prior stroke | 11 (15.9) | 24 (23.1) | 0.253[b] |
| Ischemic heart disease | 9 (13.0) | 17 (16.3) | 0.552[b] |
| Atrial fibrillation | 36 (52.2) | 60 (57.7) | 0.475[b] |
| Current smoking | 8 (11.6) | 20 (19.2) | 0.182[b] |
| Premorbid independence (pre-stroke mRS ≤2) | 69 (100.0) | 98 (94.2) | 0.082[c] |
| Previous medication | | | |
| Antiplatelet | 16 (23.2) | 29 (27.9) | 0.491[b] |
| Anticoagulant | 5 (7.2) | 18 (17.3) | 0.068[b] |
| Statin | 13 (18.8) | 19 (18.3) | 0.924[b] |
| Initial systolic BP (mmHg) | 145.7±28.7 | 147.9±24.9 | 0.588[a] |
| Initial diastolic BP (mmHg) | 84.2±15.9 | 87.4±16.4 | 0.209[a] |
| Initial blood glucose (mg/dL) | 148.6±61.6 | 157.5±57.9 | 0.337[a] |
| Initial NIHSS | 13 (8–17) | 17 (13–21) | <0.001[d] |
| Onset to ER time (min) | 69 (31–150) | 84 (39–200) | 0.603[d] |
| ER to groin time (min) | 131 (108–178) | 142 (123–191) | 0.144[d] |
| Onset to groin time (min) | 212 (172–317) | 260 (185–380) | 0.115[d] |
| Procedure time (min) | 47.6±33.8 | 64.1±37.3 | 0.004[a] |
| Location of symptomatic occlusion | | | 0.043[b] |
| Internal carotid artery | 28 (40.6) | 40 (38.5) | |
| M1 | 25 (36.2) | 53 (51.0) | |
| M2 | 16 (23.2) | 11 (10.6) | |
| M2 vs. others | 16 (23.2) | 11 (10.6) | 0.025[b] |
| CTA-SI ASPECTS | 8 (6–9) | 4.5 (2–7) | <0.001[d] |
| Clot burden score on CTA | 6 (4–8) | 6 (4–7) | 0.103[d] |
| Poor collaterals | 13 (18.8) | 56 (53.8) | <0.001[b] |
| Use of IVT | 38 (55.1) | 46 (44.2) | 0.162[b] |
| Stroke classification | | | 0.679[b] |
| Large artery atherosclerosis | 21 (30.4) | 34 (32.7) | |
| Cardioembolism | 40 (58.0) | 54 (51.9) | |
| Undetermined | 8 (11.6) | 16 (15.4) | |
| Failed recanalization | 9 (13.0) | 50 (48.1) | <0.001[b] |

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
mRS, modified Rankin Scale; BP, blood pressure; NIHSS, National Institutes of Health Stroke Scale; ER, emergency room; CTA-SI ASPECTS, CT (computed tomography) angiography source image Alberta Stroke Program Early CT Score; IVT, intravenous thrombolysis.
Variables were analyzed using [a]Independent *t*-test, [b]Chi-square test, [c]Fisher exact test, or [d]Mann-Whitney *U*-test.

of the treated large arteries or collateral vessels could be a crucial factor determining the blood flow directed to the ischemic area. In women, a smaller arterial diameter can be a disadvantageous factor for reperfusion and functional outcomes in patients undergoing thrombectomy [29]. Similarly, the relationship between vessel diameter and procedural outcomes was reported in a study of 254 patients undergoing endovascular treatment for iliac artery diseases. The investigators showed that the target vessel diameter measured using CT angiography was an independent predictor of procedural failure or vessel-specific complications [31].

On the other hand, sex-specific differences in intravascular coagulation and fibrinolysis could be responsible for the more frequent failure of recanalization in women. A study of South Asian




| | Adjusted odds ratio | 95% Confidence interval | *P*-value |
|---|---|---|---|
| A[a)] | 2.729 | 1.334–5.582 | 0.006 |
| B[b)] | 4.630 | 1.882–11.389 | 0.001 |
| C[b)] | 2.285 | 1.064–4.906 | 0.034 |
| C'[b)] | 1.670 | 0.738–3.784 | 0.219 |
| A×B[b)] | 1.038 | 1.010–1.127 | |

**Fig. 1.** Mediation analysis: failed recanalization as a mediator for the association of women with poor outcomes. mRS, modified Rankin Scale; A, the effect of women on failed recanalization; B, the effect of failed recanalization on poor outcomes additionally adjusted for women; C, total effect of women on poor outcomes; C', direct effect of women on poor outcomes additionally adjusted for failed recanalization; A×B, indirect effect between women and poor functional outcomes via failed recanalization. All analyses were adjusted for age and variables with $P<0.1$ in the univariate analysis for each dependent variable. [a)]Adjusted for age, systolic blood pressure at admission, National Institutes of Health Stroke Scale score at admission, CT (computed tomography) angiography source image Alberta Stroke Program Early CT Score (CTA-SI ASPECTS), and poor collaterals; [b)]Adjusted for age, premorbid independence, previous anticoagulant use, National Institutes of Health Stroke Scale score at admission, M2 occlusion (vs. internal carotid artery or M1 occlusion), CTA-SI ASPECTS, and poor collaterals.

stroke patients reported higher plasminogen activator inhibitor-I and factor VII levels in women [32], which suggests a decreased fibrinolytic potential and increased coagulation tendency leading to a reduced potential of reperfusion in women during thrombectomy.

### Limitations and strengths

Our study had several limitations. Above all, this was a single-center retrospective study with a small sample size, thus potentially producing a selection bias. Therefore, our results might be explained by chance and could not be generalized to other stroke populations. In addition, we could not analyze several factors affecting clinical outcomes, such as psycho-cognitive morbidities and social factors. For example, we had no information about the cohabitation of family members, although less family support may be associated with the time taken to arrive at the hospital and post-stroke functional recovery [33]. Generally, women are more likely than men to be widowed and living alone. Therefore, such uncorrected factors could intensify the deviation toward a poorer functional outcome in women [34]. Presumably, the lower proportion of women than men included in our study suggests their later arrival beyond the time window for thrombectomy due to the absence of cohabitants. This is similar to why IVT is less frequently used in women than in men [34-36]. In addition, we had no data on arterial diameter (as discussed), thrombus composition, and vascular access problems that could affect recanalization outcomes [37].

In contrast, our study has strengths in that it adds to real-world data on sex differences in stroke outcomes after thrombectomy. Clinical trial conditions are different from those of real-world clinical practice [38]. Clinical trials are designed to include patients who are most likely to benefit from the tested treatment and to exclude those who are likely to be complicated by the treatment. However, in real-world clinical practice, many emergent large-vessel occlusion patients with adverse conditions, such as low ASPECTS scores, pre-stroke disability, and multiple comorbidities, are treated with thrombectomy because there is no better option [38].

### Conclusions

In our stroke patients treated with thrombectomy, female sex was associated with failed recanalization, which mediated the association of female sex with poor functional outcomes. However, this might be explained by chance given our limited study population.

## ARTICLE INFORMATION

### Ethics statement

This study was approved with a waiver of informed consent by


https://doi.org/10.18700/jnc.220054

the Institutional Review Board of Soonchunhyang University Bucheon Hospital (No. SCHBC 2021-04-018).

**Conflict of interest**

No potential conflict of interest relevant to this article.

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Conceptualization: SJL. Data curation: SJL, TKL. Formal analysis: SJL, JEM. Investigation: SJL, TKL. Supervision: SJL. Visualization: SJL. Writing–original draft: SJL, JEM. Writing–review & editing: all authors.

**Supplementary materials**

Supplementary materials can be found via https://doi.org/10.18700/jnc.220054.

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https://doi.org/10.18700/jnc.220054

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):113-121
https://doi.org/10.18700/jnc.220068

Journal of Neurocritical Care

# Association of chloride-rich fluids and medication diluents on the incidence of hyperchloremia and clinical consequences in aneurysmal subarachnoid hemorrhage

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ORIGINAL ARTICLE

Received: July 25, 2022
Revised: September 29, 2022
Accepted: October 8, 2022

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**Background:** Chloride-rich fluid administration is frequently employed in the management of aneurysmal subarachnoid hemorrhage (aSAH). However, the incidence and consequences of hyperchloremia in aSAH remain poorly defined. This study aimed to describe the incidence of hyperchloremia in aSAH, the contribution of fluid sources to chloride exposure, and the potential associations of hyperchloremia with patient outcomes.
**Methods:** This was a single-center retrospective cohort study of patients admitted to a neurointensive care unit with aSAH. The primary outcome was incidence of hyperchloremia (chloride >109 mEq/L). Secondary outcomes included incidence of severe hyperchloremia (chloride >115 mEq/L), incidence of acute kidney injury (AKI), need for renal replacement therapy (RRT), intensive care unit (ICU) length of stay (LOS), hospital LOS, and in-hospital mortality.
**Results:** Of the 234 patients included in the analysis, hyperchloremia occurred in 75% (n=175), and 58% (n=101) developed severe hyperchloremia. Median time to onset was 3 days (interquartile range, 1–5) after admission. Hyperchloremia was associated with prolonged ICU LOS (12 vs. 8 days, $P$<0.001), duration of mechanical ventilation (16 vs. 10 days, $P$<0.001), hospital LOS (15 vs. 9 days, $P$<0.001), and in-hospital mortality (14.3% vs. 0%, $P$=0.002) compared to no hyperchloremia. No significant difference was observed in the incidence of AKI or the need for RRT. Maintenance intravenous fluids accounted for the highest proportion of the cumulative chloride burden.
**Conclusion:** Hyperchloremia occurs at a high frequency in aSAH and is associated with poor patient outcomes. Maintenance intravenous fluids accounted for the highest proportion of cumulative chloride burden.

**Keywords:** Critical care; Chloride; Fluid therapy

## INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a neurosurgical emergency with an estimated mortality rate of 20% [1]. Among survivors, nearly 45% suffer from long-term disabling side effects [2]. The neurologic consequences associated with aSAH including delayed cerebral ischemia (DCI), cerebral vasospasm, and cerebral edema portend a poor prognosis and carry a high degree of

morbidity and mortality. Aside from the direct neurologic sequelae, patients with aSAH are at a higher risk of developing secondary non-neurologic complications including cardiac dysfunction, infection, hepatic and renal failure, which negatively impact patient outcomes [3]. Despite the contemporary shift away from hypervolemia, as historically targeted in so-called Triple-H therapy, fluid administration to maintain euvolemia remains a cornerstone in the management of aSAH to mitigate the effects of DCI, prevent secondary brain injury, and optimize organ perfusion [4-6].

Furthermore, the selection of optimal fluid type in aSAH treatment remains ill-defined and lacks standardization. It is well understood that hypertonic or isotonic chloride-rich fluids such as hypertonic saline or normal saline are most commonly employed due to the perceived risk of cerebral swelling with hypotonic fluids [4]. However, hyperchloremia secondary to chloride-rich fluid administration has been linked with adverse consequences, including acute kidney injury (AKI), acid-base disturbances, and a prolonged need for mechanical ventilation in critically ill patients [7]. Moreover, in animal models, hyperchloremia has been shown to result in immunosuppression, increased presence of inflammatory markers, and a subsequent risk of infection [8]. Although the risks of fluid therapy have been well characterized in medically critically ill patients, the risks in neurocritically ill patients with aSAH remain to be elucidated.

While patients with aSAH receive a majority of the fluid intake from intravenous (IV) bolus or maintenance IV infusions, there are various hidden sources of chloride-rich fluids in the form of enteral fluids and medication diluents such as intermittent IV infusions (so-called piggybacks; for example, antibiotics, antiseizure medications) and/or titrated continuous infusion (for example, sedatives and vasoactive medications). Hidden obligatory fluid intake from medications/diluents is often an unrecognized yet significant contribution to the overall fluid balance [9]. Observational studies have shown that patients receive high volumes of crystalloid administration, with an estimated five liters or more in the acute phase of aSAH and only a modest reduction to a minimum of three liters by day 13 of hospitalization [10]. Characterizing the source and contribution of this significant volume of cumulative fluid intake in patients with aSAH will not only increase awareness of cumulative fluid burden but also assist in identifying key areas for implementation of fluid stewardship interventions.

This retrospective, single-center, cohort study aimed to describe the incidence of hyperchloremia in patients with aSAH and the contribution of fluids, medication diluents, and other fluid sources to chloride administration. We hypothesized that hyperchloremia, defined as a serum chloride level > 109 mEq/L, occurs at a high incidence in patients with aSAH due to excessive chloride-rich fluid intake, and is associated with worse patient outcomes, such as AKI, length of stay (LOS), and mortality.

## METHODS

### Setting and participants

This was a retrospective, single-center, cohort study of patients admitted to the neurointensive care unit with a diagnosis of aSAH between January 1, 2015, and August 31, 2019. Patients between 18 and 85 years were enrolled if they had an index International Classification of Diseases, 9/10 diagnosis code for aSAH, received oral nimodipine, and were admitted to the neurointensive care unit for longer than 48 hours. The receipt of oral nimodipine was chosen to ensure a homogeneous patient population with an index admission for acute spontaneous aSAH. Patients were excluded if they were diagnosed with traumatic SAH, pregnant, or incarcerated; had AKI or chronic kidney disease (CKD) requiring renal replacement therapy (RRT) on admission; were moribund; or had early withdrawal of care.

### Study outcomes and definitions

The primary outcome of the study was the incidence of hyperchloremia, defined as a serum chloride level > 109 mEq/L. [11] Secondary outcomes included the incidence of severe hyperchloremia > 115 mEq/L, incidence of AKI, need for RRT, characterization of the source of fluid intake (mL/day) and chloride intake (mEq/day), length of intensive care unit (ICU) stay (days), length of hospital stay (days), and in-hospital mortality.

### Data collection

Data were collected from the University of Kentucky electronic health record and included baseline demographics, pre-existing comorbidities, pertinent laboratory values, the presence of cerebral vasospasm, assessment of renal function (serum creatinine, urine output, need for RRT), daily IV medication/fluids, enteral sodium tablets/solution received during ICU LOS up to day 14, nephrotoxin exposure, daily total daily fluid intake and output, length of hospital/ICU stay, and mortality. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as stage 1 and above [12]. Data regarding the Hunt Hess score and modified Fisher grade were individually collected by the investigator team. Patient data were evaluated for the duration of admission, and no follow-up or data collection was performed after discharge.

To quantify the contribution of hyperchloremia from medications, daily data on IV medications administered including dilu-


https://doi.org/10.18700/jnc.220068

ent, volume, dose, and frequency were obtained. Data collection on fluid intake was limited to 14 days due to the decline in sample size after 14 days and because the first 14 days portend the highest risk for vasospasm and DCI in patients with aSAH, thus constituting the period with the most aggressive fluid supplementation. Potential nephrotoxin exposure was defined as receipt of any of the following medications: vancomycin (IV), amphotericin (IV), aminoglycosides (IV), acyclovir (IV), angiotensin-converting enzyme inhibitors (IV/ oral [PO]), angiotensin receptor blockers (PO), nonsteroidal anti-inflammatory medications (IV/PO), piperacillin-tazobactam (IV), loop diuretics (IV/PO), contrast (IV), and trimethoprim-sulfamethoxazole (IV/PO).

### Statistical analysis

The *a priori* statistical analysis plan included dividing the cohort into those who met the primary outcome of hyperchloremia and comparing the baseline characteristics and outcomes to those who did not develop hyperchloremia. No sample-size calculations were performed. Data are presented as means with standard deviations (SDs) or medians with interquartile ranges (IQRs) depending on their underlying distributions. Continuous variables were analyzed using either Student *t*-test or the Mann-Whitney *U*-test. Categorical variables were analyzed using Pearson's chi-square or Fisher's exact test as appropriate and were reported as counts with percentages. The missing values were not imputed.

### Multivariable regression

Multivariable logistic regression was used to model the primary outcome of hyperchloremia and secondary outcome of AKI. For the primary outcome, variables found to be significant in the bivariate analysis were selected for the hyperchloremia model and included basic demographic variables (age, sex), Sequential Organ Failure Assessment (SOFA) score, Hunt-Hess score, modified Fisher grade, cumulative fluid intake, baseline serum chloride concentration, mean daily chloride dose, and chloride dose within the first 48 hours of admission). Given the wide degree of variability in the volume of fluid administration and intake during the study period, cumulative fluid intake was assessed as a continuous variable and divided into quartiles ( < 25%, 25%–50%, 51%–75%, and > 75%) to improve interpretation. The primary independent variable during the study period was hyperchloremia. A backward elimination selection criterion was used at a level of 0.05. Bivariate analysis was performed using statistical software, IBM SPSS version 27 (IBM Corp., Armonk, NY, US), and multivariable modeling was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A multivariable logistic regression model was also used to identify predictive factors for AKI using the same procedures. The variables selected for this model were *a priori* and included sex, age, Hunt-Hess score, Fisher grade, development of hyperchloremia, CKD, sepsis, and nephrotoxin exposure at 48 hours.

## RESULTS

### Demographics

A total of 234 patients with aSAH admitted to the ICU over a four-year period met the inclusion criteria for the primary analysis. Baseline demographics were similar between groups. Most of the cohort was female sex (59%), with a mean age of 55 years (SD, 13). Hypertension (79.5%) and diabetes (22.2%) were the most common preexisting comorbidities. A total of 4% of the population had CKD at baseline, and none of the patients required RRT. The median Hunt-Hess score and modified Fisher scale on admission were 2 (IQR, 1–4) and 3 (IQR, 2–4), respectively. The mean SOFA score was 5.6 (SD, 3.8). The median length of ICU stay for the entire cohort was 10 days, corresponding to a median total hospital stay of 13 days. The overall mortality during hospital admission in this population was 11%. A full description of the baseline characteristics of both cohorts is provided in Table 1.

### Primary outcome

The primary outcome of the incidence of hyperchloremia (chloride > 109 mEq/L) was 75% (n = 175) of the study population, with 58% (n = 101) developing severe hyperchloremia (chloride > 115 mEq/L). The median chloride in patients who developed hyperchloremia was significantly higher at 115 mEq/L (IQR, 112–120 mEq/L) compared to 108 mEq/L (IQR, 106–109 mEq/L) in those who did not develop hyperchloremia ($P < 0.001$) (Table 2). The median time to the onset of hyperchloremia was 3 days (IQR, 1–5 days) after admission. Females were more likely to have hyperchloremia than males (64% vs. 36%; odds ratio [OR], 2.4; 95% confidence interval [CI], 1.3–4.4). No differences in the incidence of hyperchloremia were associated with race or ethnicity ($P = 0.59$). The Hunt-Hess score and modified Fisher grade were both significantly associated with an increased incidence of hyperchloremia (Table 1), although there was no significant difference. Chloride concentrations increased to the maximum mean concentration on day 4 in patients with hyperchloremia (day 2 in those without hyperchloremia) and were consistently sustained throughout the first 14 days of admission (Fig. 1).

### Secondary outcomes

The development of hyperchloremia was associated with pro-

**Table 1.** Baseline patient characteristics (n=234)

| Variable | Hyperchloremia (n=175) | No hyperchloremia (n=59) | *P*-value |
|---|---|---|---|
| Age (yr) | 55±13 | 53±13 | 0.328 |
| Race | | | 0.591 |
| Caucasian/white | 152 (87) | 53 (90) | |
| African American | 19 (11) | 4 (7) | |
| Other | 4 (2) | 2 (3) | |
| Body mass index (kg/m$^2$) | 28 (24–33) | 28 (24–34) | 1.000 |
| Female sex | 112 (64) | 25 (42) | 0.004 |
| Comorbidity | | | |
| Hypertension | 141 (81) | 45 (76) | 0.479 |
| Diabetes | 37 (21) | 15 (25) | 0.494 |
| CKD | 7 (4) | 3 (5) | 0.716 |
| Charlson comorbidity index | 3 (2–5) | 3 (2–4) | 0.200 |
| SOFA score | 8 (2–9) | 2 (1–7) | <0.001 |
| Sepsis on admission | 8 (5) | 0 | 0.206[a] |
| Hunt-Hess score | 2 (1–4) | 2 (1–4) | <0.001 |
| Fisher grade | 3 (2–4) | 3 (2–4) | <0.001 |
| Glasgow Coma Score | | | <0.001 |
| 15 | 29 (17) | 23 (39) | |
| 13–14 | 18 (10) | 17 (29) | |
| 10–12 | 27 (16) | 9 (15) | |
| 6–9 | 62 (36) | 9 (15) | |
| <6 | 38 (22) | 1 (2) | |
| Admission SCr (mg/dL) | 0.79 (0.66–0.96) | 0.83 (0.68–1.02) | 0.523 |
| Admission BUN (mg/dL) | 13 (10–17) | 12 (11–16) | 0.602 |
| Admission chloride (mEq/L) | 102±5 | 100±3 | <0.001 |
| Admission sodium (mEq/L) | 140±4 | 140±2 | 0.132 |
| Mechanical ventilation (day) | 16 (11–23) | 10 (8–13) | <0.001 |
| ICU LOS (day) | 12 (8–18) | 8 (6–10) | 0.001 |
| Hospital LOS (day) | 15 (11–22) | 9 (7–12) | 0.001 |
| Discharge disposition | | | 0.005[a] |
| Home | 139 (79) | 57 (97) | |
| Rehabilitation or SNF | 11 (7) | 2 (3) | |
| Death >48 hours or hospice | 25 (14) | 0 | |

Values are presented as mean±standard deviation, number (%), or median (interquartile range).
CKD, chronic kidney disease; SOFA, Sequential Organ Failure Assessment; SCr, serum creatinine; BUN, blood urea nitrogen; ICU, intensive care unit; LOS, length of stay; SNF, skilled nursing facility.
[a]Not reliable owing to zero observations.

longed length of ICU stay (12 vs. 8 days, $P<0.001$), duration of mechanical ventilation (16 vs. 10 days, $P<0.001$), longer length of hospital stay (15 vs. 9 days, $P<0.001$), and a higher rate of hospital mortality (14.3% vs. 0%, $P=0.002$) than in patients who did not develop hyperchloremia. The rates of AKI were similar in the two groups (4% vs. 5.1%, $P=0.716$; OR, 2.1; 95% CI, 0.6–7.5), with no further difference in KDIGO stage or the need for RRT (Table 2). The mean serum chloride level by hospital day also did not differ between patients with and without AKI (Fig. 1).

*Multivariate regression*

In the multivariable logistic regression analysis for hyperchloremia when accounting for SAH severity, age, and chloride dose within the first 48 hours, variables such as sex, higher admission SOFA score, cumulative fluid intake, serum chloride concentration on admission, and daily mean chloride dose were independently predictive of hyperchloremia (Table 3). For every 1 liter increase in chloride-rich fluid intake, the risk of hyperchloremia increased by 4% (OR, 1.04; 95% CI, 1.01–1.06). Male sex and daily chloride


https://doi.org/10.18700/jnc.220068

**Table 2.** Secondary outcomes

| Outcome | Hyperchloremia (n=175) | No hyperchloremia (n=59) | *P*-value |
|---|---|---|---|
| Daily chloride (mEq/L) | 107 (98–124) | 103 (99–106) | <0.001 |
| Maximum chloride (mEq/L) | 115 (107–145) | 108 (106–109) | <0.001 |
| Incidence of severe hyperchloremia | 101 (58) | 0 | <0.001[d] |
| Hypernatremia[a] | 143 (81.7) | 11 (18.6) | <0.001 |
| Incidence of severe hypernatremia[b] | 41 (23.4) | 0 | <0.001 |
| Acute kidney injury | 18 (10.3) | 3 (5.1) | 0.298 |
| KDIGO stage 1 | 15 (8.6) | 2 (3.4) | |
| KDIGO stage 2 | 3 (1.7) | 1 (1.7) | |
| KDIGO stage 3 or RRT | 0 | 0 | |
| Cumulative fluid intake[c] (mL) | 463,358 (293,349–60,439) | 29,662 (18,354–46,410) | <0.001 |
| Cumulative chloride exposure over first 3 days (mEq) | 824 (135–1,672) | 787 (68–1,784) | 0.879 |
| Mean daily chloride dose over first 3 days (mEq) | 275 (45–557) | 262 (23–595) | 0.940 |

Values are presented as median (interquartile range) or number (%).
KDIGO, Kidney Disease: Improving Global Outcome; RRT, renal replacement therapy; ICU, intensive care unit.
[a]Hypernatremia defined as >145 mEq/L; [b]Severe hypernatremia defined as >155 mEq/L; [c]Throughout study duration (up to 14 days of ICU stay or ICU discharge); [d]Not reliable owing to zero observations.

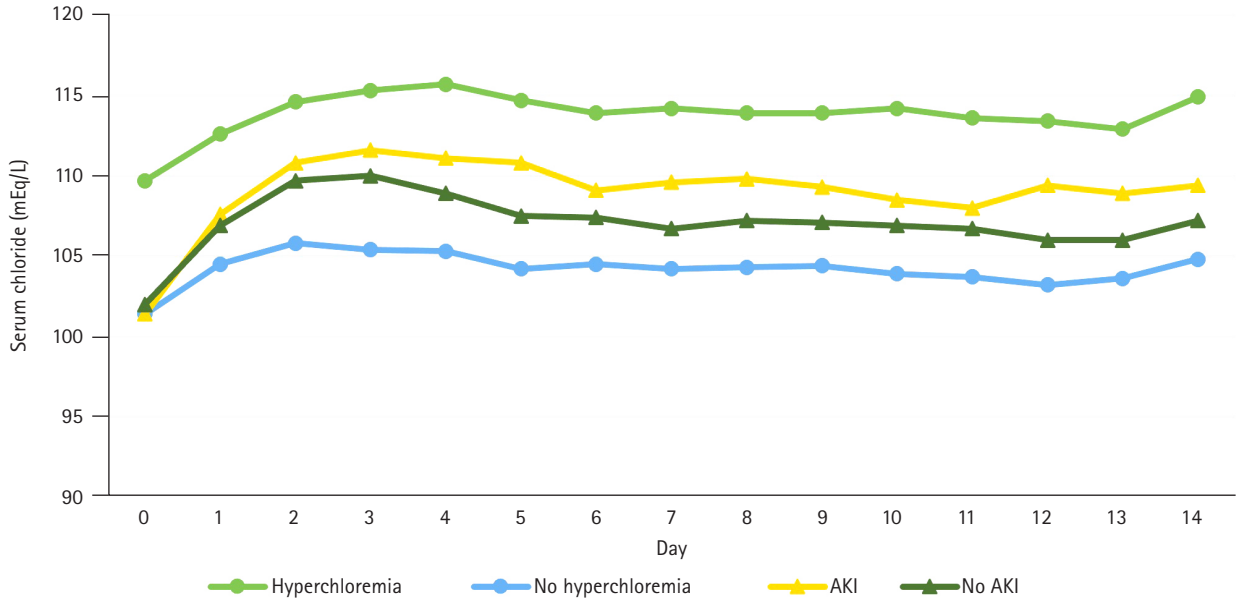


**Fig. 1.** Median daily serum chloride trend over the 14-day study period. AKI, acute kidney injury.

dose were inversely associated with the development of hyperchloremia.

In the multivariate logistic regression model for AKI, accounting for sex, age, Hunt-Hess score, Fisher grade, development of hyperchloremia, CKD, sepsis, and nephrotoxin exposure at 48 hours, the presence of CKD, sepsis, and nephrotoxin exposure were all independent predictors of AKI (Supplementary Table 1).

*Fluid intake*

While there was a statistically significantly higher median cumulative fluid intake over the first 14 days in patients who developed hyperchloremia (47.6 L vs. 26.6 L, $P < 0.0001$), there was no difference in the mean daily or median cumulative chloride exposure within the first 72 hours of hospital stay. Serum chloride mirrored daily fluid intake and overall daily fluid balance throughout the first 14 days of admission (Fig. 2). Overall, patients received a mean daily fluid intake of 3.7 liters between days 1 and 7, with only a small reduction to 3.6 liters on days 8 to 14. Maintenance IV fluids contributed to the highest volume, chloride content, and sodium content per day. Patients with hyperchloremia had a me-

dian daily chloride dose of 334 mEq (IQR, 150–683 mEq) compared to 405 mEq (IQR, 233–789 mEq) in patients with no hyperchloremia ($P=0.228$). In the overall cohort, the mean sodium and chloride dose per day was 636.5 mEq (SD, 112) and 646 mEq (SD, 113), respectively.

Over the course of the study period, the majority of fluid intake was from enteral nutrition (47%), maintenance IV fluids (19%), and titrated IV infusions (18%) (Fig. 3). The majority of fluid intake came from maintenance IV fluids early in the study period (day 1, 57.5%) but reduced in proportion over the length of the study period (Supplementary Fig. 1A). The amount of chloride administered was primarily from maintenance IV fluids (overall 48.1%) (Supplementary Fig. 1B). Enteral sodium supplementation and nutrition (31%) and IV boluses (12%, typically 3% sodium chloride) also substantially contributed to the daily chloride dose. Over the first 14 days, the percentage of chloride delivered each day shifted from maintenance IV fluids (67.1% of all chloride provided) to an almost equal split of maintenance IV fluids (43.2%) and enteral sodium supplementation (42.1%, usually sodium chloride tablets) (Supplementary Fig. 1B).

**Table 3.** Multivariable logistic regression model for hyperchloremia

| Independent variable | Odds ratio (95% CI) |
|---|---|
| Male sex | 0.43 (0.21–0.89) |
| SOFA score | 1.19 (1.07–1.33) |
| Serum chloride-day of ICU admission (mEq/L) | 1.18 (1.06–1.31) |
| Daily chloride dose (mEq) | 0.999 (0.998–1.00) |
| Cumulative fluid intake (per liter increase) | 1.04 (1.01–1.06) |
| Cumulative fluid quartile 2[a)] | 1.28 (0.51–3.22) |
| Cumulative fluid quartile 3[a)] | 3.58 (1.90–11.7) |
| Cumulative fluid quartile 4[a)] | 6.06 (1.79–20.5) |

CI, confidence interval; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit.
[a)]Cumulative fluid quartiles (throughout the 14-day study period) in reference to quartile 1 (0–29,348 mL); quartile 2 (25%–50%; 29,349–46,357 mL); quartile 3 (51%–75%; 46,358–60,438 mL); quartile 4 (>75%; >60,439 mL).

## DISCUSSION

In the current observational study of 234 patients with aSAH, a high incidence of hyperchloremia (75%) was observed. Elevated serum chloride concentrations were associated with the volume of maintenance IV infusion but not with the dose of chloride administered. While the overall outcomes of the population were similar to those expected in the aSAH population, the development of hyperchloremia was associated with worse outcomes related to prolonged duration of ICU/hospital LOS, prolonged duration of mechanical ventilation, numerically higher rates of AKI, and an increased risk of in-hospital mortality. The need for mechanical ventilation, higher SOFA score, and presence of sepsis likely contributed to the indication for increased fluid intake, resulting in hyperchloremia, and was associated with worsened outcomes in this study.

Hyperchloremia has been demonstrated to be strongly associated with AKI in critically ill patients admitted to the medical ICU [7]. In the current study, AKI occurred in 10.3% of patients over-

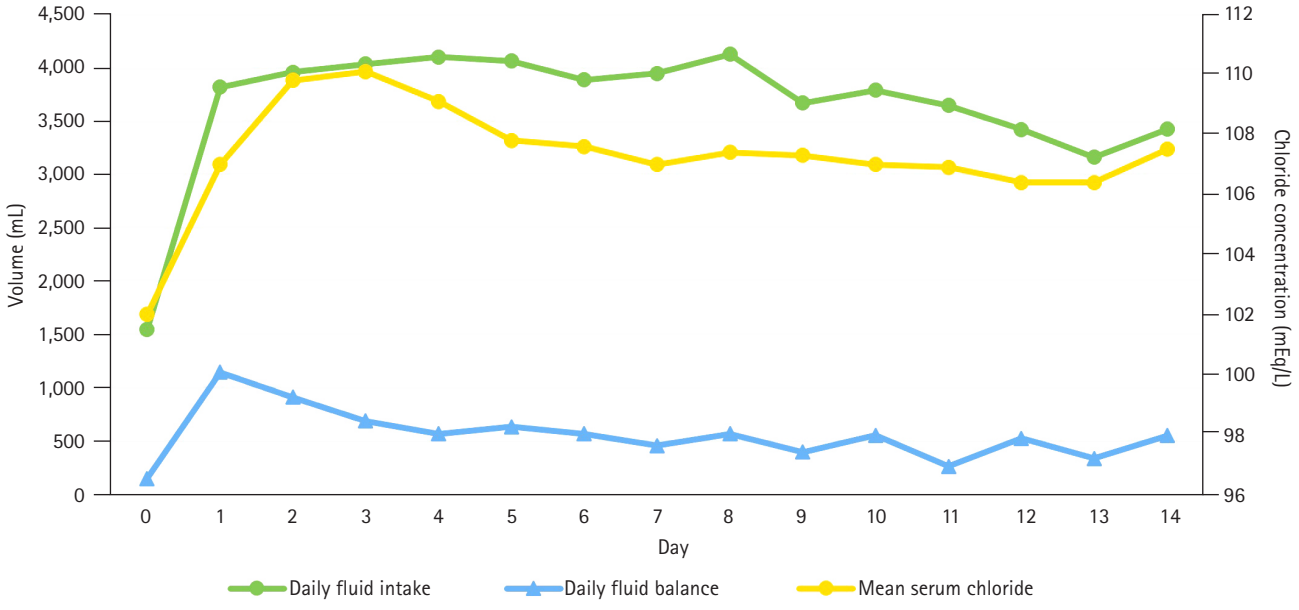


**Fig. 2.** Fluid intake, fluid balance, and serum chloride concentration by hospital day.


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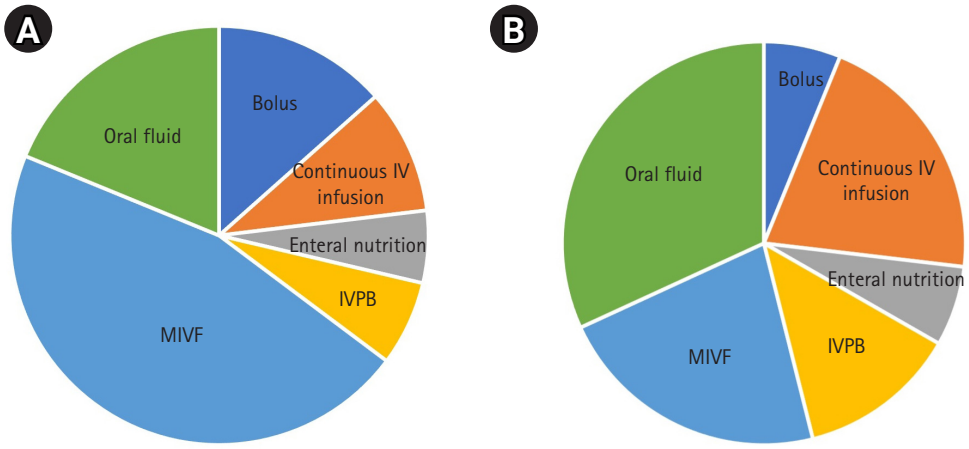


**Fig. 3.** Total fluid volume (A) and chloride dose (B) received, by category. IV, intravenous; IVPB, intravenous piggyback; MIVF, maintenance intravenous fluid.

all and was not significantly associated with the occurrence of hyperchloremia. The presence of sepsis, CKD, and nephrotoxin exposure at 48 hours was found to be an independent predictive factor for AKI, similar to previous studies evaluating the risk factors for AKI in neurologically injured patients [13]. In a retrospective analysis by Sadan et al. [1], every 10 mEq/L increase in serum chloride level was associated with a 7.39 increase in the odds of AKI among patients with aSAH (OR, 7.39; 95% CI, 3.44–18.23). Potential factors that may have contributed to the lower incidence of AKI in this population were the small population cohort and the detection of AKI based on serum creatinine levels alone.

Previous studies have identified that medication diluents contribute to the highest volume and chloride intake among critically ill patients admitted to the medical ICU [9]. Normal saline (0.9% sodium chloride) has been used as the primary diluent for most medications and was identified to independently increase the risk of hyperchloremia and subsequent AKI compared with substitution with a dextrose-containing diluent [9]. The implications of the findings by Magee et al. [9] and those of the current study suggest a potential need for intervention in substituting medication diluents as a mitigation strategy to prevent hyperchloremia. However, dextrose-containing fluids are often avoided in patients with acute neurologic injuries because of the risk of exacerbating cerebral edema or promoting hyponatremia. Potential therapeutic alternatives to normal saline to mitigate chloride exposure and avoid the use of hypotonic fluids may include the use of sodium acetate or mixed sodium acetate/chloride solution (that is, "buffered saline") [14].

The recently published ACETatE trial (A Low-Chloride Hypertonic Solution For Brain Edema) was a randomized pilot trial assessing the efficacy of 23.4% sodium chloride vs a mixture of 16.4% sodium chloride/sodium acetate for the treatment of cerebral edema. The trial demonstrated a lower chloride load and incidence of AKI in patients who had received a mixed saline/acetate solution compared to sodium chloride solution alone (11.8% vs. 53.3%, $P=0.01$) [11]. This study supports the hypothesis that excess chloride load may be a potentiator of AKI in this population and that interventions targeted at mitigating chloride load may preserve renal function among patients with aSAH. The current study found that the highest proportion of the chloride load came from the maintenance of IV fluids. Ongoing studies are needed to assess the safety and feasibility of substituting other sodium salts with sodium chloride as a maintenance IV fluid or reducing the use of hypertonic saline and targeting high serum sodium concentrations [15].

The limitations of the current study include its retrospective observational design. While the data extracted from the electronic health record were validated by selected manual confirmation, documentation of fluids in and out daily is subject to some natural variability in the course of patient care (in particular, oral consumption that may go unmeasured). However, great attention has been paid to the fluid balance of these patients after aSAH, so there is confidence that the documentation is as precise and accurate as is reasonable to expect for a non-prospective study scenario. Owing to inconsistencies in documentation, the incidence of vasospasm could not be accurately assessed in all patients based on retrospective data collection. The presence of vasospasm would be predicted to result in a higher volume of fluid administration to optimize cerebral perfusion, and thus, a higher cumulative chloride load. Patients with vasospasm may also receive more IV contrast agents or have a higher systemic inflammatory state,

both of which could increase the risk of AKI. The use of serum creatinine as a marker of kidney function has known limitations, and its use for the diagnosis of AKI may have limited accuracy. Thus, the incidence of AKI may be underreported [16]. Further studies should evaluate AKI using more accurate biomarkers of kidney injury in this population.

In this retrospective observational cohort study of 234 patients with aSAH, the incidence of hyperchloremia was 75%. Hyperchloremia was not associated with a statistically significant increased risk of AKI; however, patients who developed hyperchloremia experienced worse outcomes such as prolonged ICU LOS, hospital LOS, duration of mechanical ventilation, and mortality. Maintenance IV fluids, followed by bolus and continuous IV fluids, contributed to the highest chloride burden. Awareness of and adjustments to the chloride load in maintenance IV fluids and medication diluents may assist in reducing the chloride burden in this patient population as well as the risk of hyperchloremia. Further prospective studies are needed to assess the impact of reducing the chloride burden and the incidence of hyperchloremia in patients with aSAH on the improvement of clinically important patient outcomes.

## ARTICLE INFORMATION

### Ethics statement

This study was approved by the Institutional Review Board of University of Kentucky, and the requirement for informed consent was waived.

### Conflict of interest

No potential conflict of interest relevant to this article.

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### Supplementary materials

Supplementary materials can be found via https://doi.org/10.18700/jnc.220068.

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pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):122-125
https://doi.org/10.18700/jnc.220071

Journal of Neurocritical Care

# Management of propofol-related infusion syndrome and discussion of *POLG* mitochondrial mutation: a case report

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CASE REPORT

Received: September 3, 2022
Revised: October 19, 2022
Accepted: November 2, 2022

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**Background:** Propofol-related infusion syndrome (PRIS) is a known complication of long-term propofol infusion. Providers should be aware of PRIS risk, as early recognition is key to avoiding mortality, which can range from 30% to 60%. The underlying mechanism of PRIS is unknown, but some studies suggest that underlying mitochondrial dysfunction may predispose patients to developing PRIS.
**Case Report:** We present a case of refractory adult-onset epilepsy that was challenging due to a paradoxical response to propofol with worsening brief ictal/interictal rhythmic discharges and complicated by development of PRIS. We aimed to discuss the clinical presentations of PRIS, along with a review of the mitochondrial *POLG* mutation found in our patient, which has also been described in other case reports of refractory adult-onset epilepsy.
**Conclusion:** We discuss the treatment strategy utilized in hopes of raising awareness of the risks in managing patients with epilepsy who have a potential underlying mitochondrial disorder.

**Keywords:** Epilepsy; Propofol infusion syndrome; Mitochondrial diseases; Mutation; Propofol; Adult

## INTRODUCTION

Propofol-related infusion syndrome (PRIS) is a known complication of long-term propofol infusion. Propofol was placed on the World Health Organization's list of essential medicine in 2019, and has been used in many anesthetic settings since its discovery in 1977. Following propofol approval in 1989, the first report on PRIS was released in 1990, with the syndrome defined in 1989 by Bray et al. as a disease characterized by high anion-gap metabolic acidosis, rhabdomyolysis, hepatomegaly, lipemia, bradycardia, and eventual cardiovascular collapse that develops in patients on high-dose propofol infusions greater than 4 mg/kg/hr for more than 48 hours [1]. Providers should be aware of PRIS risk as early recognition is key to avoiding mortality, which can range from 30% to 60%. The underlying mechanism of PRIS is still unknown, but some studies suggest that an underlying mitochondrial dysfunction may predispose some patients to developing PRIS [2]. Mitochondrial mutations have been fully described in the litera-

ture with regard to their presentation in patients with pediatric epilepsy, but the genetics are poorly described in adult populations, with the two most common epileptic pathologies being mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes and myoclonic epilepsy with ragged red fibers [3]. When treating epilepsy with a potentially underlying mitochondrial defect, consideration should be made with regard to antiseizure drug (ASD) choice as some medications can theoretically compromise mitochondrial function [3]. We present a case where PRIS was successfully managed with identification of a possible underlying mitochondrial mutation.

## CASE REPORT

Our patient was a 42-year-old African-American male with newly diagnosed right temporal lobe epilepsy who presented with status epilepticus and was subsequently intubated for hypoxia post-event. Upon admission, seizures were initially controlled with valproic acid and lacosamide. After 72 hours, the patient developed intermittent periods of agitation and desaturation. The patient's electroencephalogram (EEG) became more active with new multifocal, independent sharp waves in the left frontal temporal region. Prior to admission, all electrographic spikes were observed only in the right temporal area. EEG activity continued to increase and evolved from brief ictal/interictal rhythmic discharges (BIRDs) to short bursts of seizure activity despite maximizing valproic acid and lacosamide doses and addition of fosphenytoin. The decision was made to place the patient in burst suppression, which was performed using fentanyl, midazolam, and propofol. Despite high doses of these medications, the patient's EEG demonstrated an increased frequency of BIRDs, with discharges becoming more sharply contoured (Fig. 1). Ketamine was added, following which burst suppression was achieved.

After 48 hours, the patient developed new acidosis, elevated lactate, and elevated creatine phosphokinase levels. Within a few hours, he developed significant hypotension requiring pressors, and a new T-wave inversion was noted on electrocardiogram (Fig. 2). A medical workup including inflammatory and cardiac markers and cultures was conducted to rule out other causes such as septic shock. Treatment was escalated to broad-spectrum antibiotics, and a transthoracic echocardiogram was obtained, which demonstrated stable contractility. Propofol was infused at 4.5 mg/kg/hr for almost 72 hours until it was discontinued owing to clinical suspicion of PRIS. Despite immediate cessation of propofol, the patient's bloodwork continued to demonstrate a rapid increase in creatine phosphokinase, triglycerides, lactate, and liver enzymes, with escalating vasopressor requirements. The nephrology department was urgently consult-

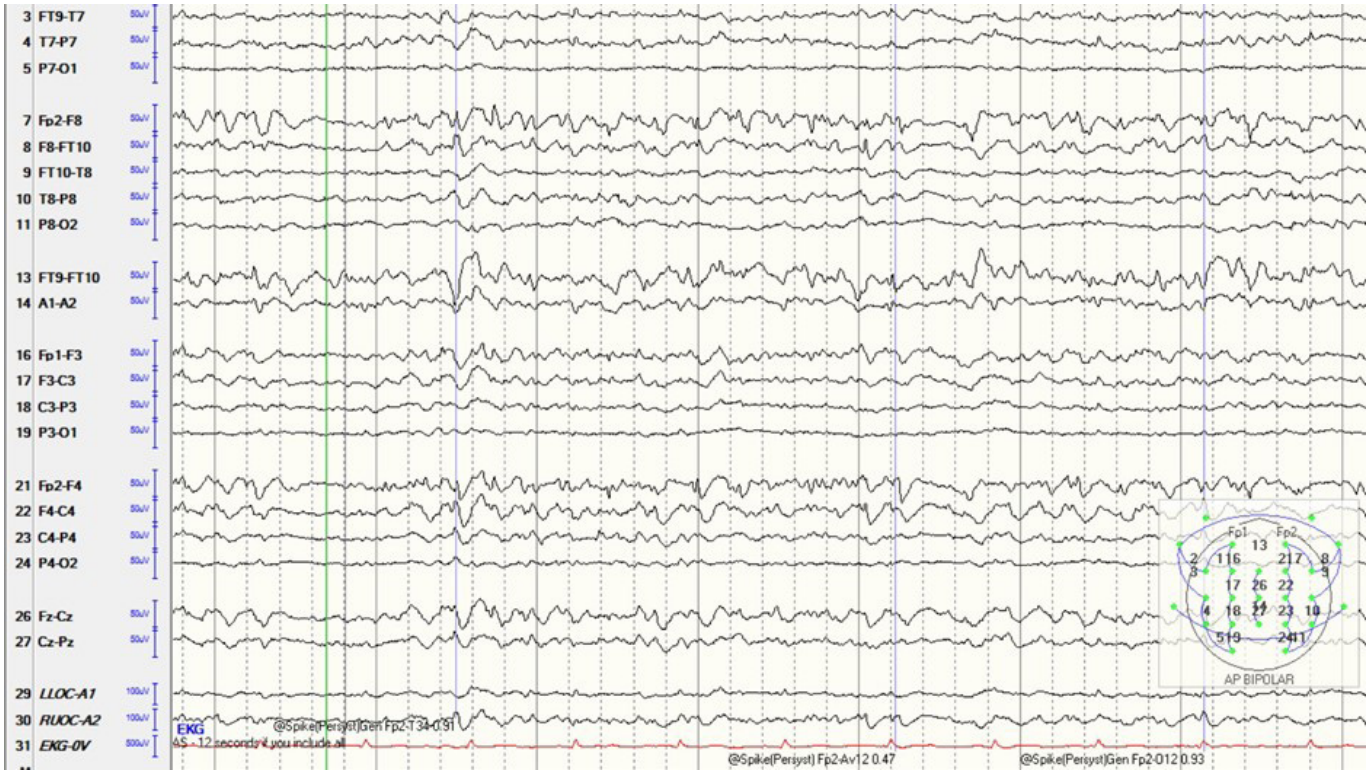


**Fig. 1.** Electroencephalogram demonstrating the refractory brief ictal/interictal rhythmic discharges pattern.

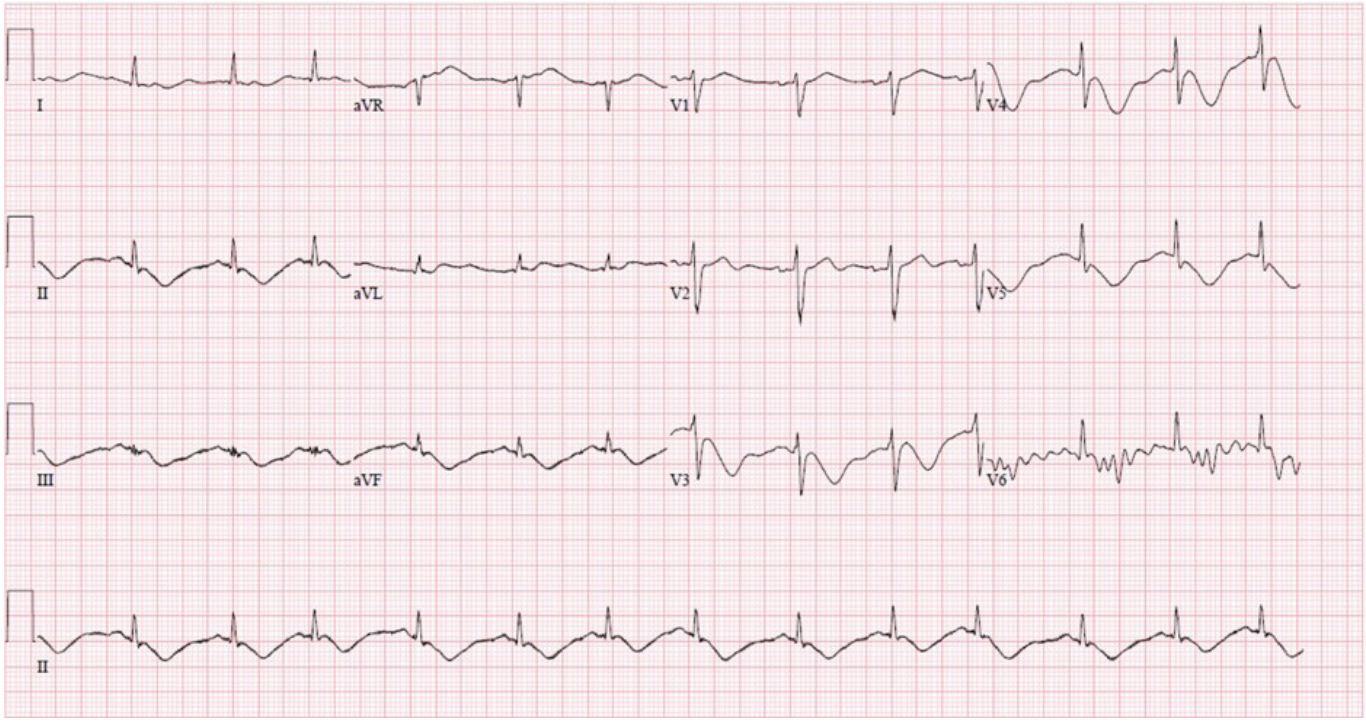


**Fig. 2.** Electrocardiogram changes showing deep T wave inversions after lab abnormalities were discovered that were not present previously.

ed, and the patient initiated continuous renal replacement therapy in the evening. Supplemental L-carnitine was added, valproic acid was discontinued, and the patient was transitioned to phenobarbital.

After propofol was discontinued, the burst suppression pattern improved, further ASDs decreased, and the previous BIRDs findings resolved and evolved into intermittent interictal spikes on EEG monitoring. The patient continued to stabilize over the next few days, and laboratory abnormalities resolved with continuous renal replacement therapy. Magnetic resonance imaging of the brain with and without contrast, along with arterial and venous phases, showed no structural or vascular abnormalities. A lumbar puncture combined with tests for abnormal epileptic mutations and autoimmune antibodies also revealed normalizing results. Genetic testing was performed through Mayo Laboratories combined mitochondrial analysis [4], and the patient tested positive for a likely pathogenic POLG gene mutation (c.3104+1G>A, Chr15:89862458) as well as two variants of uncertain significance, namely NDUFS8 (p.P7T) and TRMU (p.I99T) mutations. The patient's mentation continued to slowly improve, and he was transferred to rehabilitation, where he was eventually discharged after a few weeks with his condition close to baseline on a regimen of phenobarbital, zonisamide, and lacosamide. He has since continued to experience a gradual decline in mentation with worsening memory loss and return visits for breakthrough seizures due to medication nonadherence.

## DISCUSSION

It has been suggested that the pathophysiology of PRIS may be related to mitochondrial impairment through animal models and autopsies [5]. Recent literature is also supportive of this theory; several cases of PRIS have found that patients tended to have an underlying mutation affecting their mitochondria [2]. We describe a case of PRIS which was successfully managed with supportive care and early detection along with a genetic workup which included a genetic mitochondrial panel.

The POLG gene mutation in our patient can be seen in mitochondrial depletion syndromes, ataxia, and valproic acid-induced hepatotoxicity, which has also been described in other patients with PRIS [2]. Genetically, the POLG gene is known to encode mitochondrial DNA polymerase. Given the importance of mitochondria in aerobic metabolism and ATP generation, prior studies have proven its importance, with knockout mutations being embryonic lethal, and well over 200 mutations have been known to affect its function [6]. Disease severity can range from refractory infantile epilepsy to adult-onset ataxia. Because *POLG* mutations can present with vast clinical variations, it is important to


https://doi.org/10.18700/jnc.220071

note that apart from neurological involvement, there can also be effects on the cardiac, hepatic, gastric, and respiratory systems. In terms of neurological involvement, most described syndromes involve visual acuity, eye movements, hearing, epilepsy, ataxia, myopathies, and variable magnetic resonance imaging findings [6]. While it has been reported in small case series where there was a 23.1% prevalence of epilepsy with multifocal EEG abnormalities, this only made up 1.6% of the total number of patients with mitochondrial mutations that experienced epilepsy [3]. Further review of the *POLG* mutation and epilepsy demonstrates the potential for epilepsy refractory to medications along with subcortical myoclonus [7]. Our patient also tested positive for two variants of uncertain significance which included a NDUFS8 mutation that can be seen in autosomal recessive Leigh syndrome due to an impaired Complex I deficiency, and a TRMU mutation that can be seen in infantile liver failure.

Due to the paucity of evidence on mitochondrial mutations in adult-onset epilepsy, there are no guidelines regarding the selection of ASD. Among the three major medications used in status epilepticus, levetiracetam and fosphenytoin are not known to cause mitochondrial toxicity. Valproic acid should be used with care as some studies have reported potential toxicity, although there are also conflicting reports where patients with mitochondrial mutations tolerated the medication [5]. Patients with the *POLG* mutation developed refractory seizures, but phenobarbital and midazolam along with a ketogenic diet, a low glycemic diet, and a sodium channel blocker considered reasonable for first line therapy resulted in the best response [7]. Unlike other mitochondrial diseases, these patients have not been reported to have a baseline hepatopathy or myopathy, but the disease can be associated with valproate induced hepatotoxicity for which there have reports of successful rescue therapy with L-carnitine or N-acetylcysteine [7].

As the body of literature grows, it is possible that we may be able to identify a group of genetic mutations which place certain adult-onset epileptic patients at a higher risk of developing PRIS. Owing to the high mortality rate, it is important to be aware of PRIS as a deadly complication of high-dose propofol use. This report aims to provide further insight into the necessity of genetic testing in these patients, which may help identify a common link in the future. While it may not be feasible to screen all patients with mitochondrial disorders, patients with a known history should be cautioned about this catastrophic complication of a routine sedative, and patients who experience PRIS should undergo a mitochondrial workup to better characterize this disease and prevent future risks.

## ARTICLE INFORMATION

### Ethics statement

Approval for this study was waived in accordance with UT Southwestern policies because this study was a case report of a single patient (no more than three patients) and did not include protected health information, data analysis, or testing of a hypothesis; and was de-identified. The requirement for informed consent was waived.

### Conflict of interest

No potential conflict of interest relevant to this article.

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

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pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):126-130
https://doi.org/10.18700/jnc.220072

Journal of Neurocritical Care

# Negative-pressure helmet restores cerebral hemodynamic parameters in sinking skin flap syndrome: a case report

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CASE REPORT

Received: September 7, 2022
Revised: October 12, 2022
Accepted: October 22, 2022

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**Background:** Sinking skin flap syndrome (SSFS) is a rare complication of decompressive craniectomy (DC) and causes a wide range of neurological deficits. Its pathophysiology remains debatable, however cranioplasty may decrease the symptoms of SSFS by reducing the direct effect of atmospheric pressure on the brain and allowing the correction of cerebral blood flow (CBF) and cerebral metabolism.
**Case Report:** A 36-year-old female patient underwent DC for a right frontal hematoma and signs of increased intracranial pressure following the resection of a right frontal arteriovenous malformation. Subsequently, she developed SSFS, altered neurological status with a Glasgow Coma Scale (GCS) score of 8/15, and bacterial-resistant meningitis. We applied a custom-shaped negative pressure helmet on the bone defect and used invasive and noninvasive techniques to measure the changes in intracranial pressure, CBF and cerebral oxygen saturation. Despite improvements in the cerebral physiological parameters, the neurological status did not improve (GCS score, 8/15).
**Conclusion:** To our knowledge, this is the first reported case of SSFS treated with a negative-pressure helmet and subsequent changes in cerebral parameters that were monitored invasively and noninvasively.

**Keywords:** Cerebral blood flow; Critical care; Near-infrared spectroscopy; Decompressive craniectomy

## INTRODUCTION

Sinking skin flap syndrome (SSFS) corresponds to altered neurological status following decompressive craniectomy (DC), which results in a persistent bone defect. It was first described in 1939 by Grant and Norcross as syndrome of the trephined. Since 1977 and following the work of Yamaura and Makino [1], the term "SSFS" has been commonly used to describe this entity. Patients with SSFS may experience a wide range of neurological symptoms, which may vary from motor impairments, cognitive disturbances, impaired vigilance, headache and sensory impairments to visual symptoms or seizures [2,3]. Clinically or radiologically, physicians can observe concaving or sinking of the scalp to a plane that is lower than the edges of the skull defect [3,4].

SSFS may appear 3–10 months after DC or, in rare cases, a few days or weeks after a lumbar puncture, ventricular derivation or

removal of a bone flap [2,5-7]. The pathophysiology of SSFS remains unclear and debatable, even after the works of Yoshida et al. [8] in 1996 and Winkler et al. [9] in 2000, respectively. The fact that, in most cases, correction of the bone defect by cranioplasty results in improvements or complete recovery is in favor of a direct effect of atmospheric pressure on cerebral blood flow (CBF) and cerebral metabolism [2,3,6,7].

Herein, we describe a case of SSFS following surgical resection of an arteriovenous malformation (AVM) complicated by increase in intracranial pressure (ICP) and DC due to postoperative cerebral hematoma. In the weeks following the intervention, the patient developed persistently altered neurological status (somnolence without any response and Glasgow Coma Scale (GCS) decreased form 7-9/15 to 4/15), which correlated with the findings of cerebral tomodensitometry (TDM), such as right-sided large bone defect with sub-falcorial amygdala and temporal engagement (Fig. 1). SSFS was diagnosed but cranioplasty was contraindicated because of bacterial meningitis. To improve the neurological status, we used a negative-pressure helmet and monitored the effects on the clinic, ICP, brain tissue oxygen tension, and CBF.

## CASE REPORT

A 36-year-old female patient with well-controlled high blood pressure and history of pneumothorax pleurodesis presented in early 2021 with an index seizure caused by an unknown AVM of 3.5-cm diameter in the axial plane located in the right frontal sulcus. The AVM was graded as a stage 2 according to the Spetzler-Martin classification. It was fed by the right anterior cerebral, right Sylvian, and dural (anterior meningeal, middle meningeal, and superficial temporal) arteries, and drained by three superficial frontal veins. Antiepileptic medication was introduced with no recurrence of seizures. Before surgical resection of the AVM, the patient underwent four sessions of neuroradiological embolization to limit its blood supply.

In the immediate postoperative period after the surgical resection of the AVM, no complications or neurological deficits were observed. Three days later, the GCS decreased to 8/15, and cerebral TDM was performed. The presence of a voluminous cerebral right frontal hematoma with simultaneous vasogenic cerebral edema and elevated ICP was observed, which explained the neurological impairments. Consequently, DC was performed, which was complicated by a massive perioperative hemorrhage. An external ventricular drain (EVD) was placed due to the presence of hemoventricle.

The postoperative period was further complicated by persistently raised ICP due to cerebral edema and intraventricular hemorrhage, which necessitated the placement of two new EVDs. Two weeks later, the patient presented with diffuse beta-lactamase-producing *Escherichia coli* meningitis. Meropenem and gentamycin were administered for 4 weeks followed by a combination of ceftazidime and avibactam (Zavicefta; Pfizer, New-York, NY, USA) for 3 weeks.

Two months after the resection of the AVM, the altered neurological status persisted (GCS 8-10/15) without any signs of improvement. Magnetic resonance imaging revealed the presence of a sub-falcorial amygdala and temporal engagement that were indicative of SSFS. Therefore, we attempted to reshape the skull to improve the neurological status.

Before ordering the custom-shaped helmet, we obtained a signed agreement from her legal representative in accordance with our local ethical committee. At the time of assessments, our patient was in the neuroscience intensive care unit, intubated, and non-sedated. Monitoring included oxygen monitoring, 5-lead electrocardiogram, radial invasive blood pressure and EVD that continuously measured the ICP.

We used the Luciole monitoring solution (Luciole Medical, Zurich, Switzerland) to monitor the changes in cerebral parameters. This solution includes a frontal skin patch (RheoPatch, Luciole Medical) that uses near-infrared spectroscopy (NIRS) to non-invasively estimate cerebral oxygen saturation ($SbtO_2$) and CBF. Luciole monitoring allows the use of intravenously injected indocyanine green (ICG) dye dilution to improve the accuracy CBF. Therefore, we injected ICG (15 mg) before and after the application of negative pressure to determine the changes in CBF.

During the measurements, the patient was lying supine with head tilted up at 30°. We gently applied the Lenoir Orthopédie (Daniel Robert Orthopédie, Geneva, Switzerland) negative-pressure helmet. The helmet is shaped according to the size of the

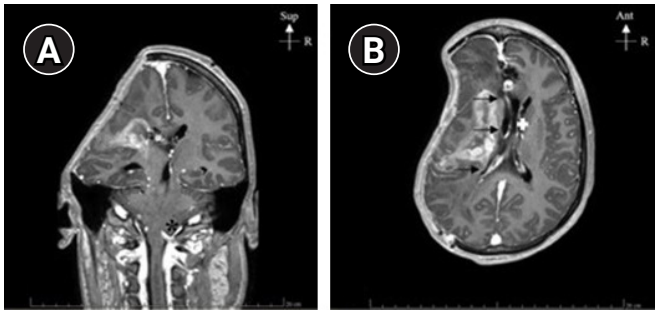


**Fig. 1.** Magnetic resonance imaging T1-weighted images showing the bone defect area of the skull of the patient. (A) Coronal T1-weighted view shows a left-sided deviation of the midline and a filling of the posterior fossa with amygdala herniation (asterisk). (B) Axial T1 view shows left-sided deviation (arrows) and shrinking of lateral ventricles (white cross). Sup, superior; R, right; Ant, anterior.

bone defect and comprises of three components (Fig. 2). The first component is a silicon layer that softly attached to the edges of the bone defect, the second component is the vacuum, and the last component is a plastic layer that is shaped in the form of the normal shape of the patient skull. A manual vacuum pump (Aircast walker like pump) was connected to act like a balloon. While pumping, progressive increase in negative pressure allows for re-expansion of the dura mater and reshaping of the skull.

Unfortunately, even after the application of the negative pressure and improvements of cerebral parameters, no clinical improvement was observed. The neurological clinical status remained unchanged (GCS score, 8/15), and no reaction to painful stimulation was observed. The long-standing increase in ICP and decrease in CBF resulted in profound cerebral and ischemic lesions that could not be reversed by our mechanical solution. Due to unfavorable outcomes and in accordance with the wishes of the patient's family, supportive therapies were discontinued.

After applying the helmet on the edges of the skull defect, we progressively decreased the pressure in the balloon according to the hemodynamic tolerance of the patient and registered the clinical parameters for 6 minutes. The heart rate, oxygen saturation (using a pulse oximeter), and mean arterial pressure did not change significantly during the procedure. The ICP significantly decreased from 6 $cmH_2O$ to –3 $cmH_2O$ with a simultaneous increase in cerebral perfusion pressure (CPP) from 62 mmHg to 73 mmHg. Indirect $SbtO_2$ and CBF parameters increased to normal values (Fig. 3). CBF increased from 50 mL/g to 65 mL/g and the cerebral saturation on the left side of the forehead of the patient increased by eight points (from 64% to 72%) (Fig. 4).

## DISCUSSION

SSFS is a rare complication of DC. However, its pathophysiological mechanism remains unclear. Some authors believe that this may be caused by the direct transmission of atmospheric pressure to the intracranial cavity, which results in a decrease in CBF in the area of bone defect. Decreased blood flow and the consequent impaired cerebral metabolism may explain the symptoms of SSFS.

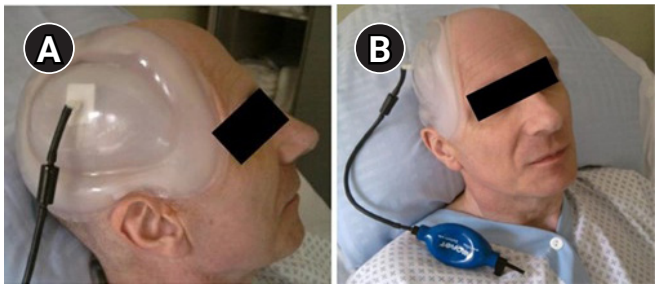


**Fig. 2.** The Lenoir Orthopédie negative-pressure helmet with a manual vacuum pump. Images obtained from Lenoir Orthopédie user manual (Lenoir Orthopédie, Daniel Robert Orthopédie, Geneva, Switzerland).

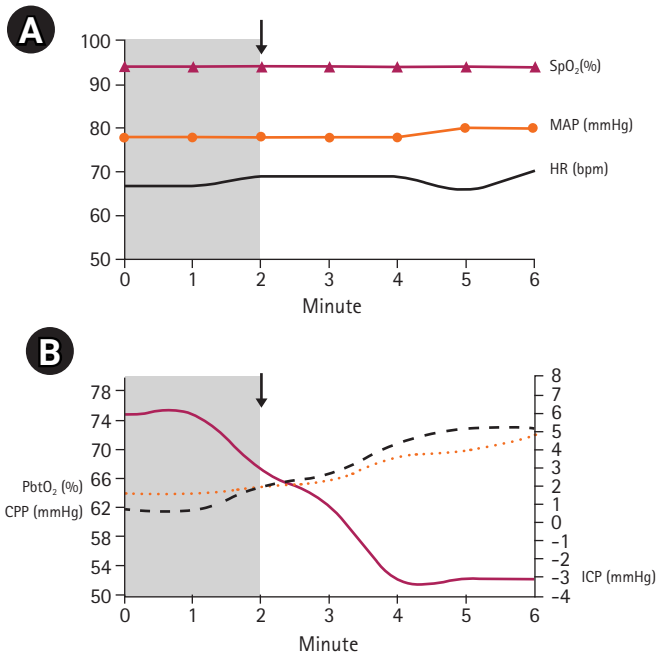


**Fig. 3.** Hemodynamic and cerebral monitoring before and after the application of negative pressure using a Lenoir Orthopédie helmet. Grey zone, the time periods before the application of the negative pressure; arrow, start application of negative pressure. The procedure was hemodynamically supported and revealed reduction of intracranial pressure (ICP) to normal values and improvements in cerebral perfusion pressure (CPP) and cerebral oxygen saturation. (A) Hemodynamic parameters before and after applying negative pressure. (B) Cerebral hemodynamic parameters before and after applying negative pressure. $SpO_2$, pulse oximeter; MAP, mean arterial pressure; HR, heart rate; $PbtO_2$, brain tissue oxygen tension.

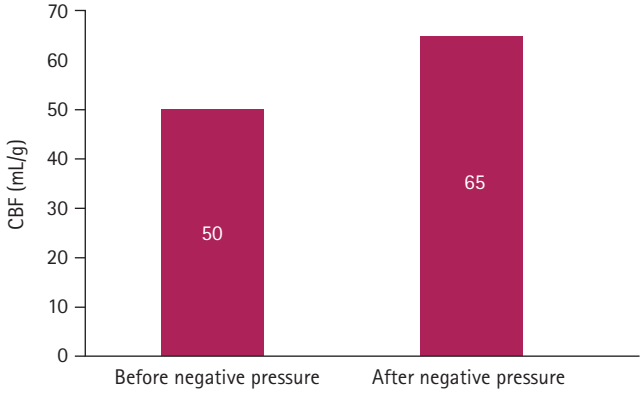


**Fig. 4.** Increase in cerebral blood flow (CBF) after applying negative pressure. The CBF increased from 50 mL/g to 65 mL/g.


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According to other authors, SSFS is a consequence of a pressure decrease in the cerebral spinal fluid (CSF) compartment, which is worsened by orthostatic changes in position [2,3,5,6]. In this case, SSFS resulted in the stretching of fiber bundles and cranial nerves owing to the direct effects of atmospheric pressure on the brain. The subsequent symptoms occur when the patient changes position from a horizontal to an upright position [10]. Cranioplasty may restore CBF by reshaping the skull and protecting from atmospheric pressure. Furthermore, improvements in CSF flow and cerebral metabolism have been elegantly demonstrated using TDM scans, TDM perfusion imaging and xenon TDM [2,3]. Improvements in CSF velocity have been reported after the closure of the bone defect. Dujovny et al. explained this modification to be a consequence of changes in the compliance of the craniospinal system [6].

In this report, we first described the correction of SSFS by applying negative pressure and measuring the direct physiological changes in CBF, ICP, and $SbtO_2$ using NIRS monitoring. Our patient could not undergo cranioplasty due to bacterial meningitis, and we used a negative-pressure helmet to treat SSFS. This system permits the reshaping of the cranial flap by creating negative pressure in the area of the bone defect. It can be used in cases of complete skull defects or the presence of a cranial flap. In the latter, the helmet must be custom-made.

In our case, when the skull was reshaped using the negative-pressure helmet, the ICP changed from a positive pressure to negative pressure of –3 $cmH_2O$. This negative pressure restored the conditions of a normally closed skull and led to decompression of the brain, which was previously subjected to direct atmospheric pressure.

The parameters of CPP and $SbtO_2$ also improved. As expected, reshaping of the skull was associated with a reduction in the ICP and subsequent improvements in CPP, CBF, and $SbtO_2$. These results correlate with the assumption that cranioplasty restores cerebral perfusion and CSF dynamics. Similar results were observed by Yoshida et al. [8] and Winkler et al. [9] who used $^{33}Xe$ computed tomography and $^{31}P$ magnetic resonance spectroscopy as well as transcranial Doppler (TCD) and positron emission tomography to assess changes in physiological parameters [8,9]. In our report, we used another bedside noninvasive method to monitor CBF using intravenous ICG and Fick's principle. This novel monitoring is presently being evaluated for this indication, but it can be a promising technique [11-13].

Nowadays, assessment of CBF using TCD is being performed when facing rapid neurological changes following extra-dural or subarachnoid hematomas or even after cerebral aneurysm rupture [14,15]. Nevertheless, studies have demonstrated a good correlation between changes in CBF using NIRS and those measured by TCD.

Cranioplasty is indicated in cases of symptomatic SSFS following DC. When facing SSFS complicated with bacterial meningitis, the use of a negative-pressure helmet appears to restore cerebral physiologic parameters and may be a helpful intervention. Using this approach, invasive and noninvasive neuromonitoring (ICP and NIRS with ICG) confirmed changes in cerebral metabolism and blood flow. Unfortunately, we observed no clinical improvement because of the profound and irreversible cerebral lesions.

## ARTICLE INFORMATION

### Ethics statement

No institutional or ethics committee approval was required for this case report. Written consent was obtained from the patient's legal representative.

### Conflict of interest

No potential conflict of interest relevant to this article.

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Conceptualization: HQ, TRN. Data curation: HQ, TRN. Formal analysis: HQ, TRN, MW. Project administration: HQ, TRN. Visualization: HQ, TRN, MW. Supervision: HQ, PB, JP. Writing–original draft: MW. Writing–review & editing: MW, TRN.

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https://doi.org/10.18700/jnc.220072

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):131-135
https://doi.org/10.18700/jnc.220078

Journal of Neurocritical Care

# Successful treatment of post–COVID-19 acute disseminated encephalomyelitis with urgent immunotherapy and neurointensive management: a case report

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CASE REPORT

Received: October 5, 2022
Revised: October 12, 2022
Accepted: October 26, 2022

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**Background:** Acute disseminated encephalomyelitis (ADEM)-like white matter disease, a rare complication of coronavirus disease 2019 (COVID-19), is a potentially life-threatening neurological disorder. The objective of this study was to report the successful treatment of post–COVID-19 ADEM with urgent immunotherapy and neurointensive management.
**Case Report:** A 53-year-old female patient was referred to our hospital with a 2-day history of progressive mental deterioration and was diagnosed with ADEM after COVID-19. The patient's symptoms worsened despite the administration of high-dose steroids, and targeted temperature management was employed to manage brain edema. Additionally, the neurointensivist decided to use intravenous immunoglobulin early for intractable post–COVID-19 ADEM. Her mental status and neuroimaging findings showed rapid improvement at about 3 months after admission.
**Conclusion:** This case highlights that if the patient's symptoms worsen despite high-dose steroid administration in the acute stage, early use of intravenous immunoglobulin is expected to have a positive effect on the prognosis of patients with post–COVID-19 ADEM.

**Keywords:** COVID-19; Encephalomyelitis; Acute disseminated encephalomyelitis; Immunotherapy; Neuroimaging

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) primarily affects the respiratory system. However, there are several cases and indications where COVID-19 infection can cause neurological complications [1-3]. It has been found that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause central nervous system (CNS) demyelination in humans and animals [4]. Neurological complications related to COVID-19 can be considered direct effects of the virus on the CNS, and are para- or postinfectious immune-mediated processes [5]. A large-scale retrospective study has recently reported that CNS complications occur in 30%–40% of the patients with COVID-19 [3,4].

Acute disseminated encephalomyelitis (ADEM) is a monophasic, postinfectious, or postvaccine acute inflammatory demyelinating disorder of the CNS [6]. It could occur several weeks after a viral infection, including COVID-19 [7]. Prepandemic ADEM is known to have good clinical outcomes and treatment responses

[8]. However, information on post–COVID-19 ADEM is limited. Clinical outcomes seem to be severe and unpredictable. Consequently, immediate initiation of immunotherapy, accompanied by proper diagnosis, is crucial in patients with post–COVID-19 ADEM [9]. Moreover, timely neurological assessment and urgent intervention are critical for preventing rapid aggravation. Herein, we describe a patient with post–COVID-19 ADEM who was successfully treated with immunotherapy and neurointensive management during the early stages of ADEM after COVID-19 infection. To the best of our knowledge, this is the first report on post–COVID-19 ADEM in Korea.

## CASE REPORT

A 53-year-old female patient with a 2-day history of progressive mental deterioration was referred to our hospital. She had been diagnosed with COVID-19 by SARS-CoV-2 polymerase chain reaction (PCR) of a nasopharyngeal swab 14 days previously. She had experienced several episodes of self-resolving low-grade fever, dry cough, sore throat, and rhinorrhea for a few days before being diagnosed with COVID-19. The patient had no previous medical illnesses. The patient started to develop unexplained drowsiness and confusion and progressed to stupor 2 days before admission. Neurological examination revealed no focal abnormalities except for decreased consciousness. The pupils were isocoric with bilateral light reflexes (+), and deep tendon reflexes were normoactive. Fundus examination results were normal. The vestibulo-ocular and corneal reflexes were also preserved. Sensory and cranial nerve examinations could not be performed due to poor patient cooperation. She was intubated and mechanical ventilation was initiated. Her initial blood pressure was 122/91 mmHg. Her pulse rate was 66 beats/min, and her temperature was 37.0°C. Chest radiograph was normal. Initial magnetic resonance imaging (MRI) was performed without gadolinium contrast on hospital day (HD) 1. It showed scattered hyperintense lesions on diffusion-weighted imaging (DWI)/apparent diffusion coefficient (ADC) map/fluid-attenuated inversion recovery (FLAIR) imaging in deep and juxtacortical white matter. FLAIR high signal intensity in both hemispheric juxtacortical white matter showed more extensive lesions than DWI (Fig. 1A). Cerebrospinal fluid (CSF) analysis revealed 9 white blood cells, 4,000 red blood cells, 90 mg/dL protein, and 66 mg/dL glucose. Bacterial, tuberculosis, and fungal cultures and PCR panels (including tuberculosis, herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, and John Cunningham virus) were all negative. Serum tests for antinuclear antibodies, antineutrophil cytoplasmic antibodies, syphilis, human immunodeficiency virus, myelin oligodendrocyte glycoprotein, and aquaporin-4 antibodies were negative or normal. The CSF venereal disease research laboratory result was negative.

Paraneoplastic autoantibodies in the serum and CSF were negative. Electroencephalography, performed on the day of admis-

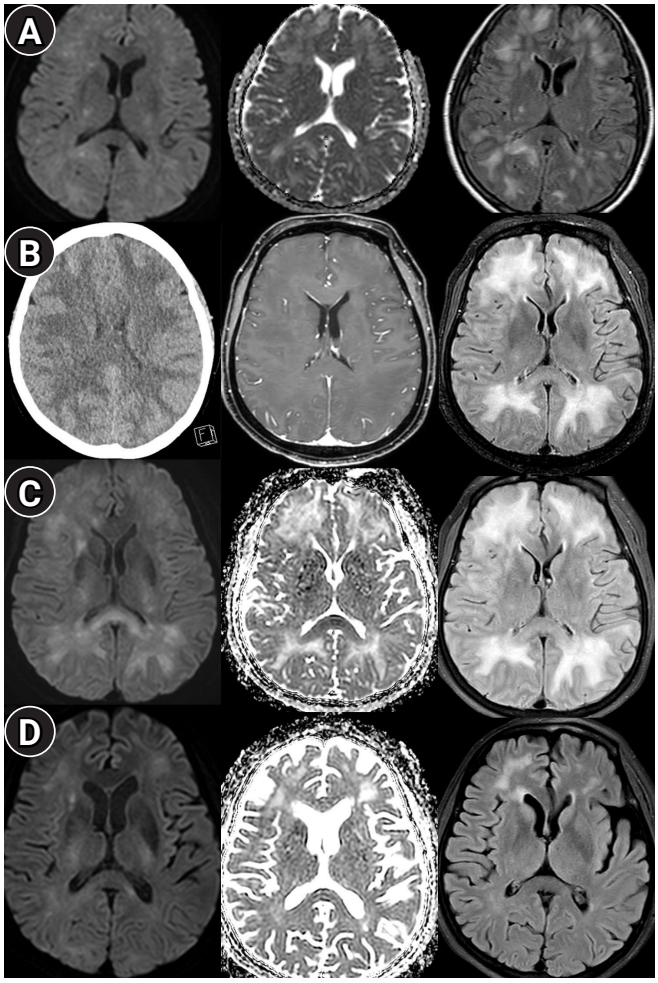


**Fig. 1.** Serial neuroimaging changes of the patient. (A) Initial magnetic resonance imaging (MRI) showing scattered hyperintense lesions on diffusion-weighted imaging (DWI)/apparent diffusion coefficient (ADC) map/fluid-attenuated inversion recovery (FLAIR) imaging in deep and juxtacortical white matter. A FLAIR high signal intensity in both hemispheric juxtacortical white matter showed more extensive lesions than DWI, suggesting edematous demyelination. (B) Neuroimaging performed during deterioration of the patient. Brain computed tomography showing marked white matter edema with sulcal effacement. There was no significant contrast uptake on T1 or FLAIR enhancement images along the edematous white matter. (C) MRI on hospital day 16 showing more progression and extension of DWI/ADC/FLAIR hyperintensities in the juxtacortical white matter. (D) The last follow-up DWI/ADC/FLAIR performed on the 39th day after admission demonstrating markedly reduced sizes of hyperintense lesions.


https://doi.org/10.18700/jnc.220078

sion, revealed diffuse cerebral dysfunction without significant epileptic discharge. The patient was immediately started on intravenous (IV) methylprednisolone 1 g daily for 5 days after admission. Three days after admission, her pupils were dilated with a decreased neurological pupil index (0.8/1.2). Brain computed tomography showed marked white matter edema with sulcal effacement. There was no significant contrast uptake on T1- or FLAIR enhancement images along the edematous white matter (Fig. 1B). To manage cerebral edema, therapeutic hypothermia was performed using a surface cooling device (Arctic Sun; Medivance, Louisville, CO, USA) at a target temperature of 36°C with emergent administration of 3% hypertonic saline and mannitol. Conscious sedation was performed during the targeted temperature management. The targeted mean arterial pressure was >60 mmHg to maintain the cerebral perfusion pressure. The neurointensivist decided to additionally administer IV immunoglobulin at 0.4 mg/kg daily for 5 days. On HD 12, a follow-up brain MRI was performed. Scattered lesions showed high signal intensity on DWI with slightly restricted diffusion on the ADC, which is inconsistent with ischemic stroke. FLAIR imaging revealed progressive multiple asymmetric hyperintense lesions involving extensive subcortical white matter. On HD 16, the patient was extubated after confirming that the mental status had markedly improved. However, repeat MRI of the brain on HD 16 showed increased progression and extension of DWI/ADC/FLAIR hyperintensities in the juxtacortical white matter (Fig. 1C). The last follow-up DWI/ADC/FLAIR performed on the 39th day after admission demonstrated markedly reduced sizes of the hyperintense lesions (Fig. 1D). Although she showed significant cognitive decline after the illness, independent daily life was possible at about 3 months after admission.

## DISSCUSSION

Few reports of post–COVID-19 ADEM have been published [7,9,10]. Our case fulfilled the 2012 revised criteria for ADEM: (1) the first clinical event with a presumed inflammatory cerebral demyelinating cause, (2) typical MRI features of ADEM during the acute phase, and (3) exclusion of other possible causes [11]. Also, our patient developed ADEM at 14 days after the confirmed diagnosis of COVID-19. This temporal relationship supports the diagnosis of post–COVID-19 ADEM. The clinical characteristics of post–COVID-19 ADEM reported that the duration from confirmed COVID-19 infection to the development of ADEM was mostly within 15–30 days. The majority of neurologic manifestations demonstrate subacute progression (between 24 hours and 10 days) of the illness. Initial neurological manifestations showed that progressive encephalopathy was the most common clinical symptom [9].

There are diverse mechanisms for neurologic complications of post–COVID-19 infection, including direct neuroinvasion of the CNS, peripheral nervous system, or muscles and immune response following an infectious trigger [1,10]. ADEM is usually considered a postinfectious immune-mediated disorder [6]. A viral infection, such as COVID-19, can result in nervous tissue damage, which can cause segregated antigens to leak into the systemic circulation through an inflamed blood-brain barrier [6,12]. Structural similarity between viral pathogen and myelin proteins of the patient can also provoke B- and T-cells, which are activated during an immune response to infection [1]. They can enter the CNS and react with the presumed viral antigen presented by the homolog myelin protein.

The post–COVID-19 ADEM should be distinguished from COVID-19 encephalitis and acute autoimmune encephalitis associated with COVID-19. COVID-19 encephalitis occurs as a result of direct infection of the brain parenchyma by the SARS-CoV-2. It is generally infected as part of systemic COVID-19, and additional signs and symptoms of other organ involvement might be present [13]. However, having common clinical features and etiologic pathomechanism with post–COVID-19 infection, the differential diagnosis is not always straightforward. Nevertheless, the most discriminative feature of post–COVID-19 ADEM compared to encephalitis seems to be the neuroimaging pattern. Post–COVID-19 ADEM involves a brief but intense inflammatory attack (swelling) in the brain that damages myelin. Thus, post–COVID-19 ADEM predominantly affects the white matter of the brain, manifesting as an acute-onset encephalopathy associated with multifocal neurologic deficits [7]. Neuroimaging patterns of COVID-19 encephalitis show one or more diffuse areas of high intensity, affecting the cortical gray matter and subjacent white matter. Sometimes, the gray matter of the basal ganglia or brainstem might be involved, which is a very different pattern from that seen in post–COVID-19 ADEM [14]. CSF analysis of post–COVID-19 ADEM usually shows features indistinguishable from that of COVID-19 encephalitis (i.e., lymphocytic pleocytosis, elevated protein levels, normal glucose, and negative cultures) [6]. Unlike the usual encephalitis, a viral culture or the PCR exam of pathogens is negative.

Although post–COVID-19 ADEM rarely occurs, its prognosis is very poor. Approximately 60% of the patients need ventilator care in the intensive care unit [3,4], and approximately 30% of the patients die during follow-up. Post–COVID-19 ADEM occurs mainly in adults, whereas prepandemic ADEM is more common in children with a good prognosis (mortality rates of 1%–3%)

[8,15]. Therefore, determining when and which treatment regimen to use is more important in post–COVID-19 ADEM than in prepandemic ADEM. The rarity of post–COVID-19 ADEM may render the diagnosis difficult, leading to diagnostic delays or misdiagnosis. This can also lead to missed opportunities for early immunotherapy in post–COVID-19 ADEM. Therefore, collecting these cases could facilitate the diagnosis of post–COVID-19 ADEM and improve patient prognosis. Moreover, there are no reports of post–COVID-19 ADEM in Korea. Our patient showed severe neurological deficits and progressive diffuse white matter demyelination at an early stage. Timely initiation of immunotherapy including IV corticosteroids plus immunoglobulin with appropriate neurointensive management of brain edema clearly improved the patient's prognosis.

As in our patient, if the patient's symptoms worsen despite the administration of high-dose steroids, early use of IV immunoglobulin is expected to have a beneficial effect on the patient's prognosis. Additional studies are needed to decipher the mechanisms of massive white matter demyelination in patients with post–COVID-19 ADEM.

## ARTICLE INFORMATION

### Ethics statement

Ethics approval of Institutional Review Board of Jeju National University Hospital (No. JEJUNUH 2022-07-005) was granted in accordance with the national requirements, and the need for written informed consent was waived.

### Conflict of interest

No potential conflict of interest relevant to this article.

### Acknowledgments

This work was supported by the 2022 Education, Research, and Student Guidance Grant funded by Jeju National University.

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Conceptualization: JSL. Data curation: JSL, JGK. Formal analysis: HJK, JGK. Funding acquisition: JSL. Methodology: JSL. Project administration: JGK. Visualization: JGK, HJK. Writing–original draft: JSL, JGK. Writing–review & editing: all authors.

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pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):136-140
https://doi.org/10.18700/jnc.220066

Journal of Neurocritical Care

# Fixed and dilated pupils by pupillometer in lateralized periodic discharges: a case report in the neurocritical care unit

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CASE REPORT

Received: July 8, 2022
Revised: September 10, 2022
Accepted: September 30, 2022

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**Background:** Fixed and dilated pupils (FDPs) have become synonymous with devastating neurological damage and brainstem injury commonly associated with mass effect and herniation. Infrequently, changes in pupillary light response have been described with seizures; however, the loss of pupillary response with documented Neurological Pupil index has not been well established in patients with seizures.
**Case Report:** We present a case report describing a middle-aged female patient with focal status epilepticus with intermittent FDPs. An abnormal pupillary response occurred with right hemispheric lateralized periodic discharges and resolution with anti-seizure medication escalation. To our knowledge, this is the first description of objective documentation of reversible FDP as a possible clinical correlate of lateralized periodic discharges.
**Conclusion:** The use of handheld automated pupillometry in conjunction with electroencephalogram (EEG) has provided the therapeutic direction. Further research is warranted to fully describe the mechanistic underpinnings of these observations.

**Keywords:** Seizure; Epilepsy; Eye; Pupils; Autonomic; Critical

## INTRODUCTION

Pupillary size and light response are valuable components of neurological examination, especially in the care of critically ill patients when pupillary size and reactivity to light may provide an objective finding of neurological changes. Abnormal pupillary response to light, based on reactivity or pupil size and asymmetry, can be seen in a variety of conditions, ranging from benign or congenital conditions to a life-threating intracranial process [1]. Fixed and dilated pupils (FDPs) are commonly associated with mass effect in several conditions (vascular, neoplastic, demyelinating, or inflammatory), leading to damage in the midbrain, oculomotor nuclei, or efferent fiber pathways [2]. Alterations in pupillary light response have been described with seizures [1,3]; however, the loss of pupillary response and pathophysiologic mechanism remains unknown in this population. Furthermore, reports of pupillary changes during seizures are often singular events without objective data. We describe a patient with focal status epilepticus with FDPs documented by Neurological Pupil index (NPi) and interpret a possible pathophysiologic correlate on continuous

electroencephalogram (cEEG).

## CASE REPORT

A right-handed female patient in her late 50s with human immunodeficiency virus (HIV) complicated by recurrent cryptococcal meningitis and seizures was admitted to the neurosciences critical care unit after presenting with bilateral tonic-clonic seizure evolving into focal motor status epilepticus with impaired awareness and left-hand twitching. The patient was compliant with her home regimen of levetiracetam and antiretroviral therapy for HIV. On arrival, she was afebrile, hemodynamically stable, unable to follow instructions, and had notable left-sided hemiparesis.

She was initially treated with lorazepam and lacosamide with resolution of movements; however, persistent tactile stimulation was required to maintain arousal. Ultimately, the patient was intubated to protect the airway. cEEG was started and showed focal slowing over the right parietotemporal region, without clinical events. Over the course of several days, the patient exhibited intermittent left forehead, cheek, and thumb twitching. On cEEG, these movements corresponded with right hemispheric lateralized rhythmic delta activity with sharp waves at 1.5–2 Hz with frequent evolution into well-formed seizures, meeting the criteria for electroclinical status epilepticus (occupying >20% of a 60-minute EEG period) [4]. Anti-seizure regimen was escalated to valproic acid, levetiracetam, lacosamide, briefly perampanel, and ultimately midazolam and ketamine infusion. The electroclinical motor seizures were controlled with anti-seizure medications; however, EEG continued to be highly epileptiform with near continuous right hemispheric lateralized periodic discharges (LPDs) with sharp wave morphology, occurring at approximately 0.7–1.0 Hz.

Brain magnetic resonance imaging showed cortical restricted diffusion in the right parietal, temporal, and occipital lobes, as well as bilateral temporal lobe encephaloceles with associated encephalomalacia without evidence of a midbrain lesion or effacement of the peri-mesencephalic cisterns. Two lumbar punctures were performed over the course of 1 week given her history of recurrent cryptococcal infections and potential elevated intracranial pressure (ICP) driving her focal seizure activity. The cerebrospinal fluid had a white blood cell count of <3 cells/μL, an red blood cell count of <1 cell/μL, glucose levels of 53 and 79 mg/dL, and protein levels of 23 and 28 mg/dL. The opening pressure was 18 $cmH_2O$.

On hospital day 9, the patient had new FDPs documented by NPi using a NeurOptics NPi-200 pupillometer (Neuroptics Inc., Irvine, CA, USA). Computed tomography (CT) head imaging showed no signs of herniation, and CT perfusion was most consistent with hyper-perfusion in the right temporal and occipital lobes concerning focal status epilepticus (Fig. 1) [5]. EEG monitoring showed continuous right hemispheric LPDs (Fig. 2). Four hours after her initial imaging, she once again developed FDP on examination, and a repeat head CT showed no change.

Without imaging evidence of ICP increase or mass effect, management was focused on the treatment of focal status epilepticus rather than cerebral herniation. The patient's pupils were reactive following the administration of a midazolam bolus. Anesthetics were escalated to achieve burst suppression EEG along with escalating anti-seizure medications. She exhibited an abnormal pupillary light response 12 additional times over 4 days (Supplementa-

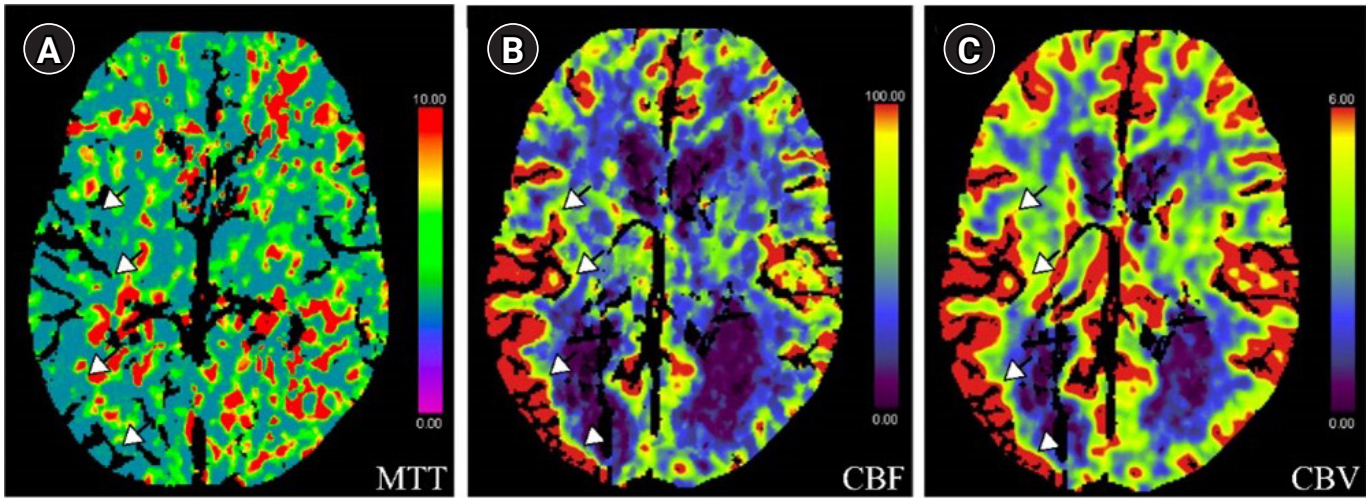


**Fig. 1.** Computed tomography perfusion imaging. (A) Mean transit time (MTT), (B) cerebral blood flow (CBF), (C) cerebral blood volume (CBV), consistent with hyper-perfusion in the right temporal and occipital lobes (arrows).

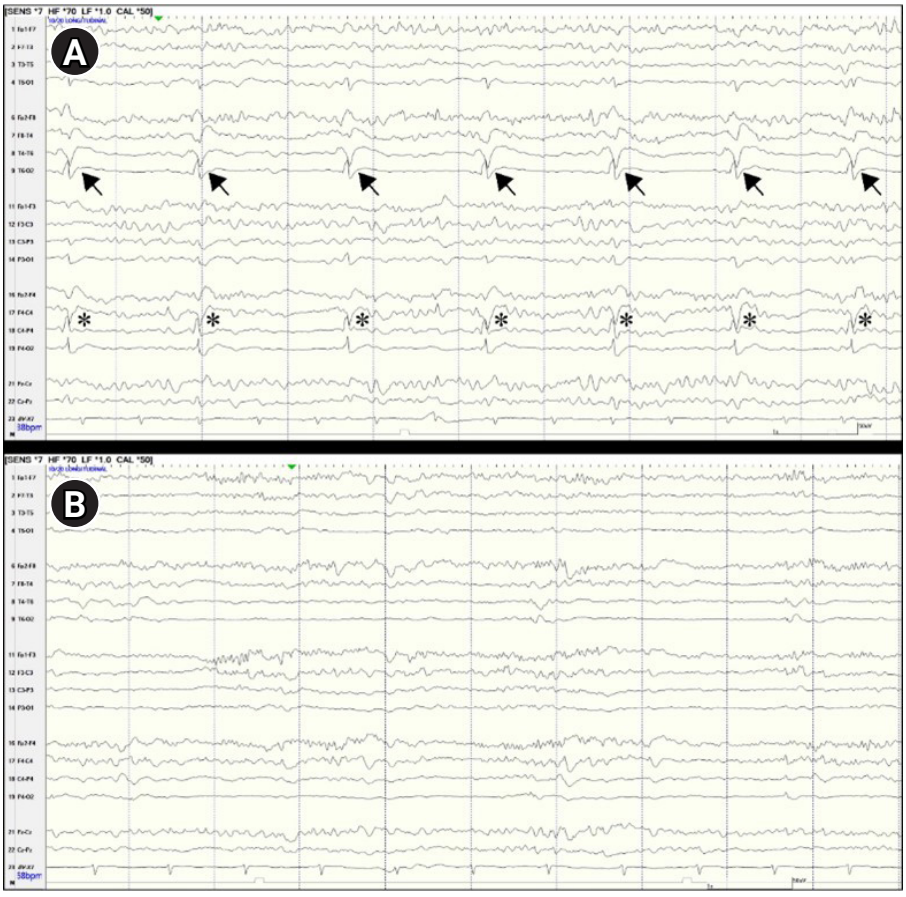


**Fig. 2.** Screenshot of a 10-second clip of an electroencephalogram in bipolar montage displaying, (A) continuous right hemispheric lateralized periodic discharges with sharp wave morphology, occurring at approximately 0.7–0.8 Hz, noted by an arrow and asterisk, coinciding with fixed and dilated pupil (FDP). (B) Ten-second clip of an electroencephalogram following the administration of a 5-mg midazolam bolus with appearing transient improvement of lateralized periodic discharges and resolution of FDP.

ry Table 1). More often, she exhibited bilateral pupil dilation (9/12, 75%) with a single event of brisk left pupil and fixed right pupil (approximately 2.3-mm size bilateral) and single event of fixed, dilated left pupil and sluggish right pupil (left pupil dilated approximately 6 mm and right approximately 3 mm). As anticonvulsants were adjusted and a ketogenic diet was initiated, the associated LPDs decreased over the following days with resolution of pupil abnormalities throughout the subsequent 10-week hospital course. Her mental status improved moderately following simple instructions by family members. She underwent tracheostomy and was discharged with close support from her family and therapy teams.

## DISCUSSION

The patient displayed FDP on pupillometry, which coincided with the clinical and electrographic occurrence of focal motor status epilepticus and without evidence of third nerve compression in relation to cerebral herniation syndrome. Conversely, FDP using pupillometry resolved the anesthetic escalation and resolution of the right LPDs. Together, these observations suggest a direct relationship between FDP and focal seizures.

Pupil alterations during seizures were described as early as 1881 by Sir William Richard Gowers [1]. He noted during the course of a generalized tonic-clonic seizure brief episodes of bilateral pupillary miosis during the tonic phase and bilateral pupil mydriasis during the clonic phase. Other studies have reported similar findings of FDP with absence seizures, which were associated with other autonomic symptoms, such as facial flushing, followed by a perceived postictal pupillary miosis [3]. In a case series of medial temporal lobe epilepsy, 42 of 66 patients who underwent depth EEG for surgical planning had dilated and unreactive pupils to light early in the course of a seizure [6]. Although the seizure type, localization, and EEG data were not described in a previous study, the FDP appeared to correspond with the onset of impaired awareness. The authors [6] suggest that seizure spread through-


https://doi.org/10.18700/jnc.220066

out subcortical midline structures plays a pathophysiologic role in the abnormal pupillary response. Still, cases describing pupillary changes during seizures appear sparse, with less information regarding lateralization, localization, or significance.

Several case reports have discussed lateralization of unilateral mydriasis during several seizure types, termed ictal mydriasis, which is most often focal and associated with conjugate gaze deviation [7,8]. In these limited reports, lateralization of pupil dilation is correlated with frontal (contralateral mydriasis) or occipitotemporal (ipsilateral mydriasis) focus localization, albeit with a few exceptions. Studies in macaques and human models have noted a similar association between cortical stimulation and the lateralization of the dilated pupil [9].

Automated pupillometry is a noninvasive, portable diagnostic technique that provides a standardized quantitative assessment of the patient's pupils and their pupillary light reflex. These devices generate a standardized light stimulus using an infrared light-emitting diode and capture pupil images before, during, and after the stimulus. These images are then immediately processed to obtain a series of standardized and metric data. Proprietary device-specific metrics include the commonly used and studied NPi, ranging from 0 to 5, with 0 being nonreactive, 5 being fully reactive, and NPi of < 3 generally considered to be less than the normal limits.

Changes in pupil size, shape, and light reflex are traditionally interpreted as markers of elevated ICP and cerebral herniation [10]. The initial concern for brain herniation syndrome, typically uncal herniation, presents with asymmetric pupillary changes, the earliest sign being sluggishly reactive to light, which progresses to dilated and nonreactive to light. Most often, supratentorial mass lesions, such as acute hemorrhage, produce downward compression of the superolateral aspect of the ipsilateral oculomotor nerve or, occasionally, contralateral oculomotor nerve compression [2]. Automated pupillometry is thought to be a more reliable method for assessing these changes. Changes in NPi have been shown to be correlated with the earlier detection of ICP changes, CT evidence of midline shift and cisternal effacement in stroke, and cerebral herniation [10,11]. However, pupillary changes can be associated with any condition that disturbs the balance of autonomic control that regulates pupillary size/shape and not just changes in ICP [12]. Medications such as barbiturates can alter the pupillary light reflex and can present with a nonreactive pupil [13]. Lastly, NPi and differences in NPi between the left and right pupils have been found to be predictive of the occurrence and resolution of nonconvulsive status epilepticus [14].

In our patient, EEG showed LPDs with sharp wave morphology over the right parietotemporal region, occurring 0.7–1.0 Hz in FDP (Fig. 2A). LPDs are defined as "repetition of a waveform with a relatively uniform morphology and duration, with a quantifiable inter-discharge interval between consecutive waveforms, and recurrence of the waveform at nearly regular intervals, occurring for at least six cycles [4]." Although there is a consensus definition and agreement regarding LPDs, they represent a diverse EEG pattern with variable clinical and prognostic connotations [15] and can represent either an ictal or interictal state. In our case, LPDs appeared to be associated with increased blood flow to the corresponding area on perfusion imaging and pupillary abnormalities (electroclinical seizure), suggesting an ictal state.

Our study, as a single case within our academic neurosciences critical care unit, has limited generalizability but presents direct and quantified evidence for the association. However, this observation requires further validation in a cohort of patients.

To our knowledge, this is the first description of objective documentation of symmetric FDP by pupillometry as a manifestation of LPDs in a critically ill patient with return of the pupillary light reflex after management with anti-seizure medications. FDPs may be a clinical manifestation of LPDs. The use of handheld automated pupillometry within the neurocritical care unit, in conjunction with cEEG, provided the therapeutic direction. Further research is warranted to fully describe the mechanistic underpinnings of these observations.

## ARTICLE INFORMATION

### Ethics statement

Approval for this study was waived in accordance with policies of our institution because this study did not include protected health information, data analysis, or testing of a hypothesis, and was de-identified. The requirement for informed consent was waived.

### Conflict of interest

No potential conflict of interest relevant to this article.

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Conceptualization: CTP, RGG. Data curation: all authors. Methodology: all authors. Project administration: all authors. Visualization: CTP, KSH. Writing–original draft: all authors. Writing–review & editing: all authors.

**Supplementary materials**

Supplementary materials can be found via https://doi.org/10.18700/jnc.220066.

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https://doi.org/10.18700/jnc.220066

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):141-145
https://doi.org/10.18700/jnc.220059

Journal of Neurocritical Care

# Cerebral hyperperfusion syndrome after endovascular stent graft reconstruction for postirradiated carotid blowout syndrome: a case report

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CASE REPORT

Received: May 13, 2022
Revised: May 27, 2022
Accepted: June 30, 2022

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**Background:** Cerebral hyperperfusion syndrome (CHS) is a failure of autoregulation after a revascularization procedure. It has rarely been reported in patients with no pre-existing cerebral hypoperfusion.
**Case Report:** We present a rare case of a patient who underwent stent graft implantation to treat postirradiated carotid blowout syndrome. The patient developed hypertension, focal neurological deficit, and seizures after the procedure; neuroimages revealed ipsilateral cerebral edema, swelling, and increased cerebral perfusion. CHS was diagnosed based on clinical and radiological findings. The patient recovered gradually after receiving supportive care.
**Conclusion:** Owing to the risk of CHS, monitoring for cerebral perfusion and prevention of hypertension is suggested for patients who undergo stent graft placement for postirradiated carotid blowout syndrome.

**Keywords:** Cerebrovascular circulation; Stents; Hypertension; Case report

## INTRODUCTION

Cerebral hyperperfusion syndrome (CHS) is an uncommon complication experienced by patients who have undergone revascularization for neurovascular disorders. CHS is most often reported in patients who have undergone carotid endarterectomy or carotid artery stenting, although it has also been reported in patients who have undergone other intracranial procedures [1]. Impaired cerebral autoregulation due to long-standing chronic ischemia is the most commonly reported mechanism underlying this condition. The occurrence of CHS in patients without an underlying chronic neurovascular steno-occlusive disease has rarely been reported. We report a case of CHS after endovascular stent grafting of the extracranial carotid artery for postirradiated carotid blowout syndrome (CBS).

## CASE REPORT

A 66-year-old male patient presented with bloody discharge from a left neck wound for 3 days. The patient had a history of nasopharyngeal cancer diagnosed 16 years prior and had received concurrent chemoradiotherapy and left neck dissection for the initial

and recurrent disease. The patient's neck was heavily treated. He received 70 Gy in the left upper neck, 50 Gy in the right upper neck, and 116 Gy in the bilateral lower neck. Neoplastic disease was reported to be stable for the preceding 11 years. However, extensive radiation necrosis of the neck soft tissue occurred 6 years prior to the patient's presentation at our clinic. Twelve months before presentation, the patient underwent total laryngectomy, esophagectomy, C6 vertebral corpectomy, and pectoralis major myocutaneous flap reconstruction owing to pharyngocutaneous fistula and deep neck infection. Poor healing and infection of the patient's chronic neck wound developed several times thereafter. The patient was admitted to our hospital for antibiotic therapy.

Sudden-onset massive left neck wound bleeding occurred 3 days after admission. An otolaryngologist on duty immediately applied epinephrine gauze packing to the wound. On examination, high blood pressure (212/130 mmHg) was noted. Emergency computed tomography angiography (CTA) revealed a pseudoaneurysm in the left distal common carotid artery (Fig. 1). No obvious stenosis was observed in the left extracranial carotid or cerebral arteries. Endovascular treatment with a stent graft (8 mm × 10 cm) from the internal carotid artery to the common carotid artery (VIABAHN Endoprosthesis; Gore & Associates, Flagstaff, AZ, USA), along with external carotid artery coil embolization, was performed immediately after CTA (Fig. 2). The procedures were performed under local anesthesia. No further angioplasty was performed, and no antiplatelet agents were prescribed before or immediately after the procedure. Neck bleeding subsided thereafter. Eleven hours after stent graft implantation, the patient exhibited right-hand clonic movement and right-leg clenching toes, followed by two episodes of tonic-clonic convulsive seizures. The patient's blood pressure was 151/103 mmHg. Consciousness disturbance (Glasgow coma scale E3M4V2 status) was noted after seizures. Non-contrast computed tomography (CT) revealed left-hemispheric cortical swelling (Fig. 3A). CT perfusion showed elevated cerebral blood flow and cerebral blood volume in the left cerebral hemisphere compared to that in the right hemisphere (Fig. 3B and C). The stent graft was patent, and no intracranial large-vessel occlusion was observed. Levetiracetam (300 mg) was administered intravenously. The patient's systolic blood pressure was maintained at < 140 mmHg. In the following 2 days, his consciousness level recovered to the baseline condition. Magnetic resonance imaging (MRI) revealed left frontal and parietal subcortical white matter with abnormal hyperintense signals on fluid-attenuated inversion recovery/T2-weighted images (Fig. 3D) 6 days post-seizure activity. No abnormal hyperintense signals were observed on diffusion-weighted imaging (Fig. 3E).

## DISCUSSION

CBS is a life-threatening condition requiring emergency management [2]. Endovascular treatment, including both destructive and reconstructive methods, is the current mainstay of CBS treatment [3]. Destructive methods, namely those causing damage to the in-

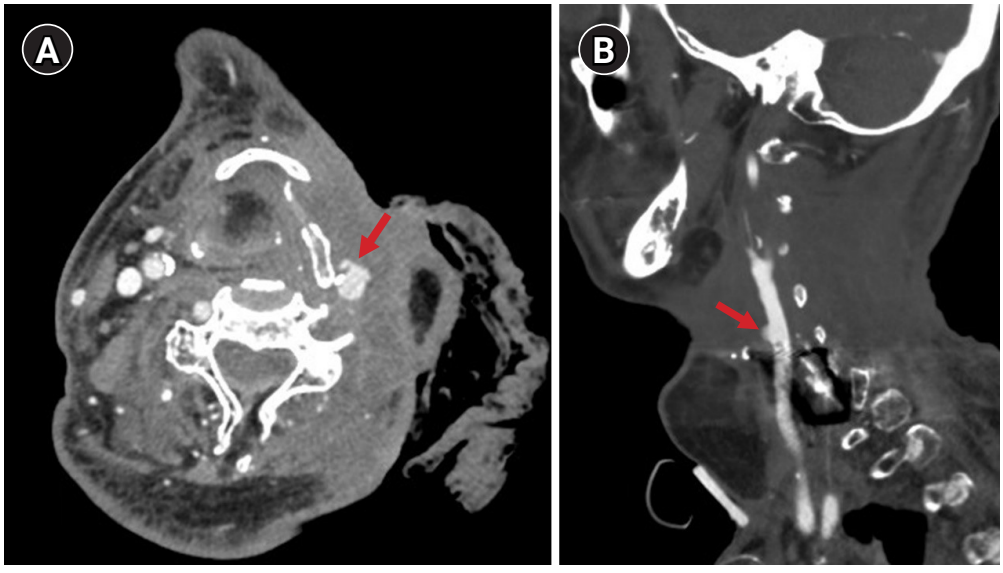


**Fig. 1.** Left carotid blowout syndrome diagnosed using preoperative computed tomography angiography. (A) Axial computed tomography (CT) revealing irregular focal protrusion of the left common carotid artery (arrow). (B) Sagittal reformatted CT depicting the location of a pseudoaneurysm (arrow) in relation to the surrounding free flap. No obvious stenosis noted in the carotid artery.


https://doi.org/10.18700/jnc.220059

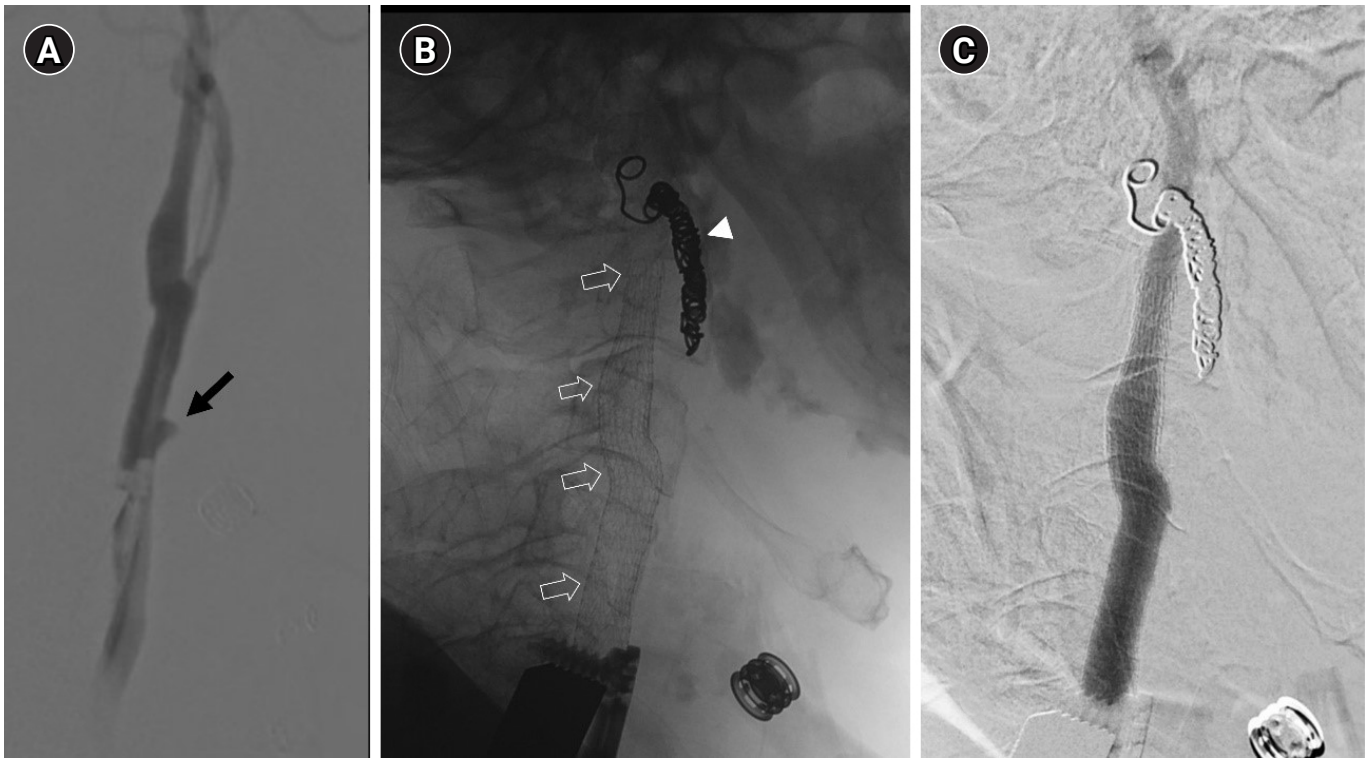


**Fig. 2.** Endovascular treatment for carotid blowout syndrome. (A) Lateral view of the left common carotid revealing a pseudoaneurysm of the left distal common carotid artery (black arrow) corresponding to the computed tomography angiography finding. (B, C) After placement of a stent graft (white arrows) and coils (white arrowhead), the pseudoaneurysm was obliterated. The diameter of the carotid artery did not change considerably after the procedure.

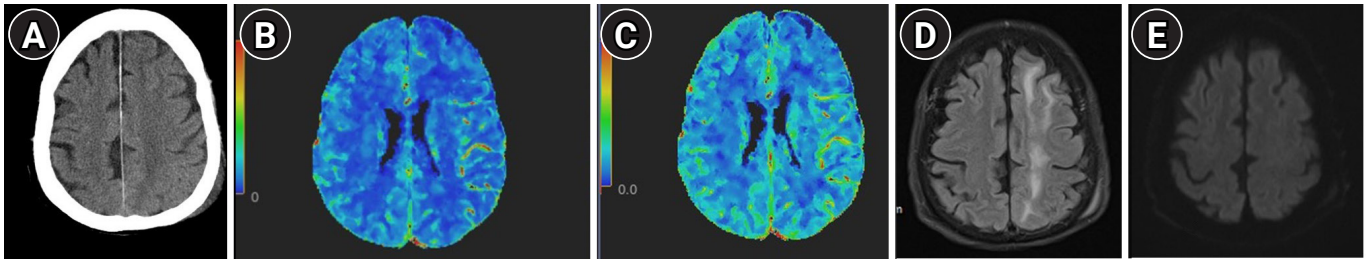


**Fig. 3.** Postoperative neuroimaging findings. (A) Non-contrast computed tomography (CT) revealing substantial sulcal effacement at the left frontoparietal lobe, suggestive of cerebral swelling. No frank hypodensity or hemorrhage is observed. (B, C) CT perfusion revealing elevated cerebral blood flow (B) and cerebral blood volume (C) of the left posterior frontal and parietal lobe, and CT angiography revealing dilatation of the left convexity leptomeningeal arteries compared to those in the contralateral right hemisphere. (D, E) Magnetic resonance imaging revealed subcortical hyperintensity on the fluid-attenuated inversion recovery image but not on the diffusion-weighted image, suggestive of vasogenic edema.

volved perforated carotid artery, are typically more secure than reconstructive methods but are associated with a higher risk of immediate postoperative ischemic stroke. Employing reconstructive methods involving stent graft exclusion from the ruptured site is an alternative approach to achieving short-term hemostasis. Reported stent graft complications include recurrent hemorrhage, thromboembolism, and brain abscesses [4]. One major concern of the immediate post-procedural period is thromboembolic risk, especially when antiplatelet therapy is not administered in hemorrhagic conditions. Standard post-procedural care usually includes monitoring for these complications, prudent hydration, avoidance of hypotension, and antibiotic use. In patients with CBS, stent grafts are usually deployed in vessels without underlying stenosis, while angioplasty is reserved for endoleaks. Therefore, in addition to neurological examination, cerebral perfusion is not routinely monitored. Nevertheless, the patients' presentation quickly raises

suspicions of CHS, considering their temporal relation to stent graft implantation.

Conceptually, the diagnosis of CHS is based on elevation of cerebral blood flow in the affected territory. CHS is commonly diagnosed based on clinical and radiological features because there is no consensus on the diagnostic criteria for CHS [1]. Headache, elevated blood pressure, seizure, and focal neurological signs are characteristic findings of anterior circulation CHS, which our patient experienced. In addition, immediate CTA revealed leptomeningeal arterial dilatation, and subsequent MRI revealed subcortical white matter edema without frank infarction. At the time of diagnosis, our patient's presentation was consistent with the clinical features of CHS, and other differential diagnoses were excluded. After supportive care, including antihypertensive control, the patient gradually recovered from neurological symptoms.

Although impaired cerebral autoregulation is the mechanism most commonly presumed to underlie the pathophysiology of CHS, other theories have been proposed. Injury from free radicals, baroreflex breakdown, and abnormal trigeminovascular reflux may also play a role in the development of CHS [5-7]. Previous literature has suggested that baroreflex failure can result from irradiation [8]. In our study, because the patient might have experienced irradiation-associated baroreflex failure, the adaptation to the radial force of the stent graft might have been impaired. During and after the procedure, we did not observe overt hypotension or bradycardia, which commonly occur in patients who have undergone carotid artery stenting. Paradoxically, the patient's blood pressure persistently increased after the procedure. There have been case reports of CHS without pre-existing significant stenosis in patients undergoing aneurysm coiling [9]. Hirai et al. [10] reported a case of CHS after carotid stent grafting for a giant extracranial internal carotid artery aneurysm. They performed spectrophotometric measurements during the procedure and used CT perfusion to monitor the patient's cerebral perfusion status postoperatively. However, preoperative ipsilateral cerebral hypoperfusion was observed, suggesting the need for an aggressive surveillance strategy. Hence, this case report suggests that CHS can develop in patients with radiation-associated carotid disease but without critical stenosis.

CHS can occur after stent graft placement in the postirradiated neck without luminal stenosis. Practitioners must be familiar with the presentation and diagnosis of CHS and should carefully monitor the cerebral perfusion and systemic blood pressure of patients with this condition.

## ARTICLE INFORMATION

### Ethics statement

This study was approved by the Research Ethics Committee of the National Taiwan University Hospital (No. RIND9561703046). The requirement for written informed consent was waived.

### Conflict of interest

No potential conflict of interest relevant to this article.

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https://doi.org/10.18700/jnc.220059

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pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):146-147
https://doi.org/10.18700/jnc.220080

Journal of Neurocritical Care

# Axitinib-induced posterior reversible encephalopathy syndrome in a patient with renal cell carcinoma

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IMAGES IN NEUROCRITICAL CARE

Received: October 18, 2022
Revised: November 17, 2022
Accepted: November 21, 2022

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A 51-year-old male patient presented with a generalized tonic-clonic type seizure. He had a history of renal cell carcinoma and had received axitinib 2 weeks before this seizure event due to the unresponsiveness to the previous chemotherapeutics. He did not experience any neurologic symptoms previously. His vital rhythm showed elevated blood pressure and tachycardia. He became deeply drowsy soon after the seizure attack, with no definite lateralizing or localizing signs.

Electroencephalogram showed no epileptiform discharges. Magnetic resonance imaging revealed extensive increased signal changes in the bilateral hemispheres and cerebellum, suggestive of posterior reversible encephalopathy syndrome (PRES) (Fig. 1). Axitinib was withdrawn and antiseizure medication was given. His mental status did not recover after that, possibly because of the extensive parenchymal lesions and aggravating medical condition. The patient expired 9 days later due to tumor progression

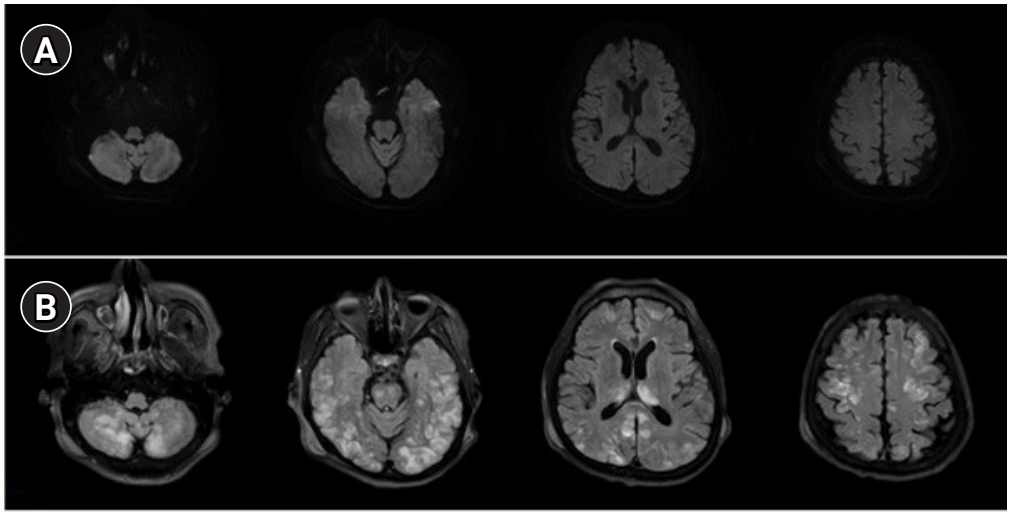


**Fig. 1.** Brain magnetic resonance imaging scans performed 2 hours after the seizure. (A) Diffusion-weighted images did not show any remarkable findings. (B) Fluid-attenuated inversion recovery images showed extensive multifocal high signal change at bilateral cerebral cortex, subcortical white matter, bilateral medial thalamus, pons and cerebellum.

and complications including aspiration pneumonia and acute kidney injury.

Anti-vascular endothelial growth factor (VEGF)-targeted compounds including axitinib are reported to be associated with PRES [1-3]. Administration of anti-VEGF agents is commonly complicated by hypertension, which may lead to neuro-vascular toxicities resulting in PRES [2,3]. This first-reported case of axitinib-induced PRES in Korea indicates that physicians should be aware of the possible neurologic complications of certain chemotherapeutic agents.

## ARTICLE INFORMATION

### Ethics statement

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

### Conflict of interest

No potential conflict of interest relevant to this article.

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pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):148-149
https://doi.org/10.18700/jnc.220081

Journal of Neurocritical Care

IMAGES IN NEUROCRITICAL CARE

# Longitudinal extensive transverse myelitis after COVID-19 vaccination (Spikevax mRNA-1273, Moderna) in a patient with rheumatoid arthritis

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Received: October 21, 2022
Revised: November 7, 2022
Accepted: November 8, 2022

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A 45-year-old male patient with rheumatoid arthritis visited the emergency department complaining of fever and urinary retention, which began 15 days after receiving his first dose of coronavirus disease 2019 (COVID-19) vaccination. He was treated with methotrexate 15 mg/week, hydroxychloroquine 200 mg/day, and sulfasalazine 1,000 mg/day. Neurological examination revealed bilateral leg weakness (Medical Research Council grade 3) and hypoesthesia below T11 dermatome. Spinal cord magnetic resonance imaging (MRI) showed high signal intensity lesions extending from medulla to L2 level (Fig. 1A). Cerebrospinal fluid (CSF) results were as follows: white blood cell 38/mm$^3$, red blood cell 4/mm$^3$, protein 123 mg/dL, and glucose CSF/serum 64/168 mg/dL. The CSF bacterial and virology, serum anti-myelin oligodendrocyte glycoprotein antibodies, anti-aquaporin receptor-4 antibodies, oligoclonal bands, and immunoglobulin G index were all negative. Acute transverse myelitis (ATM) was suspected, and intravenous methylprednisolone was administered for 5 days (1 g/day) followed by 21 days tapering course of oral prednisolone starting at 60 mg daily. Neurologic symptoms gradually improved 4 days after steroid administration and MRI repeated after 14 days of admission showed interval improvement (Fig. 1B). After 6 months, the patient was able to walk without assistance with mild hypoesthesia of both feet. There have been many reports of extensive ATM after different vaccinations [1]. Although previous reports showed focal ATM after administration of the Spikevax mRNA-1273 vaccine [2], our patient showed longitudinal extensive ATM with brainstem involvement. Autoimmune reactions between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein and tissue protein may result in central nervous system inflammation.

## ARTICLE INFORMATION

### Ethics statement

This study was approved by the Institutional Review Board of Hanyang University Hospital (No. 2022-10-020). Informed consent was waived by the Board.

### Conflict of interest

No potential conflict of interest relevant to this article.

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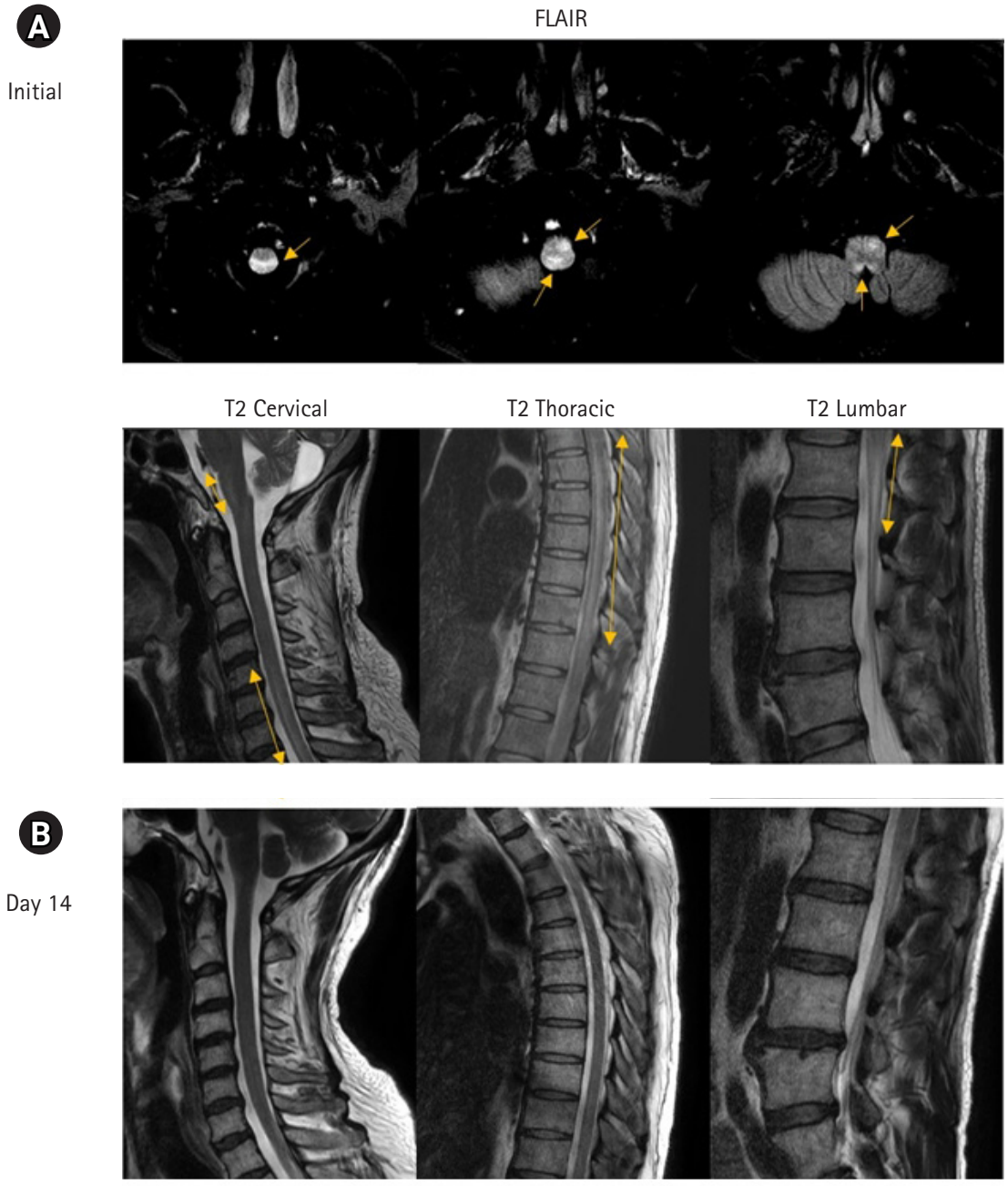


**Fig. 1.** (A) Initial brain fluid-attenuated inversion recovery (FLAIR) axial view images and spinal cord T2-weighted sagittal view images show high signal intensity lesions (arrows) compatible with longitudinal extensive transverse myelitis. (B) Spinal cord T2-weighted sagittal view images show interval improvement of high signal intensity lesions after steroid pulse therapy.

**Author contributions**

Conceptualization: YSK. Data curation: SC. Formal analysis: SC. Methodology: YSK. Project administration: YSK. Visualization: SC. Writing–original draft: SC. Writing–review & editing: YSK.

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pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):150-152
https://doi.org/10.18700/jnc.220082

Journal of Neurocritical Care

# Massive microbleeds in posterior circulation territory in an immunocompromised patient with sepsis

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IMAGES IN NEUROCRITICAL CARE

Received: October 21, 2022
Revised: November 10, 2022
Accepted: November 16, 2022

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Diffuse microbleeds in cerebral white matter have been reported in critically ill patients [1]. We present a case of extensive microbleeds in the bilateral cerebellum and pons accompanied by sepsis. A 16-year-old female patient complained of severe headache, dizziness, and drowsiness while being admitted for treatment of cellulitis of the left malleolus. She was diagnosed with juvenile rheumatoid arthritis and treated with immunomodulators (sulfasalazine 500 mg and prednisolone 7.5 mg) for 5 years. Three hours after the first complaint of headache and dizziness, she presented with right hemiparesis with stuporous mentality, eventually progressing to coma. Although brain computed tomography images did not show hemorrhage, T2*-weighted gradient echo magnetic resonance imaging revealed massive microbleeds confined mainly to the bilateral cerebellum and brainstem (Fig. 1). Despite intensive care, the patient died of sepsis and extensive brain edema.

Microbleeds in the brain are detected in conditions such as microangiopathy, Moyamoya disease, vasculitis, and posterior reversible encephalopathy syndrome [2]. Meanwhile, Thurnher et al. [3] reported diffuse microsusceptibility changes, including in the brainstem and cerebellum, in critically ill immunocompromised patients undergoing mechanical ventilation and oxygenation. In our case, the precise diagnostic evaluation of other diseases that can provoke massive microbleeds and brain edema was not possible due to the patient's critical condition. However, images presenting with normal angiography and the absence of antibodies associated with vasculitis could indicate a condition prone to microbleeds in the brainstem with secondary brain edema due to the critically ill state.

## ARTICLE INFORMATION

### Ethics statement

This study was reviewed and approved by the Institutional Review Board of Hanyang University Seoul Hospital (No. HY 2022-10-029). The need for informed consent was waived by the Board.

### Conflict of interest

No potential conflict of interest relevant to this article.

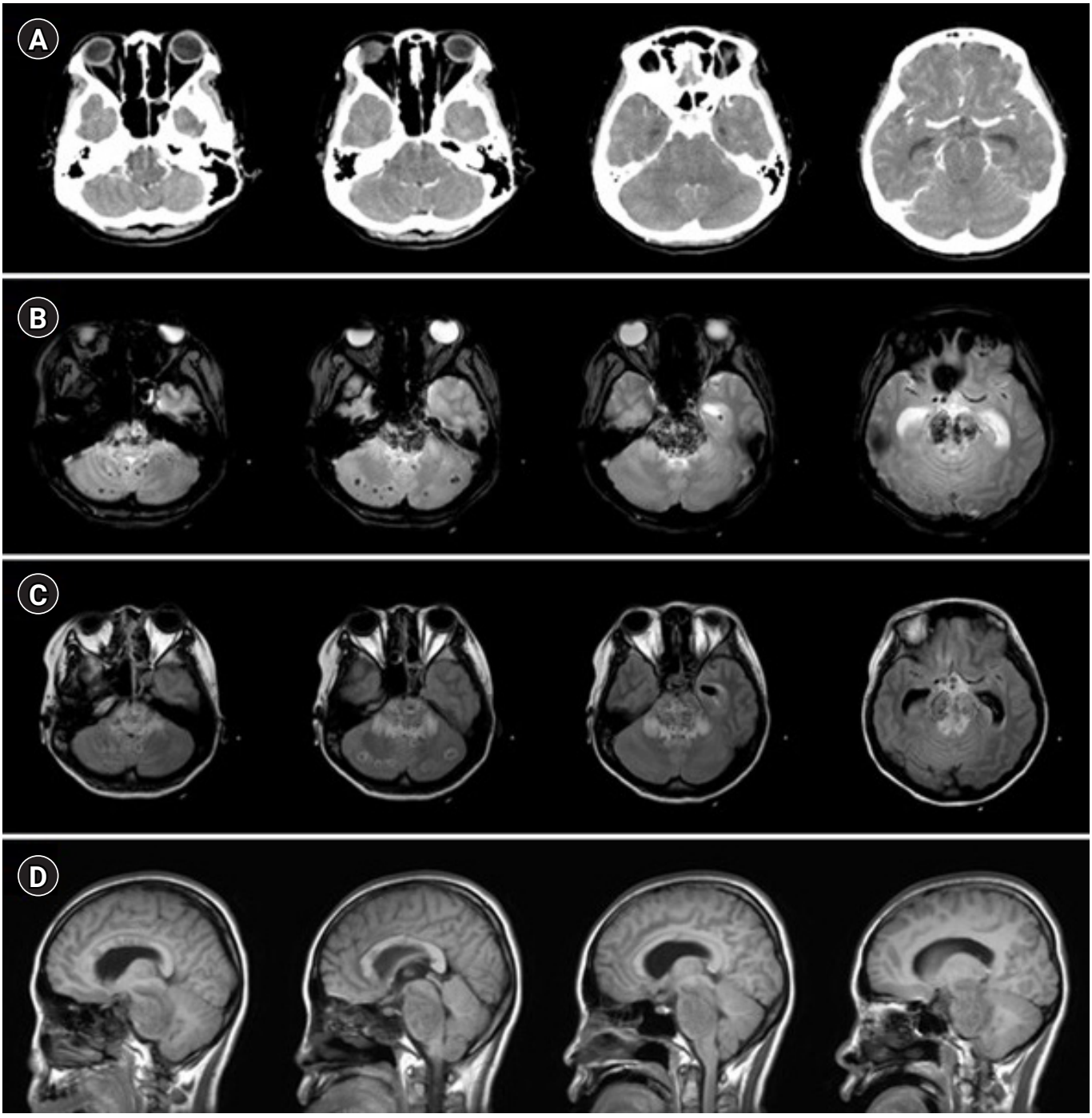


**Fig. 1.** Computed tomography (CT) and magnetic resonance imaging (MRI) scans of the brain. (A) CT images demonstrate edematous brainstem without overt hemorrhage. (B, C) T2*-weighted gradient echo MRI images present extensive small foci of hypointensity, compatible with microbleeds, diffusely dispersed throughout the brainstem and cerebellum. T2-weighted fluid-attenuated inversion recovery images reveal edematous change around lesions. (D) Sagittal T2-weighted images indicate swollen brainstem, resulting in hydrocephalus.

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https://doi.org/10.18700/jnc.220082

pISSN 2005-0348 • eISSN 2508-1349
J Neurocrit Care 2022;15(2):153-154
https://doi.org/10.18700/jnc.220083

Journal of Neurocritical Care

# Diffuse cerebral microbleeds in a patient with HIV and disseminated intravascular coagulation

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IMAGES IN NEUROCRITICAL CARE

Received: October 24, 2022
Revised: November 02, 2022
Accepted: November 21, 2022

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Hypoxemia and critical illnesses such as sepsis and disseminated intravascular coagulopathy (DIC) are possible causes of massive microbleeds in the brain parenchyma [1]. We report a patient with human immunodeficiency virus (HIV) showing extensive cerebral microbleeds. A 59-year-old male patient presented with generalized tonic-clonic seizures. After admission, he was diagnosed with HIV infection while evaluating for pneumonia. Ten days after antiretroviral therapy (ART), DIC occurred as a result

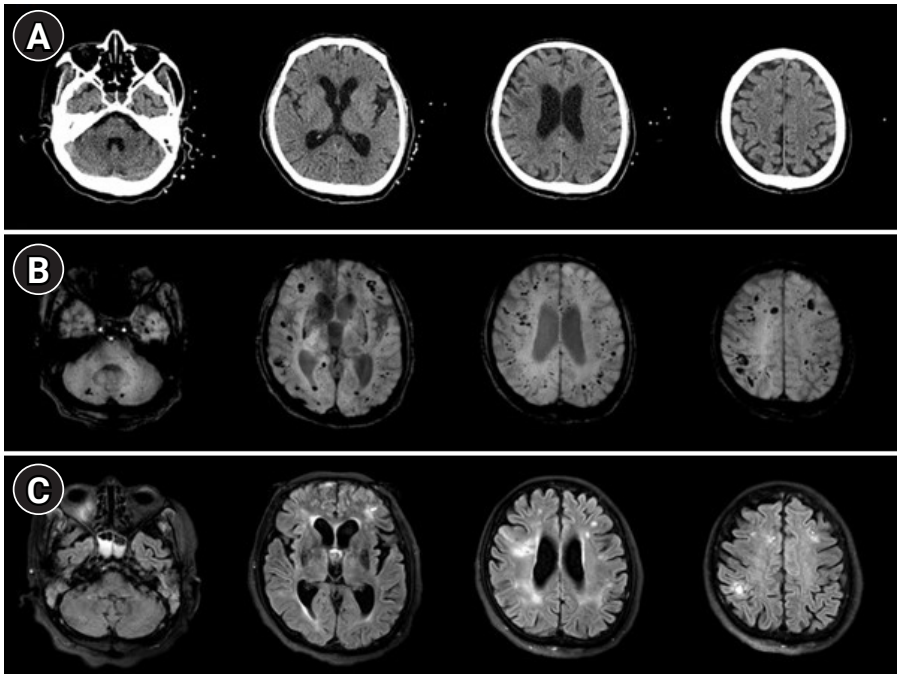


**Fig. 1.** Computed tomography (CT), susceptibility-weighted image (SWI), and fluid-attenuated inversion recovery (FLAIR) images in magnetic resonance imaging of the brain. (A) CT images demonstrate no definite evidence of intracranial hemorrhage. (B) However, SWI presents with multiple hypointensities in the bilateral cerebral hemisphere cerebellum, predominant at the gray and white matter junction, suggestive of microbleeds. (C) FLAIR images show multiple hyperintense lesions involving cerebral cortices and white matter in regions with large microbleeds on SWI.

of pneumonia progression, compatible with immune reconstitution inflammatory syndrome (IRIS). Blood analysis showed elevated D-dimer levels (1,750 ng/mL), prolonged prothrombin time (16.1 seconds), and low platelet count ($63 \times 10^3/\mu L$). He was stuporous with normal brainstem signs of brainstem injury. While the patient's brain computed tomography images were unremarkable (Fig. 1A), susceptibility-weighted images demonstrated innumerable hypointense foci in the cerebrum and cerebellum suggestive of microbleeds (Fig. 1B). Multifocal hyperintense lesions were also observed in the fluid-attenuated inversion recovery images, which could induce a symptomatic seizure (Fig. 1C). Meanwhile, the cerebrospinal fluid examination was within the normal range. Anti-epileptic drugs were administered, and the patient's mental status improved from stuporous to alert.

Thus, IRIS triggered by ART initiation can affect the central nervous system in patients with HIV [2]. Therefore, clinicians should consider brain involvement presenting as extensive microbleeds in critically ill HIV patient.

## ARTICLE INFORMATION

### Ethics statement

This case was reviewed and approved by the Institutional Review Board of Hanyang University Seoul Hospital (No. HY 2022-10-034). The need for informed consent was waived by the Board.

### Conflict of interest

No potential conflict of interest relevant to this article.

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

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https://doi.org/10.18700/jnc.220083

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Journal of Neurocritical Care

Enacted April 1, 2008
Last revised September 1, 2021

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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.

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# Conflict of Interest Statement

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

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).

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