

Journal of
Neurocritical
Care

eISSN 2508-1349

Journal of Neurocritical Care Vol. 12 No. 2 December 2019

Journal of Neurocritical Care

Vol. 12
No. 2

December 2019



www.e-jnc.org

pages 67-121 THE KOREAN NEUROCRITICAL CARE SOCIETY



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THE KOREAN NEUROCRITICAL CARE SOCIETY

Journal of Neurocritical Care

Vol. 12, No. 2, 31 December 2019

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

Editor-in-Chief

Sang-Beom Jeon
Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine,
88 Oylimpic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3440, Fax: +82-2-474-4691, E-mail: editor@e-jnc.org

Correspondence

The Korean Neurocritical Care Society
Department of Neurology, The Catholic University College of Medicine,
222 Banpo-Daero, Seocho-Gu, Seoul, 06591 Korea
Tel: +82-2-2258-2816, Fax: +82-2-599-9686, E-mail: office@neurocriticalcare.or.kr
Website: <http://www.neurocriticalcare.or.kr>

Printing Office

M2community Co.
8th FL, DreamTower, 66 Seongsui-ro, Seongdong-gu, Seoul 04784, Korea
Tel: +82-2-2190-7300, Fax: +82-2-2190-7333, E-mail: journal@m2community.co.kr

Published on December 31, 2019

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Targeted temperature management for ischemic stroke

Ji Man Hong, MD, PhD

Department of Neurology, Ajou University School of Medicine, Suwon, Republic of Korea

REVIEW ARTICLE

Received: October 5, 2019

Revised: November 29, 2019

Accepted: November 29, 2019

Corresponding Author:

Ji Man Hong, MD, PhD

Department of Neurology, Ajou
University School of Medicine, 164
World cup-ro, Yeongtong-gu, Suwon
16499, Republic of Korea

Tel: +82-31-219-5175

Fax: +82-31-219-5178

E-mail: dacda@hanmail.net

Therapeutic hypothermia (TH) or targeted temperature management is an intentional cooling or temperature control technique using a thermostatic equipment (i.e., surface, endovascular, and focal devices) for specific therapeutic purposes. Given the modifiable determinants in the therapeutic process of acute ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage, several studies strongly reported that fever is closely associated with more harmful neurological outcomes. Fever or hyperthermia can deteriorate the cellular ischemic cascade, causing more cerebral damage owing to increased metabolic demands, enhanced release of excitatory neurotransmitters, and increased toxic free radical production. Despite the disappointing results of various clinical trials on TH in the stroke field, many studies have repeatedly clarified its fundamental mechanisms, which proved its strong neuroprotection in experimental stroke models. In particular, the potential effectiveness of TH can be revisited in the era of endovascular thrombectomy for patients undergoing emergent large-vessel occlusion because neuroprotection is maximized in ischemia-reperfusion injury models. This review aims to incorporate current literature into risks and benefits in patients with ischemic stroke.

Keywords: Hypothermia; Hypothermia, induced; Reperfusion injury; Reperfusion

INTRODUCTION

Stroke is a heterogeneous syndrome caused by the disruption of cerebral blood flow with subsequent tissue damage [1]. Epidemiologically, it is a serious neurological disease considered as the major cause of death and disability worldwide [2,3]. It can be classified into ischemic or hemorrhagic, with 85% of strokes being ischemic, an episode of neurological dysfunction caused by vascular stenosis or occlusion within a specific vascular territory [4].

Despite making up to only 2% of the total body weight, the

brain consumes 20% of the body's total energy and relies on a constant supply of glucose and oxygen to maintain its function and structural integrity [1]. Therefore, focal cerebral ischemia with severe hypoperfusion falling below the infarct threshold triggers a cascade of ischemic injury [5]. Therapeutic hypothermia (TH), which prevents irreversible neuronal necrosis and cerebral infarction, has strongly been investigated in animal studies and clinical trials with more effectiveness in postcardiac arrest and neonatal encephalopathy, primarily to prevent ischemia-reperfusion injury [6-8].

MECHANISMS OF ACTION OF THERAPEUTIC HYPOTHERMIA IN ACUTE ISCHEMIC INJURY

The brain injury mechanism after an ischemic stroke refers to the interaction of complex pathophysiological processes such as excitotoxicity, inflammatory pathways, oxidative damage, blood-brain barrier disruption, angiogenesis, and its restoration [4]. Current neuroprotection treatments for ischemic stroke injuries are not proven beneficial in the case of cerebral ischemia due to the complexity and disappointing results of various drug experiments in human clinical trials [9]. In contrast, TH is believed to inhibit or at least reduce the progression of this cascade at multiple levels (Fig. 1). Ischemic injury cascade starts with cerebral hypoxia, resulting in a loss of adenosine triphosphate (ATP) production and dysfunction of ATP-dependent Na⁺-K⁺ pumps in the cell membrane. The key cascades of this pathological process also commonly occur in various ischemic strokes. While the precise mechanism has not been fully understood, numerous hypotheses have

suggested the neuroprotective effects of TH such as prevention of blood-brain barrier disruption; reduction of cerebral glucose metabolism and oxygen consumption; reduction of excitotoxic neurotransmitter accumulation, intracellular acidosis, intracellular calcium influx, and oxygen-free radical production; alteration of cold shock protein expression; reduction of brain edema; reduction of thrombosis risk; and reduction of the risk of epileptic activities [10]. In addition, TH can function as an antiedema therapy to prevent the increase in intracerebral pressure or impending cerebral herniation during an acute period of ischemic stroke [11]. In summary, potential mechanisms of TH can be described as “neuroglial protectors” for acute ischemic stroke.

COMPLICATIONS OF THERAPEUTIC HYPOTHERMIA

As mild hypothermia (34°C to 35.9°C) is relatively well tolerated, deep hypothermia (< 32°C) appears to be related to more deleterious

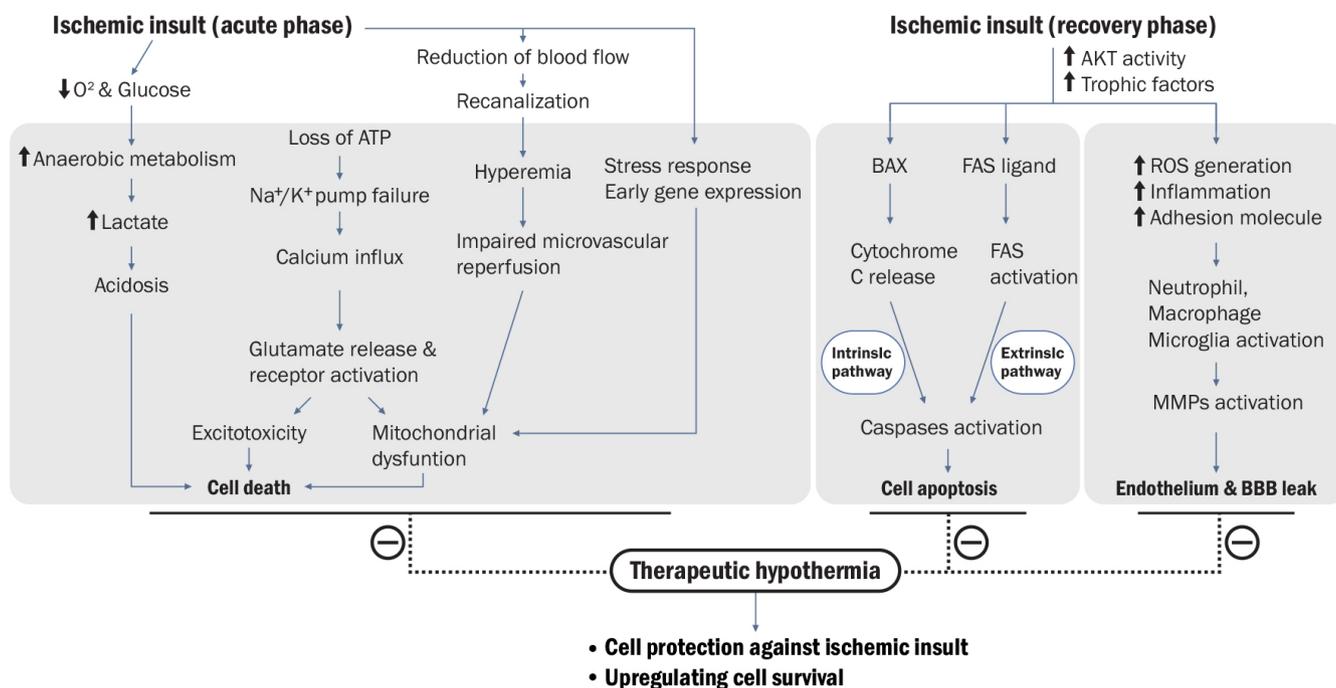


Fig. 1. Possible tissue damage mechanisms that therapeutic hypothermia (TH) can alleviate in ischemic stroke from acute stage to recovery phase [10]. (A) Acute events, such as loss of oxygen and glucose after stroke, can lead to energy loss (adenosine triphosphate [ATP] loss) and ion pump failure. The resulting loss of concentration gradients allows ions (Na⁺/K⁺) to flow down their concentration gradients, leading to cellular swelling (cytotoxic edema) and release of excitatory amino acids. Reperfusion injury after recanalization may also occur, and tissue hypoxia can increase anaerobic metabolism. All of these events will lead to acute cell death. TH can alleviate almost all ischemic cascades that lead to cell death. (B) There are possible mechanisms that TH can alleviate the recovery phase of ischemic stroke. Ischemia activates both intrinsic and extrinsic pathways that will lead to cell apoptosis. It also triggers reactive oxygen species (ROS) production and inflammatory reaction. These promote endothelial cell damage and blood-brain barrier (BBB) disruption. As a result, TH has been associated with suppression of both apoptotic and inflammatory pathways, while upregulating cell survival pathways. BAX, Bcl2 associated X protein; MMP, matrix metalloproteinase.

rious side effects directly caused by the intervention itself [12]. Physiological changes should be carefully considered and closely monitored on a daily basis in intensive care units (ICUs), and patients considering TH should be admitted to the ICU [13,14].

Side effects of TH can be categorized as cardiac, hematologic, immunologic, and metabolic complications [14,15]. Fig. 2 shows examples of complications during induction, maintenance, and rewarming of TH. Shivering in response to hypothermia can undermine the intentional goal of therapeutic cooling by generating heat that leads to increased core temperature and oxygen consumption. It is most prominent in the TH induction process; therefore, the use of sedatives and paralytics during this period should be carefully considered [16].

PREVIOUS STUDIES ON ACUTE ISCHEMIC STROKE

Several small phase II pilot trials have investigated the safety and feasibility of TH for acute ischemic stroke. These included the Cooling for Acute Ischemic Brain Damage (COOL-AID) trial [17]. This endovascular cooling trial demonstrated positive results of slower infarct growth in the TH group compared to that in the control group. As a result, the Intravascular Cooling in the treatment of stroke longer tissue plasminogen activator (tPA) window (ICTuS-L) was a phase I trial originally designed to establish the safety of endovascular cooling combined with tPA. Unfortunately, this trial was an eventual failure owing to a significantly increased proportion of pneumonia cases in the TH group [18].

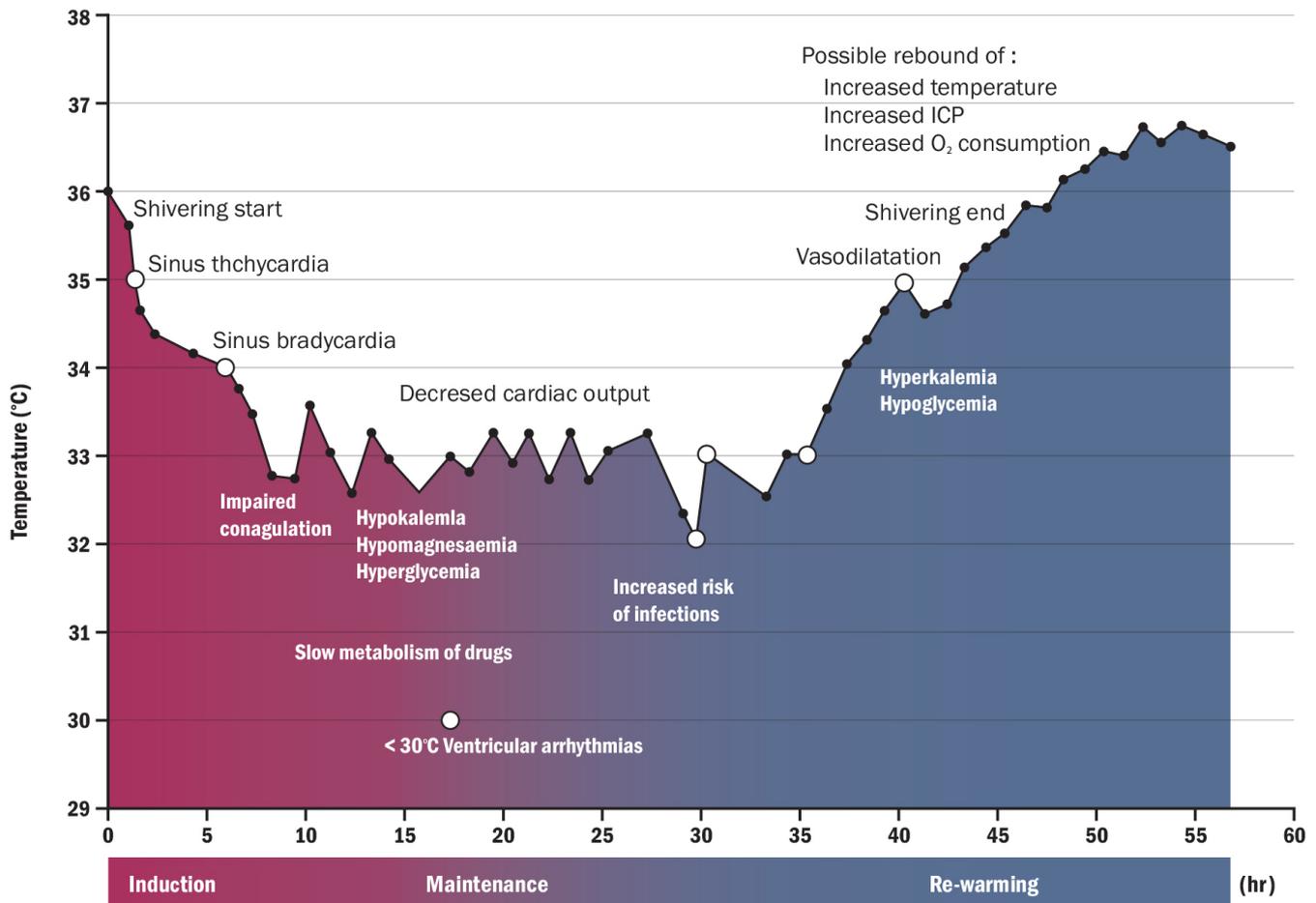


Fig. 2. Physiological changes (open circle) according to temperature variation and possible complications (closed circle) during the three phases of therapeutic hypothermia: induction, maintenance, and rewarming [14]. Possible cooling complications may present as reverse patterns of rewarming complications (hyperkalemia, hypoglycemia, and rebound of increased intracranial pressure, among others). ICP, intracerebral pressure.

For safety procedures and faster cooling than that in the previous ICTuS-L trial, the protocol of ICTuS 2 trial was modified in a prospective, multisite phase 2/3 pivotal, tissue plasminogen activator (tPA) trial combined with intravascular cooling catheter hypothermia in awake patients with moderate-to-severe middle cerebral artery (MCA) infarction with cold saline bolus and permissive hypothermia [19]. Unfortunately, this also did not show the usefulness of TH [20]. Recently, a phase III trial, an European randomized open-label clinical investigation with blinded outcome assessment (EuroHYP-1), provided no evidence that active cooling to a target of 34.0°C to 35.0°C for 12 to 24 hours initiated within 6 hours after the onset of ischemic stroke has an impact on the functional outcomes at 3 months [21]. This trial was discontinued after including 98 of the originally intended 1,500 patients because of slow recruitment and cessation of funding. This trial also was substantially underpowered to detect any clinically relevant benefit or harm [21]. Moreover, ICTuS 3 study poorly detected the clinical benefits owing to issues in patient enrollment during the study. These studies also raised questions about the feasibility of inducing hypothermia in relatively awake, spontaneously breathing stroke patients who tend to shiver vigorously and are prone to experience discomfort with hypothermia (unlike intubated and cardiac arrest patients).

Decompressive hemicraniectomy has been considered a powerful beneficial option to reduce the mortality of severely ill patients with a space-occupying MCA infarction; however, a considerable number of patients are still suffering from serious disability or even face death. Therefore, TH can be clinically beneficial in those with severe stroke treated with hemicraniectomy because of its strong antiedema therapy during the acute phase of ischemic stroke. Nonetheless, several clinical data demonstrated that hypothermia treatment had no additional benefits on the functional outcome as compared with hemicraniectomy alone [11,22,23]. Therefore, we should include specific candidates who would be more feasible targets for detecting the clinical efficacy and safety of TH in future trials.

COMPARATIVE LESSONS ON THERAPEUTIC HYPOTHERMIA: SUCCESSFUL GLOBAL ISCHEMIA VS. FAILED FOCAL ISCHEMIA

Since 2002, when the trial “Hypothermia after Cardiac Arrest (HACA)” study group demonstrated the clinical benefits of TH in improving neurological and mortality outcomes in postcardiac arrest patients with shockable rhythms, many studies have shown the positive effects of hypothermia on the neuronal protection in global brain ischemia [6,7].

However, the evidence of TH for focal cerebral ischemia in stroke remains inconclusive. Preclinical studies support that TH is much more beneficial and consistent in temporary MCA occlusion than in permanent MCA models [24]. In addition, several studies reported that despite the association of TH with increased risk of pneumonia, longer duration of ICU stay, and prolonged mechanical ventilation dependency, these factors did not affect the neurological outcome and ICU survival [25]. Compared to the conventional TH guideline on postcardiac arrest syndrome, some data showed a beneficial tendency in case of longer duration of cooling and rewarming in cardiac arrest [26], ischemic stroke [27], and traumatic brain injury [28]. Generally, clinical deterioration after an ischemic stroke attributable to HT and cerebral edema usually occurs between 2 and 5 days after stroke [29]. The time course of edema after stroke and extrapolation from traumatic brain injury hypothermia studies suggesting a prolonged course of TH with slow and controlled rewarming may be important for the success of TH protocols in patients with stroke. Therefore, animal and clinical studies suggest that TH with a long-duration and specific protocol might be more effective in patients with severe stroke who underwent successful recanalization by preventing ischemia-reperfusion injury in endotracheal intubation obligation such as cardiac arrest or perinatal postanoxic status.

LESSONS FROM PREVIOUS *IN VIVO* EXPERIMENTS

Although some trials showed positive efficacy of longer TH duration from different clinical situations, its optimal duration remains unclear. Considering that neurovascular damage after an acute ischemic attack occurs over hours to days, the longer the duration of hypothermia is, the more significantly improved the outcomes can be. In support of this hypothesis, some experiments have already demonstrated better outcomes with longer duration of cooling [10]. Interestingly, van der Worp et al. [30] concretely reported an inverse relationship between the duration of TH and infarct volume in a systemic review and meta-analysis of animal models. As compared to shorter (3 hours) periods of hypothermia in Sprague-Dawley rats with transient middle cerebral artery occlusion (tMCAO), infarct size reduction was greater and better outcomes were observed in patients treated in longer hours (21 hours) [31]. This can lead to an expansion of time window and number of patients for the treatment of endovascular recanalization in patients who had emergent large vessel occlusion (ELVO) stroke. Although no guidelines have recommended the exact therapeutic timeframe for TH, time-sensitive characteristics of hypothermia induction cannot be easily disputed due to solid results of

previous experiments [32]. In summary, available experimental data showed that TH could be (1) more successful when applied quickly; (2) when applied with sufficient duration; and (3) when applied to the ischemia-reperfusion model.

TARGETED TEMPERATURE MANAGEMENT DURING OR AFTER AN ENDOVASCULAR RECANALIZATION

Endovascular treatment (EVT) such as mechanical clot retrieval has become a proven therapeutic strategy for acute ischemic stroke with an ELVO recently [33]. Many of these patients are at high risk of brain injury owing to their large stroke volume and of reperfusion injury even if recanalization was successful. Among the neuroprotective strategies, TH has been attempted to evaluate the outcome benefits in experiments and clinical trials [4,9]. In a recent postreperfusion TH study, several patients (approximately 45%) had favorable outcomes based on the modified Rankin Scale 0, 1, 2 at 3 months despite low baseline Alberta stroke pro-

gram early CT score (ASPECTS) and large lesion volume (> 80 mL) [34]. Recent EVT trials showed that EVT was useful for patients with a large core volume, and reperfusion rate was a predictor of good outcomes [35-37]. However, several studies in patients with malignant MCA trait demonstrated that low ASPECTS on computed tomography (initially large parenchymal lesion) was a predictor of poor outcomes despite successful recanalization. Such contradictory results demonstrate that reperfusion itself does not always guarantee a good functional outcome, especially in patients with “malignant MCA infarction trait” [33,38]. Neuroprotection after recanalization is evident in the EVT era to improve the clinical outcomes of these contradictory groups. Failure of previous neuroprotective drugs can be overcome by achieving endovascular recanalization, a similar mode of ischemic-reperfusion model in preclinical experiments. In this context, immediate postreperfusion cooling can be a promising option to minimize reperfusion-related complications. The rate of infarct growth has also been known to vary depending on an individual’s diversity, such as the collateral blood flow in patients with acute ischemic

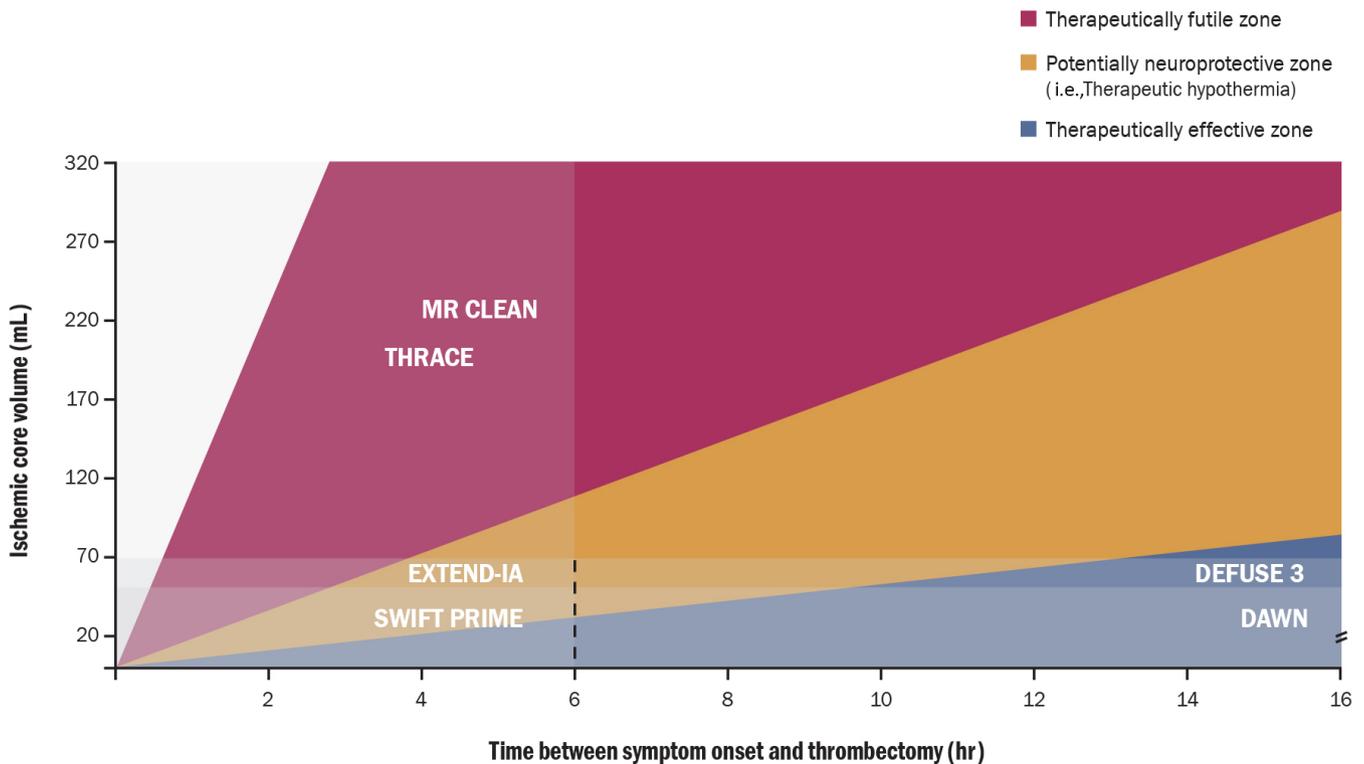


Fig. 3. A simplified diagram of the symptom onset, infarct core volume, and potential neuroprotectant (i.e., therapeutic hypothermia) according to the inclusion criteria described in previous successful endovascular treatment trials.³⁵ The red zone represents the fast progressor of the infarct core, the yellow zone the intermediate progressor, and the green zone the slow progressor. Reduction of reperfusion injury can be more effective in patients who are not classified as either fast or slow progressors, such as those in the yellow zone (potentially neuroprotective zone). However, massive reperfusion injury can easily occur in the red zone area (therapeutically futile zone).

stroke. Recent success of the late window EVT trials may be because of the selection of “slow progressors” in the infarct growth process [35]. In the future, neuroprotective modalities, including TH and other agents for reperfusion injury, may be promising for patients not classified as either fast and slow progressors (Fig. 3). A recent study has shown that neurocritical care treatments including TH are feasible even in patients with a malignant infarct core [39]. Therefore, the strategy reducing reperfusion injury using TH will be another option for vulnerable patients suffering from acute ischemic stroke in the EVT era. Although TH protocols remain debatable [40], it can be combined with existing therapies to improve outcomes of patients with acute ischemic stroke through the technological development of EVT.

CONCLUSION

TH can play a pivotal role in the era of endovascular thrombectomy for patients undergoing emergent large-vessel occlusion because neuro-glial protection can be maximized in ischemia-reperfusion injury model.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

ORCID

Ji Man Hong, <https://orcid.org/0000-0001-6803-1207>

Author contributions

Conceptualization: JMH. Data curation & Formal analysis: JMH. Visualization & Writing—original draft: JMH. Writing—review editing: JMH.

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Cefepime-induced neurotoxicity

Se-Jin Lee, MD, PhD

Department of Neurology, Yeungnam University College of Medicine, Daegu, Republic of Korea

REVIEW ARTICLE

Received: November 4, 2019

Revised: December 9, 2019

Accepted: December 9, 2019

Corresponding Author:

Se-Jin Lee, MD, PhD

Department of Neurology, Yeungnam
University College of Medicine, 170
Hyeonchung-ro, Nam-gu, Daegu
42415, Republic of Korea

Tel: +82-53-620-3683

Fax: +82-53-627-1688

E-mail: sejinmayo@ynu.ac.kr

Cefepime, a widely used fourth-generation cephalosporin, has been reported to cause neurotoxicity because it crosses the blood-brain barrier. Although cefepime-induced neurotoxicity (CIN) occurs in patients with renal dysfunction administered a high dosage, CIN has also been reported in patients with normal renal function administered the appropriate dosage. CIN is characterized by toxic encephalopathy and electroencephalography abnormalities, such as triphasic wave, currently renamed as generalized periodic discharge (GPD) with triphasic morphology, and nonconvulsive status epilepticus (NCSE). Toxic encephalopathy appears 2 to 6 days after cefepime administration and disappears 3 days after discontinuation of cefepime. Electroencephalography abnormalities in most reported cases are GPD with triphasic morphology rather than NCSE. CIN is reversible in most cases if early detection and discontinuation of cefepime is possible, which is the only definitive treatment; however, anticonvulsant therapy is unnecessary except for patients with convulsive seizures or definite NCSE. Emergent hemodialysis may also be helpful in life-threatening situations.

Keywords: Cefepime; Neurotoxicity syndromes; Generalized periodic discharges; Triphasic waves; Nonconvulsive status epilepticus

INTRODUCTION

Cefepime, a fourth-generation cephalosporin antibiotic, was approved for use in 1996. It is widely used to treat severe bacterial infections because it acts against both gram-negative and gram-positive bacterial strains, and has antipseudomonal activity. Safety data of cefepime in clinical trials were relatively favorable when initially approved. Approximately 3% of 2,032 patients treated with cefepime experienced adverse central nervous system (CNS) effects including headache (2.4%), dizziness (0.7%), and

insomnia (0.6%) [1]. Eleven (0.2%) patients developed seizures but only three (0.1%) of these cases were considered to have a probable or unknown relationship to cefepime therapy [1].

Cefepime-induced neurotoxicity (CIN) was first reported in a patient with end-stage renal disease (ESRD) on hemodialysis in 1999 [2]. He developed altered mental status, myoclonus, and a generalized tonic-clonic seizure with elevated serum cefepime concentration. He recovered after urgent hemodialysis but electroencephalography (EEG) was not performed. Thereafter many cases of CIN with triphasic wave (TW) or nonconvulsive status

epilepticus (NCSE) have been reported. CIN is composed of toxic encephalopathy and TW or NCSE in EEG. There is debate about EEG findings regarding whether it is true NCSE or TW.

CIN mainly occurs in patients with impaired renal function who have been administered cefepime without dose adjustment, because 85% of cefepime is removed through renal excretion [3-11]. However, it has also occurred in patients who have received appropriate doses based on renal function [12-18] and even in patients with normal renal function [5,18-22]. Therefore, the U.S. Food and Drug Administration (FDA) issued a safety warning that recommended dose reduction in patients with renal dysfunction, that is, estimated glomerular filtration rate (GFR) < 60 mL/min [23]. CIN is reversible in most cases if early detection and discontinuation of cefepime is possible, which is the only definitive treatment. Frequent neurologic examination and monitoring of renal function are needed, especially in the elderly with impaired renal function or previous CNS injury.

After a review of cases, case series, and meta-analysis, we have described the incidence, pathogenic mechanism, risk factors, clinical manifestation, EEG abnormalities, and appropriate management of CIN. We have also analyzed all the cases of CIN reported in the Korean medical literature.

INCIDENCE

The reported incidence of CIN is quite variable because of differences in the diagnostic criteria of CIN, the protocol for dose adjustment of cefepime, degree of renal dysfunction, characteristics of included patients, and severity of underlying illness or comorbidity. In addition, small sample size and retrospective study design are also likely to influence the results.

In a prospective cohort study, the incidence of CIN in patients with medical illness was 1%; however, in patients with GFR 60 to 15 mL/min and GFR < 15 mL/min, CIN incidence increased to 4.5% and 16.6%, respectively [4]. Incidence in critically ill patients [6] and in patients with hematologic malignancies [24] was 15% and 4.1%. The incidence of CIN in a retrospective case-control study in Korean patients was 0.85% [25]. The incidence in ESRD patients was 7.5%, but was 22.2% in ESRD patients with preexisting CNS morbidity [17]. In a recent retrospective study, the incidence of CIN was 0.2% [9].

Therapeutic drug monitoring (TDM) studies show that the incidence of CIN has increased, from 11% to 23.2% [26-28]. In the French pharmacovigilance database on serious CNS adverse effects, cefepime was the most common drug among cephalosporins to be associated with CNS adverse effects [29].

The incidence of CIN was higher immediately after the approv-

al of cefepime than that in recent times, because initially dose adjustment was recommended for patients with impaired renal function when the GFR was < 50 mL/min by the manufacturer [30]. Furthermore, the physicians were not exactly aware of the clinical manifestations and risk factors of CIN. Therefore, many cases of CIN might have occurred in hospitals where cefepime was widely used, as in Geneva Cantonal Hospital [31].

PHARMACOLOGY

Cefepime has a low molecular weight of 480.6 daltons and is known to display linear (first-order) pharmacokinetics regardless of the treatment duration [32]. Serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

Renal excretion and half life

In normal subjects, the total body clearance of cefepime is dose-independent. Urinary excretion of unchanged cefepime accounts for approximately 85% of the administered dose [32]. Therefore, the cefepime dosage should be reduced according to renal function in patients whose GFR is \leq 60 mL/min [33]. The half-life in healthy volunteers is 2 hours whereas that in patients with ESRD requiring hemodialysis is 13.5 hours and that in patients requiring continuous ambulatory peritoneal dialysis (CAPD) is 19 hours [33,34].

Hepatic metabolism

Only a small proportion of cefepime is metabolized to N-methylpyrrolidine (NMP) which is rapidly converted to N-oxide (NMP-N-oxide) [35]. Less than 1% of the administered dose is recovered from urine as NMP. The pharmacokinetics of cefepime were unaltered in patients with hepatic impairment who received a single 1 g dose.

PATHOGENIC MECHANISMS

Although the pathophysiology of CIN is not fully understood, it is supposed to be related to the concentration dependent competitive inhibition of γ -aminobutyric acid (GABA) A receptors in animal studies [36]. Cephalosporins may also decrease GABA release from nerve terminals or increase excitatory amino acid release [37]. Through these mechanisms, cefepime treatment results in hyperexcitation of neurons and depolarization of the post-synaptic membrane, which are consistent clinically with the occurrence of seizures, myoclonus, and encephalopathy.

RISK FACTORS OF CIN

Impaired renal function and excessive dose are the most important and common predisposing factors of CIN. Preexisting brain injury, old age, high-dose therapy, and increased CNS penetration of cefepime are known risk factors [6,9,10,17,38]. However, CIN has also been reported in patients with normal renal function [5,18-22,39,40] and in those administered the appropriate dose based on renal function [12-18,41-43]. The cause of CIN in these patients is not known.

Renal dysfunction

A meta-analysis revealed that 80 to 87% of patients with CIN had renal dysfunction [9,10]. In patients with renal failure, cerebrospinal fluid (CSF) concentrations of cefepime may increase due to competitive inhibition of active transport of cefepime from CSF to blood by organic acids [44], an increase in blood-brain barrier (BBB) permeability, and a decrease in serum protein binding [45]. Moreover, renal function may be overestimated by the Cockcroft-Gault formula under debilitating conditions such as malnutrition and amyotrophy [26]. Thus, an excessive dose of cefepime may be administered.

Excessive dosing

The results of a meta-analysis showed that 25% to 50% of patients with CIN received an excessive dose of cefepime. This may be due to either failure of dose adjustment or miscalculation of dosage.

Preexisting brain injury

CNS penetration of cefepime may be increased in patients with a previous brain injury. The incidence of CIN in ESRD patients with preexisting CNS morbidity was 22.2%, which is three times higher than that in ESRD patients without previous CNS injury [17]. From the data of a meta-analysis, 8% of the reported patients had preexisting CNS disease [10].

Old age

Most of the reported patients were of old age, with a median of 69 years, ranging from 54 to 75 years [10]. The elderly are thus susceptible to renal dysfunction and CNS adverse effects.

Increased CNS penetration

In patients with sepsis, CNS infection, uremia, and previous brain injury, BBB integrity may be disrupted, resulting in increased CNS penetration of cefepime up to 45%, which is much higher than the 10% in normal conditions [46,47]. Blood levels of unbound cefepime, which is the biologically active fraction of cefepime avail-

able for entry into the CNS, are increased in patients with hypoalbuminemia due to renal or hepatic dysfunction [45].

Patients with adjusted dose or normal renal function

Quarter to half of patients with CIN appeared to receive an appropriate dosage according to their renal function [9,10]. CIN occurrence in patients with adjusted dose or normal renal function may be due to the following reasons: (1) individual variations in pharmacokinetics or pharmacodynamic susceptibility [9]; (2) although renal function was normal before initiation of cefepime treatment, renal dysfunction may occur during cefepime treatment due to aggravation of systemic conditions and nephrotoxicity of combined medications such as aminoglycosides [4,45,46,48,49]; (3) competitive inhibition of active transport of cefepime from CSF to blood. An increase in BBB permeability, hypoalbuminemia, and a decrease in serum protein binding may act as provocative factors.

DOSE ADJUSTMENTS

Cefepime dose should be adjusted based on current renal function (Table 1). Normal renal function is defined as a creatinine clearance of 60 mL/min [23]. Moreover, the physician needs to take into account age, preexisting brain injury, hypoalbuminemia, and septic conditions.

In patients with severe infection or critical illness, dose adjustment according to serum cefepime levels may be helpful. Dose adjustment is not necessary in patients on continuous renal replacement therapy (CRRT) [2,50]. However, it is reasonable to consider the severity of the infectious disease during dose adjustment to prevent treatment failure [17].

SERUM CEFEPIME CONCENTRATION

Some investigators measured serum cefepime concentrations and demonstrated the association between serum cefepime concentrations and the occurrence of CIN [28,45,51]. Others described that clinical improvement of CIN was associated with a decrease in the blood concentration of cefepime [2,26,45,46].

Although the target serum trough concentrations of cefepime have not been well established, the neurotoxic threshold may be around 20 mg/L based on the data of published reports, and interpersonal variability is observed [26,27,52]. TDM may be useful to avoid neurotoxicity, especially in patients with high-dose therapy, renal dysfunction, and on CRRT.

Table 1. Recommended dosing schedule of cefepime based on renal function in adults

CrCl (mL/min)	UTI ^{a)}	Pneumonia ^{b)}		
		UTI ^{a)} , pneumonia ^{b)}	UTI ^{c)} , SSSI ^{d)} , intra-abdominal ^{e)}	Febrile ^{f)} neutropenia
>60	500 mg q 12 hr	1 g q 12 hr	2 g q 12 hr	2 g q 8 hr
30–60	500 mg q 24 hr	1 g q 24 hr	2 g q 24 hr	2 g q 12 hr
11–29	500 mg q 24 hr	500 mg q 24 hr	1 g q 24 hr	2 g q 24 hr
<11	250 mg q 24 hr	250 mg q 24 hr	500 mg q 24 hr	1 g q 24 hr
CAPD	500 mg q 48 hr	1 g q 48 hr	2 g q 48 hr	2 g q 48 hr
Hemodialysis ^{g)}	1 g on day 1, then 500 mg q 24 hr thereafter	1 g on day 1, then 500 mg q 24 hr thereafter	1 g on day 1, then 500 mg q 24 hr thereafter	1 g q 24 hr

CrCl, creatinine clearance; UTI, urinary tract infection; SSSI, skin and skin structure infection; q, qua; CAPD, continuous ambulatory peritoneal dialysis.

^{a)}For mild-to-moderate uncomplicated or complicated UTIs including pyelonephritis; ^{b)}For moderate-to-severe pneumonia; ^{c)}For severe uncomplicated or complicated UTIs including pyelonephritis; ^{d)}For moderate-to-severe uncomplicated SSSIs; ^{e)}For complicated intraabdominal infections when used with metronidazole; ^{f)}Empirical therapy for febrile neutropenia; ^{g)}Cefepime should be administered after hemodialysis on hemodialysis days.

CLINICAL AND EEG MANIFESTATIONS

Clinical manifestations are composed of toxic encephalopathy including altered mental status, tremor, myoclonus, and seizure, and EEG abnormalities comprise generalized periodic discharge (GPD), TW, or NCSE.

Symptoms of encephalopathy

From the data of a recent meta-analysis [9,10], clinical symptoms include depressed consciousness, disorientation, aphasia, tremor, and myoclonus. Depressed consciousness (47% or 80%) includes drowsiness, stupor, or coma, and disorientation comprising confusion, delirium, and agitation. Although the main clinical feature is encephalopathy, CIN is a heterogeneous syndrome.

Patients develop altered mental status, which usually occurs within 4 days (2 to 6) after cefepime administration [9,10]. The latency may depend on the serum or CSF concentrations of cefepime, which are associated with the dosage of cefepime, status of renal function, CNS penetration, and individual variation in pharmacokinetics.

Clinical improvement and resolution of EEG abnormalities were observed within 2 days (1 to 3) after discontinuation of cefepime [10].

Seizures and NCSE

In about a third of the reported cases, electrographic NCSE without abnormal behavior suggestive of seizure was reported [9]; however, convulsive seizures were extremely rare [2,4,6,10,14,17,43]. Many patients with CIN develop myoclonus and severe myoclonus may look like a clonic seizure [6].

TW or NCSE, which is true?

TW, currently renamed as GPD with triphasic morphology [53],

is a descriptive term based on morphology and is traditionally associated with hepatic and uremic encephalopathy. Now, it is well known that GPD with triphasic morphology can be observed in a wide range of encephalopathies. It has been suggested that GPD is associated with the development of electrographic seizure; however, the clinical significance of GPD and its relationship with seizures has been debated [54].

GPD appears in other toxic encephalopathies such as serotonin syndrome and valproate-induced hyperammonemic encephalopathy, and in drug intoxication by lithium, baclofen, levodopa, pentobarbital, tiagabine, pregabalin, levetiracetam, or ifosfamide [55–63].

EEG abnormalities in the reported cases of CIN comprise two patterns, slow typical TW with triphasic morphology at 1 Hz with background slowing, and fast atypical TW with triphasic morphology may represent “TW look-alikes” such as with drug intoxication by lithium, baclofen, levodopa, pregabalin, and tiagabine (Fig. 1) [64]. The latter pattern is difficult to differentiate from NCSE and many investigators interpret it as NCSE.

Diagnosis of NCSE should be strictly relied on the current working clinical criteria [65] and the standardized terminology of the American Clinical Neurophysiology Society (ACNS) [53]. Definite NCSE in comatose patients may be regarded as proven, if both the EEG and clinical state resolves with antiepileptic drug (AED) treatment [65,66]. Regardless of the etiology and pathophysiology, advanced coma stages are frequently accompanied with continuous epileptiform or periodic abnormalities [67]. It had been suggested that continuous epileptiform EEG in patients with encephalopathy may be an epiphenomenal character [68] and continuous epileptiform patterns found in advanced coma stage may represent an end-stage of irreversible coma, as in anoxic brain injury [67,69].

For the same or quite similar clinical symptoms and EEG ab-

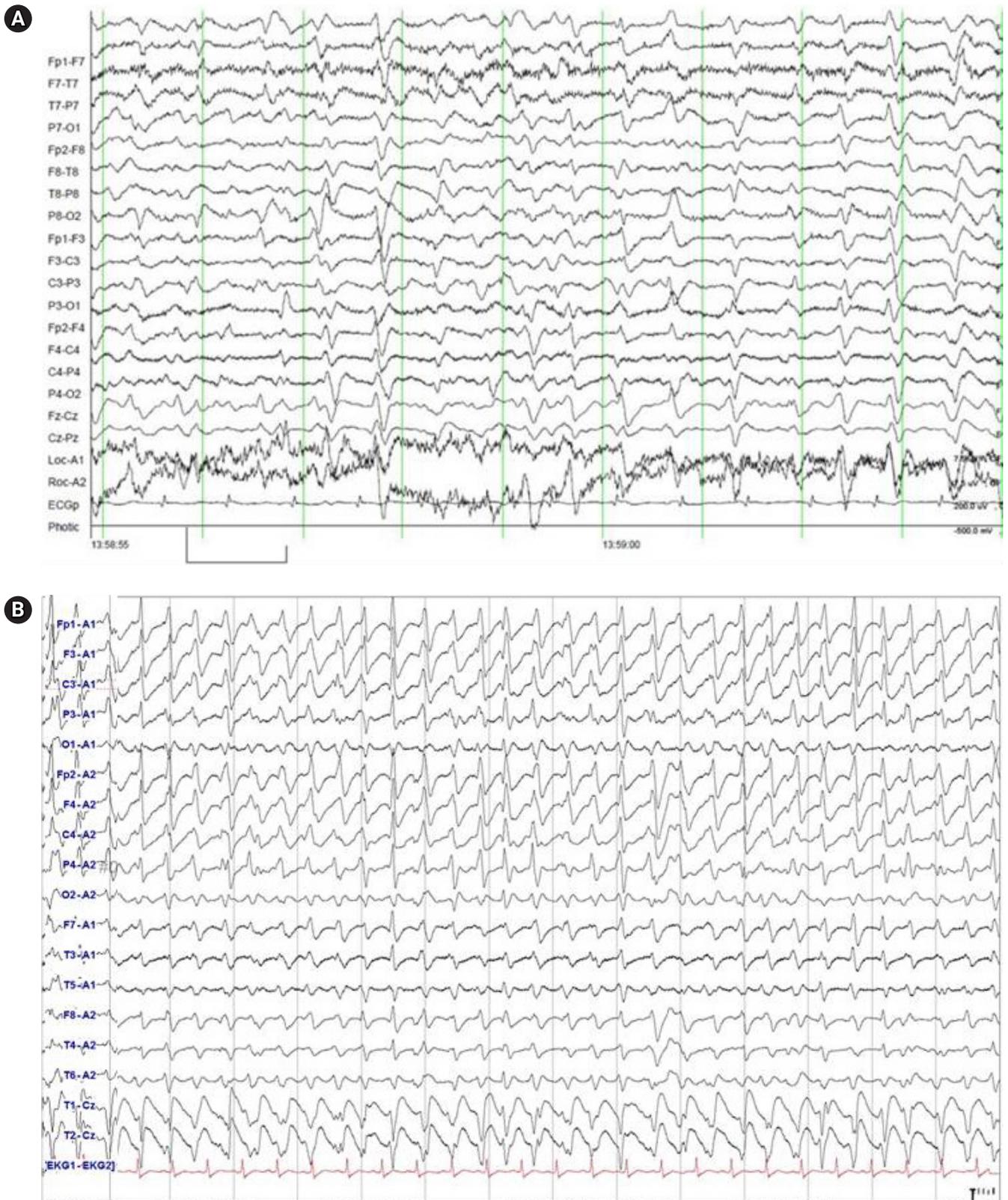


Fig. 1. Example of triphasic wave (TW) pattern in patients with cefepime-induced neurotoxicity. Electroencephalography showing slow, typical TW (A) and fast, atypical TW (B), "TW look-alikes"; the latter is difficult to differentiate from nonconvulsive status epilepticus. (A) Modified from Baek et al. [41], according to the Creative Commons License; (B) is a personal case of the author.

normalities, some described as CIN with TW or GPD [3,15,17,22,24,43,49,70-76], whereas others reported these as CIN with NCSE [4-6,13,14,16,18,20,21,42,45,77-84], depending on the author's view. Some investigators proposed that encephalopathies with GPD or severe metabolic encephalopathies with continuous epileptiform EEG abnormality are not NCSE, and that a coma with continuous generalized epileptiform discharges (coma-GED) should be differentiated from NCSE proper [67,69].

The FDA released drug safety communications about the risk of seizure, which included 59 cases of NCSE associated with cefepime from the approval of cefepime in 1996 to 2012 [23]. However, recently Triplett et al. [43] analyzed 37 EEG samples of CIN cases reported in the literature as NCSE (n = 30) or TW (n = 7), and reported that most EEG did not satisfy the working criteria for NCSE, with 33 showing TW, one showing GEDs, and three being uninterpretable. They concluded that most cases of electrographic NCSE in the literature may be a misinterpretation of continuous GPD as follows. First, their EEG did not satisfy the working clinical criteria for NCSE [65]. Most of the reported cases showed transient or partial improvement of EEG after intravenous administration of benzodiazepines [13,21,44,48,70,77,83]; however, GPD with triphasic morphology can be also suppressed by intravenous benzodiazepines [43,85,86]. Immediate clinical improvement occurred exceptionally in few cases [20,76,81]. Second, most patients recovered after discontinuation of cefepime alone; furthermore, rapid elimination of cefepime through hemodialysis markedly sped their recovery compared with anticonvulsant therapy, from 2 to 1 day [2,10,14,45,74,82]. Third, if EEG abnormalities in patients with CIN indicate true NCSE, anticonvulsant therapy hastens clinical improvement [43,76]; however, AED was not effective in the recovery of EEG and clinical symptoms [10].

DIAGNOSIS

The diagnostic criteria used in the literature are defined as follows: (1) neurological symptoms emerging several days after initiation of cefepime treatment; (2) accompanying EEG findings are consistent with GPD with triphasic morphology; (3) symptoms and abnormal EEG resolved within several days after discontinuation of cefepime; (4) no other cause of toxic or metabolic encephalopathy that is likely to be the cause of altered mental status; and (5) abnormally increased serum concentrations of cefepime if available [4,6,9,10,17,43,76].

High index of suspicion is very important in the early diagnosis of CIN, especially in patients with risk factors or new onset of altered mental status after initiation of cefepime. Thus, frequent monitoring of renal function and mental status, recording of EEG,

and measurement of serum levels of cefepime appear to be of value in patients with risk factors of CIN.

CIN may sometimes be difficult to diagnose since critically ill patients often present comorbidities or comedications that could at least partially account for the neurological symptoms.

MANAGEMENT

Discontinuation of cefepime

The only definite treatment of CIN is discontinuation of cefepime. The result of a meta-analysis revealed that the most common intervention was withdrawal (81%) or interruption of treatment with reduction of cefepime dosage (4%), which led to clinical recovery or improvement within 1 to 3 days in about 90% of the patients [10].

Dialysis

Hemodialysis rapidly removes cefepime from blood and CSF and hastens recovery, especially in life-threatening situations. There have been several reports of emergent hemodialysis with successful results [2,6,14,41,45,46,74,82].

Meta-analysis showed that 8% or 14% of the cases received hemodialysis [9,10]. Hemodialysis resulted in more rapid recovery of encephalopathy and disappearance of GPD than those observed in the AED group, and the median time to clinical improvement dropped from 2 to 1 day [10].

A single 3-hour hemodialysis session is efficient to remove 70% of a given dose due to the low protein binding, low molecular weight, and low volume distribution of cefepime [33]. Hemodialysis reduces the elimination half-life of cefepime from 13.5 to 2.3 hours in patients with ESRD requiring hemodialysis.

CAPD is much less efficient in clearing cefepime with only 9% of the cefepime clearance in hemodialysis [34].

CRRT also easily removes cefepime from blood, and is more effective than CAPD but less so than hemodialysis [87].

Anticonvulsants

A meta-analysis revealed that a third of the reported cases received anticonvulsants including benzodiazepines, phenobarbital, phenytoin, levetiracetam, and valproic acid [9,10]. Although EEG showed temporary suppression of GPD after intravenous injection of benzodiazepine, there was no immediate and permanent recovery of mental status or EEG. Clinical and EEG recovery within 2 to 3 days of intervention is related to discontinuation of cefepime rather than anticonvulsant therapy [10,43,76]. Therefore anticonvulsant therapy is not warranted anymore for the treatment of CIN except for patients with convulsive seizures

Table 2. Nine cases of cefepime-induced neurotoxicity reported in Korea

Study	Age/sex	Renal dysfunction	Dose (g)	Clinical symptoms	Latency (day)	Improvement after Tx (day)	EEG description	Treatment	Remark
Ryu et al. [49]	84/M	Yes	2 bid (excessive)	Confusion, stupor, myoclonus	3	2	TW at 1.5 Hz	AED for myoclonus	GPD at 1.5 Hz
Ryu et al. [49]	74/F	Yes	2 bid (adjusted)	Confusion	2	7	TW		No EEG sample
Baek et al. [41]	71/F	Yes	2 qd (adjusted)	Agitation, stupor	3	3	TW at 1.5 Hz	HD	Albumin 1.9 g/L
Lee et al. [42]	68/F	Yes (HD)	? (adjusted)		6	NA	NCSE	AED	GPD at 2 Hz
Kim et al. [88]	71/F	Yes (CRRT)	2 bid (adjusted)	Stupor, myoclonus	5	3	NCSE	AED	GPD at 2 Hz
Kim et al. [39]	75/M	No	2 tid (appropriate)	Drowsy, tremor	2	2			EEG-uninterpretable
Kwon et al. [89]	36/M	Yes	2 tid (excessive)	Global aphasia Rt hemiplegia	NA	2	NCSE (continuous SW at 2.5 Hz on the Lt frontal)		Old structural lesion and continuous SWs at the Lt frontal area
Lee [90]	31/M	Yes (HD)	2 tid (excessive)	Stupor, myoclonus	4	5	NCSE		GPD at 2 to 3 Hz
Park et al. [40]	74/F	No	2 bid (appropriate)	Stupor, myoclonus	6	4	NCSE	AED	GPD at 2 Hz

Tx, treatment; EEG, electroencephalography; bid, twice a day; TW, triphasic wave; AED, antiepileptic drug; GPD, generalized periodic discharge; qd, daily; HD, hemodialysis; NA, not available; NCSE, nonconvulsive status epilepticus; CRRT, continuous renal replacement therapy; Rt, right; SW, spike-wave; Lt, left.

or definite NCSE [43,76].

ANALYSIS OF KOREAN CASES

There have been nine case reports of CIN in Korean medical journals (Table 2) [39-42,49,88-90]. Six of the nine were diagnosed as NCSE [39,40,42,88-90] and four received anticonvulsants; however, three cases were described as CIN with TW or GPD [39,41] and did not receive anticonvulsants. In the eight EEG samples of the nine reported cases (no EEG in one case [49]), six showed GPD with triphasic morphology at 2 to 3 Hz. One had symptomatic aphasic status epilepticus associated with a preexisting brain injury and cefepime intoxication, and the other showed uninterpretable EEG [39].

PREVENTION

Prevention of CIN is the best treatment. For prevention, adjustment of dosage is most important when renal function is impaired or the serum level of cefepime is abnormally increased. Careful monitoring of renal function is recommended to allow daily adjustment of the cefepime dose. TDM of cefepime can be helpful if available.

PROGNOSIS

An early diagnosis and discontinuation of cefepime is a major key to a favorable outcome. CIN is reversible in most patients. Death may occur due to underlying illness or a delay in diagnosis. Unexplained mortality in patients with CIN has been reported many times, although a causal relationship between neurotoxicity and mortality has not been demonstrated [71,91]. The FDA reported that a statistically significant increased mortality in patients on cefepime compared to that in patients on other cephalosporines was not identified upon meta-analysis [92].

CONCLUSION

CIN is a toxic encephalopathy with GPD in most cases rather than NCSE, which usually occurs at 2 to 5 days after cefepime initiation and improves in 1 to 3 days after discontinuation. For prevention of CIN, dose adjustment according to renal function is essential in patients with renal insufficiency, and then, careful monitoring of renal function and neurological status is required. CIN should be suspected when new onset of acute neurological deficits occurs in patients with risk factors of CIN. However, CIN may also occur in patients with normal renal function and adjusted dose based on renal function. A diagnosis of CIN can be made after excluding other

causes of altered mental status, supported by GPD on EEG or increased serum levels of cefepime. CIN is reversible after prompt discontinuation of cefepime, and in life-threatening situations, emergent hemodialysis may be helpful. Anticonvulsant therapy is necessary only for patients with convulsive seizures or definite NCSE.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

ORCID

Se-Jin Lee, <https://orcid.org/0000-0001-7438-691X>

Author contributions

Conceptualization: SJL. Data curation & Formal analysis: SJL. Visualization & Writing—original draft: SJL. Writing—review editing: SJL.

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Prior antithrombotic use is significantly associated with decreased blood viscosity within 24 hours of symptom onset in patients with acute ischemic stroke

Joong Hyun Park, MD¹; Jeong Yeon Kim, MD, PhD¹; Jong Sam Baik, MD, PhD¹; Jae Hyeon Park, MD, PhD¹; Hyo Suk Nam, MD, PhD²; Sang Won Han, MD¹

¹Department of Neurology, Inje University Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Republic of Korea

²Department of Neurology, Yonsei University College of Medicine, Seoul, Republic of Korea

ORIGINAL ARTICLE

Received: July 30, 2019

Revised: September 3, 2019

Accepted: September 3, 2019

Corresponding Author:

Sang Won Han, MD

Department of Neurology, Inje University Sanggye Paik Hospital, Inje University College of Medicine, 1342 Dongil-ro, Nowon-gu, Seoul 01757, Republic of Korea

Tel: +82-2-950-4832

Fax: +82-2-950-1955

E-mail: swhan@paik.ac.kr

Background: Blood viscosity (BV) is the intrinsic resistance of blood to flow and is a measure of blood stickiness. Several clinical and epidemiologic studies have demonstrated an association between BV and the occurrence of major thromboembolic events. Although BV is significantly higher in cases of lacunar or cardioembolic strokes, its relationship with demographic and laboratory parameters during the acute stage of ischemic stroke is unknown. We investigated the relationship between baseline characteristics of acute ischemic stroke and BV within 24 hours of symptom onset in patients with acute ischemic stroke.

Methods: We enrolled patients aged 40 years or older with documented histories of ischemic stroke or transient ischemic attack within 24 hours of symptom onset. A scanning capillary-tube viscometer was used to assess whole BV.

Results: The mean age was 69.6±12.03 years and 44.4% of the patients were female. Of 189 patients, 68.3% had a history of hypertension; 27%, diabetes; 42.9%, hypercholesterolemia; 3.7%, coronary artery disease; and 18%, stroke. Additionally, 40.7% were current smokers. Sixty-one patients (32.3%) were regularly taking antithrombotics. Multiple linear regression analysis revealed that hematocrit was positively correlated with increased BV and prior antithrombotic use was correlated with decreased BV. Hematocrit-adjusted partial correlation demonstrated that prior antithrombotic use was significantly associated with decreased BV.

Conclusion: Prior antithrombotic use is significantly associated with decreased BV within 24 hours of symptom onset in patients with acute ischemic stroke. Our findings indicate that antithrombotic medications may change the hemorheological profile in these patients.

Keywords: Aspirin; Blood viscosity; Hematocrit; Blood platelets; Stroke

INTRODUCTION

Blood viscosity (BV) is defined as the intrinsic resistance of blood to flow and serves as a measure of blood “stickiness” [1-3]. BV is an essential hemorheological factor and is determined by hematocrit,

plasma viscosity (PV), and properties of red blood cells (RBCs) [4]. Increases in these factors correspond to increases in BV. High aggregation and low deformability of RBCs can also increase BV. High BV, in turn, increases thromboembolic risk and plays an important role in cerebro- cardiovascular diseases [2,3,5-7]. Several

clinical and epidemiologic studies have demonstrated an association between BV and the occurrence of major thromboembolic events [8,9]. BV can also be altered during various physiopathological conditions including obesity, cigarette smoking, chronic heart failure, hypertension, and diabetes [10]. Furthermore, BV can be modified using medical treatments such as antithrombotics or statins. Although high BV is known to contribute to stroke occurrence, few studies have examined BV in acute ischemic stroke [1,3,10,11]. There is evidence to show that BV is significantly higher in cases of lacunar or cardioembolic strokes [1,3,12]. However, the relationship between BV and biochemical parameters during the acute stage of ischemic stroke have not yet been elucidated. Therefore, we investigated the relationship between baseline characteristics of acute ischemic stroke and BV within 24 hours of symptom onset in such patients.

METHODS

Patients

We enrolled patients aged 40 years or older with documented histories of ischemic stroke or transient ischemic attack (TIA) within 24 hours of symptom onset between January 2018 and December 2018. In order to be eligible for inclusion in the study, the symptom complex of TIA patients had to encompass weakness, speech disturbance, dysarthria or dysphasia for greater than 5 minutes [13]. Patient demographics, clinical information including vascular risk factors, and medical histories were assessed during hospital admission. A skilled pharmacist checked the medications each patient took regularly during the week preceding their admission. The laboratory findings affecting BV, including hemoglobin, hematocrit, white blood cells, platelets, random plasma glucose, and prothrombin time-international normalized ratio (PT-INR) were examined during initial blood sampling in the emergency room (ER). Blood protein, fasting blood sugar, and lipid profiles were obtained after a 12-hour fast. All patients underwent systemic investigations of brain magnetic resonance imaging and at least one vascular imaging study, such as conventional angiography, magnetic resonance angiography, or computed tomographic angiography. Echocardiography and 24-hour Holter monitoring were done in a patient with embolic stroke of undetermined etiology to detect the cardioembolic source. Stroke subtypes were assigned according to the Trial of ORG 10172 in the Acute Stroke Treatment classification system, and the criteria for classification were strictly enforced. We excluded patients diagnosed with stroke subtypes of other determined etiologies, such as nonatherosclerotic vasculopathy, hypercoagulable states, and hematologic disorders.

BV measurement

A scanning capillary-tube viscometer (SCTV) (Hemovister, Pharmode Inc., Seoul, Korea) was used to assess the whole blood viscosity (WBV). The SCTV assesses systolic WBV (SBV) and diastolic WBV (DBV). SBV and DBV characterize viscosities at high and low shear rates, respectively. A WBV measured at a shear rate of 300 second^{-1} was selected as the SBV and at 1 second^{-1} as the DBV [3]. A 3 mL of whole blood from each patient was collected in an ethylenediaminetetraacetic acid anticoagulant-coated tube and stored at 4°C . All BV levels were obtained before hydration therapy in the ER, and measurements were taken within 24 hours of collection.

Statistical analysis

Variables were tested for normality using the Kolmogorov-Smirnov test. The baseline parameters of each group were analyzed using one-way analysis of variance (ANOVA) with a Tukey *post hoc* test for continuous variables wherever applicable. Univariate analyses of demographics, vascular risk factors, and medical history were performed using an independent sample *t* test or the Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables. Multivariate linear regression models were used to investigate the relationship between significant univariate variables. A multivariate analysis was performed using all variables with $P < 0.05$ in the univariate analysis. Descriptive data were expressed as number (percent) or mean \pm standard deviation. Statistical analyses were performed using SPSS version 25.0 for Windows (IBM Co., Armonk, NY, USA).

Institutional Review Board/Institutional Animal Care and Use Committee approval

The Research Ethics Committee of Inje University Sanggye Paik Hospital approved the present study (2018-08-025). The requirement for informed consent was waived because the database was accessed only for purposes of analysis; personal information was not used.

RESULTS

The patient profile and reasons for exclusion from the study have been outlined in Fig. 1. Of 189 patients, 22 had TIA (11.6%). The most frequent stroke subtype was lacunar stroke ($n = 65$, 34.4%), followed by stroke of undetermined etiology, negative workup ($n = 43$, 22.8%), large artery atherosclerosis ($n = 32$, 16.9%), and cardioembolism (CE) ($n = 27$, 14.3%). The baseline characteristics of the study population are shown in Table 1. The mean age was 69.6 ± 12.03 years, and 44.4% were female. Of these, 68.3%

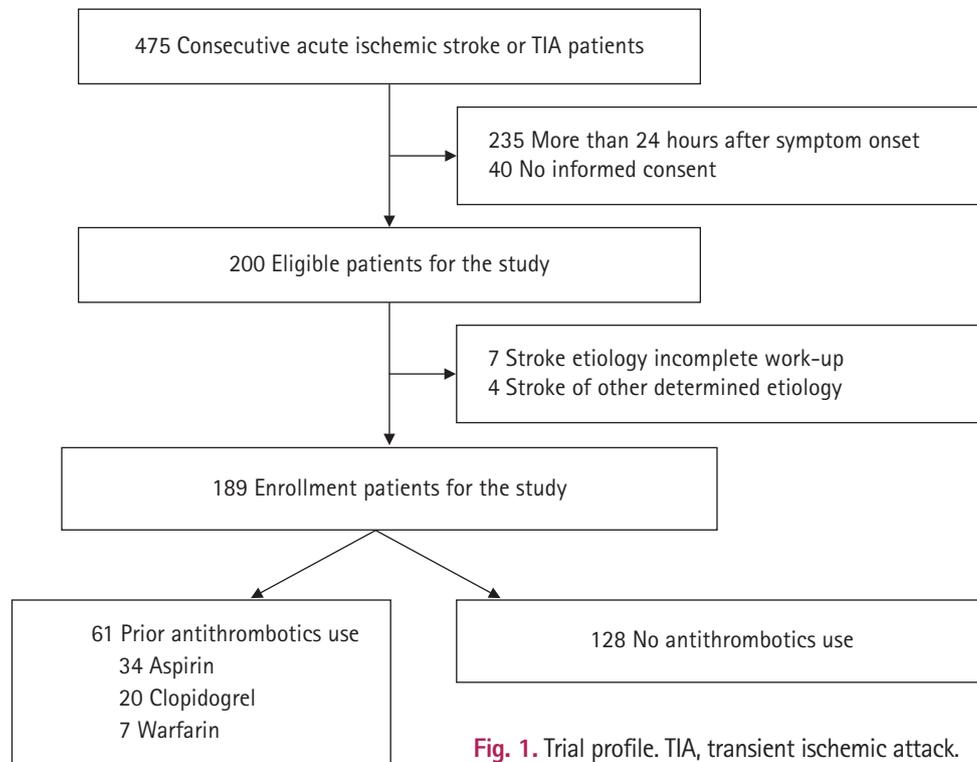


Fig. 1. Trial profile. TIA, transient ischemic attack.

had a history of hypertension; 27%, diabetes; 42.9%, hypercholesterolemia; 3.7%, coronary artery disease; and 18%, stroke. Additionally, 40.7% were smokers at the time of the study. Sixty-one patients (32.3%) were regularly taking antithrombotics (aspirin, 56%; clopidogrel, 33%; warfarin, 11%). There were no patients taking dual antiplatelet therapy or a new oral anticoagulant. Older age was highly correlated with antithrombotic use ($r = 0.324$, $P < 0.0001$). Though INR was higher in patients with prior antithrombotic use (1.09 vs. 1.01, $P = 0.045$), there was no difference in INR between antiplatelet and anticoagulant user groups (1.09 vs. 1.14, $P = 0.645$). Patients with CE were older, had higher INR, lower smoking rates, and lower low-density lipoprotein cholesterol (LDL-C) levels, likely related to the higher number of female patients and higher use of antithrombotics among patients in this category (Table 1). Table 2 shows the difference in BV based on the history of prior antithrombotic use. Prior antithrombotic use was positively associated with decreased BV but no significant differences in BV were observed among treatment groups.

Univariate linear regression analyses were performed on baseline characteristics relative to SBV and DBV. SBV and DBV were significantly associated with age, smoking, hemoglobin, hematocrit, white blood cell count, platelet count, total cholesterol level, LDL-C level, and prior antithrombotic use. Prior statin use did not influence BV levels (SBV, $P = 0.485$ vs. DBV, $P = 0.766$). Multiple linear regression analysis revealed that hematocrit, platelet

count, and prior antithrombotic use were associated with SBV and DBV (Table 3). Hematocrit was positively related with increased SBV, and hematocrit and platelet count were positively associated with increased DBV. Prior antithrombotic use was significantly related with decreased SBV and DBV. Hematocrit-adjusted partial correlation revealed that prior antithrombotic use was significantly associated with decreased SBV and DBV ($r = -0.227$, $P = 0.014$ vs. $r = -0.231$, $P = 0.013$) (Fig. 2).

DISCUSSION

BV reflects frictional interactions between RBCs and other blood components within the systemic vascular system [2]. The major determinants of BV are the aggregation and deformability of RBCs, hematocrit, and PV. BV can provide important information regarding stroke risk and can be modified by therapeutic modalities. In this study, we investigated the relationship between patient characteristics and BV within 24 hours of symptom onset in acute ischemic stroke. We found that prior antithrombotic use was associated with decreased BV.

As discussed earlier, aggregation and deformability of RBCs are some of the main factors that influence BV. Upon reaching the arterioles, RBC aggregates are dispersed due to increased shear. Once they pass through the arterioles, RBCs flow as individual cells through the capillaries. After capillary passage, they again ag-

Table 1. Baseline characteristics of the study population

Characteristic	Total (n=189)	LAA (n=32)	Lacune (n=65)	SUDn (n=43)	CE (n=27)	TIA (n=22)	P value
Demographic							
Age (yr)	69.6±12.03	71.9±11.28	66.7±10.87	71.1±12.32	76.9±9.51	62.8±13.32	<0.001 ^{a)}
Female sex	84 (44.4)	11 (34.4)	27 (43.5)	20 (35.8)	14 (51.9)	12 (54.5)	0.538
Medical history							
Hypertension	129 (68.3)	20 (62.5)	44 (67.7)	30 (69.8)	24 (88.9)	11 (50)	0.056
Diabetes mellitus	51 (27)	11 (34.4)	21 (32.3)	8 (18.6)	9 (33.3)	2 (9.1)	0.113
Hypercholesterolemia	81 (42.9)	13 (40.6)	29 (44.6)	15 (34.9)	15 (55.6)	9 (40.9)	0.545
Stroke	34 (18)	7 (21.9)	11 (16.9)	6 (14)	9 (33.3)	1 (4.5)	0.097
Coronary artery disease	7 (3.7)	1 (3.1)	1 (1.5)	0 (0)	4 (14.8)	1 (4.5)	0.087
Smoking	77 (40.7)	18 (56.2)	32 (49.2)	15 (34.9)	5 (18.5)	7 (31.8)	0.017
Antithrombotic use	61 (32.3)	10 (31.2)	17 (26.2)	9 (20.9)	20 (74.1)	5 (22.7)	<0.001 ^{a)}
Stain use	62 (32.8)	9 (28.1)	20 (30.8)	15 (55.6)	11 (26.2)	7 (31.8)	0.150
Laboratory finding							
Hemoglobin (g/dL)	13.7±2.05	13.7±2.45	13.9±1.69	13.7±2.05	13.2±2.24	14±1.85	0.745
Hematocrit (%)	40.8±5.73	40.9±6.27	40.9±4.6	41±5.73	39.5±6.29	41.4±5.12	0.828
White blood cells (10 ³ /μL)	8.01±3.09	9.21±4.02	7.07±2.23	8.14±3.11	9.08±3.04	7.34±2.95	0.316
Platelets (10 ³ /μL)	238±70.5	269±86.23	234±66.43	234±58.51	223±75.77	228±61.39	0.300
Random plasma glucose (mg/dL)	145±60.04	137±48.64	153±65.85	136±62.7	160±62.22	129±42.98	0.262
Total cholesterol (mg/dL)	157±38.24	152±36.73	168±40.49	152±35.79	146±36.52	154±36.05	0.087
LDL-C (mg/dL)	97±29.06	96±26.85	106±30.71	94±27.93	85±25.14	95±28.74	0.027 ^{a)}
HDL-C (mg/dL)	40±7.25	39±9.26	41±8.23	40±9.47	44±13.38	41±7.25	0.492
Triglyceride (mg/dL)	121±113.59	106±39.01	129±68.77	119±59.45	116±114.8	132±62.59	0.684
INR	1.04±0.18	1.03±0.65	0.99±0.64	1.02±0.79	1.18±0.4	1.04±0.64	<0.009 ^{a)}
SBV (cP)	4.39±0.91	4.47±1.02	4.49±0.77	4.23±0.87	4.42±1.11	4.26±0.94	0.574
DBV (cP)	13.66±3.15	13.91±3.42	14.06±2.74	13.08±3.01	13.76±3.83	13.12±3.27	0.498

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

LAA, large artery atherosclerosis; SUDn, stroke of undetermined etiology, negative work-up; CE, cardioembolism; TIA, transient ischemic attack; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; INR, international normalized ratio; SBV, systolic whole blood viscosity; cP, centipoise; DBV, diastolic whole blood viscosity.

^{a)}Significant P values.

Table 2. Differences in blood viscosity based on prior use of antithrombotics

Variable	SBV (cP)	P value	DBV (cP)	P value
No antithrombotics (n=128)	4.5±0.96		14.1±3.39	
Prior antithrombotics (n=61)	4.1±0.56	0.001 ^{a)}	12.6±2.13	0.003 ^{a)}
Antiplatelets (n=54)	4±0.58	0.002 ^{a)}	12.5±2.17	0.003 ^{a)}
Aspirin (n=34)	4±0.54	0.001 ^{a)}	12.5±2.37	0.002 ^{a)}
Clopidogrel (n=20)	4.1±0.59	0.002 ^{a)}	12.5±2.04	0.003 ^{a)}
Warfarin (n=7)	4.1±0.47	0.363	13±1.98	0.447
Antiplatelets vs. Warfarin		0.709		0.603
Aspirin vs. Warfarin		0.725		0.804
Clopidogrel vs. Warfarin		0.734		0.826
Aspirin vs. Clopidogrel		0.897		0.872

Values are presented as mean±SD.

SBV, systolic whole blood viscosity; cP, centipoise; DBV, diastolic whole blood viscosity.

^{a)}Significant P values.

gregate within collecting venules [2]. Factors that increase RBC aggregation also increase flow resistance in microcirculation. In

this scenario hematocrit, the volume fraction of RBCs in whole blood, becomes a vital factor that affects BV. Changes in the he-

Table 3. Multivariate linear regression analyses of baseline characteristics with regard to SBV and DBV

Variable	SBV			DBV		
	B (SE)	Standardized β	P value	B (SE)	Standardized β	P value
Age	0.007 (0.005)	0.096	0.156	0.021 (0.016)	0.085	0.190
Smoking	-0.01 (0.109)	-0.006	0.924	-0.174 (0.368)	-0.028	0.638
Hemoglobin	0.005 (0.037)	0.029	0.900	0.037 (0.124)	0.066	0.768
Hematocrit	0.329 (0.104)	0.758	0.002 ^{a)}	1.147 (0.35)	0.749	0.001 ^{a)}
White blood cells	0.029 (0.016)	0.106	0.072	0.089 (0.054)	0.093	0.099
Platelets	0.001 (0.001)	0.113	0.073	0.005 (0.002)	0.135	0.026 ^{a)}
Total cholesterol	-0.001 (0.005)	-0.042	0.843	-0.001 (0.016)	-0.011	0.955
LDL-C	0.003 (0.006)	0.101	0.633	0.005 (0.022)	0.048	0.812
Antithrombotic use	-0.259 (0.109)	-0.135	0.019 ^{a)}	-0.892 (0.368)	-0.132	0.017 ^{a)}

SBV, systolic whole blood viscosity; DBV, diastolic whole blood viscosity; SE, standard error; LDL-C, low-density lipoprotein cholesterol.

^{a)}Significant P values.

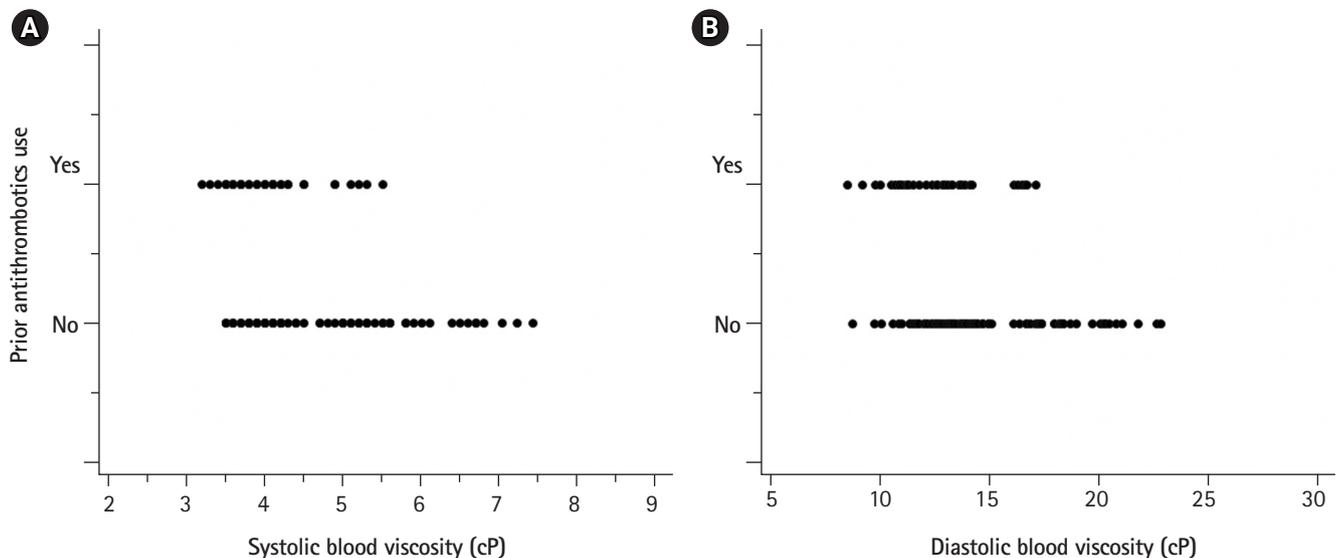


Fig. 2. (A, B) Scatterplots of the relationship between prior antithrombotic use and blood viscosity (BV). Hematocrit-adjusted partial correlation shows that prior antithrombotic use is significantly associated with decreased systolic and diastolic whole BV ($r=-0.227$, $P=0.014$ vs. $r=-0.231$, $P=0.013$). cP, centipoise; r , Pearson's partial correlation coefficient.

matocrit significantly contributes to rheological discrepancies. A 10% increase in hematocrit increases the SBV by 5%, whereas the same increase in hematocrit increases the DBV by 30% [14]. Due to the variations of hematocrit in small vessels, its influence on BV is more pronounced in the microcirculation [15]. One of the more conspicuous impacts of BV is on microcirculatory tissue perfusion. A hematocrit-induced increase in BV may lead to a decrease in tissue perfusion.

BV can be modified using drugs such as vasodilators, statins, or antithrombotics [2,16,17]. A few studies have examined the effect of antithrombotics on BV [17-19] and found that warfarin, heparin, and argatroban can decrease BV [17,20]. Varying results have

been observed with antiplatelets, depending on the experimental protocol used in the study. Aspirin and cilostazol do not change BV but dipyridamole and clopidogrel decrease BV upon treatment [18,21,22]. Antithrombotics may decrease BV by inhibiting platelet aggregation and improving RBC deformability. Our results showed that prior antithrombotic use was significantly associated with decreased BV. The use of both anticoagulants and antiplatelets were related to a decrease in BV. Although we could not find plausible explanations for these discrepancies among studies, patient-specific differences may be a contributing factor. We studied patients with an ischemic stroke or TIA within 24 hours of symptom onset. Informative studies of BV and acute ischemic stroke

are limited and previous studies have not examined this period [1,3,10]. Further studies focusing on this specific time period in ischemic stroke patients are required to assess the influence of prior antithrombotic use and BV. An older study has demonstrated significantly lower cerebral blood flow (CBF) in patients with hematocrit in the range of 47% to 53% than in a group with 36% to 46% [23]. In the former group, phlebotomy increased CBF, implying that optimal hematocrit and BV levels may exist for CBF. Another factor that is possibly associated with increased BV is dehydration. One study showed that BV at admission was significantly higher in patients with lacunar stroke but normalized after 2 weeks of normal hydration [1]. In our study, all blood samples for BV measurement were collected before hydration therapy.

The present study had several limitations. This was a small cross-sectional and observational study, implying the existence of concealed confounders. We could not measure plasma components such as fibrinogen or C-reactive protein in all patients, both of which can affect BV. We enrolled only Korean patients, which limited our ability to generalize the inferences of the study to non-Korean patients. In concordance with our multivariate analysis results, previous studies show that antithrombotics reduce the BV significantly in patients with acute ischemic stroke. However, the statistical power to support our conclusion is fairly weak, mainly due to the small sample size and lack of age-matched controls. These limitations should be considered when interpreting our data.

In conclusion, we found that prior antithrombotic use is significantly associated with decreased BV within 24 hours of symptom onset in patients with acute ischemic stroke. Our results indicate that antithrombotic medications may change the hemorheological profile in acute ischemic stroke patients. Further studies are essential to evaluate the role of BV plus antithrombotic therapy on the risk of stroke occurrence.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

ORCID

Joong Hyun Park, <https://orcid.org/0000-0001-6118-4833>

Jeong Yeon Kim, <https://orcid.org/0000-0002-7106-2773>

Jong Sam Baik, <https://orcid.org/0000-0002-5300-203X>

Jae Hyeon Park, <https://orcid.org/0000-0003-4523-9384>

Hyo Suk Nam, <https://orcid.org/0000-0002-4415-3995>

Sang Won Han, <https://orcid.org/0000-0002-9503-1883>

Author contributions

Conceptualization: SWH. Data curation & Formal analysis: JHP and SWH. Funding acquisition: JHP. Investigation: JHP and SWH. Methodology: JHP and SWH. Project administration: JHP. Resources: JHP. Software: JYK. Supervision: JSB. Validation: JSB. Visualization & Writing—original draft: HSN and JHP. Writing—review editing: HSN and SWH.

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Sex disparity in acute ischemic stroke outcomes in Korea

Byung Cheol Gwak, MD¹; Ga Yeon Kim, MD¹; Hyo Ji Park, BS²;
Su Min Kwon, BS²; Seung Il O, BS²; Dae-Hyun Kim, MD, PhD¹;
Jin-Heon Jeong, MD^{1,2,3}; Jae-Kwan Cha, MD, PhD¹

¹Department of Neurology, Dong-A University Hospital, Busan, Republic of Korea

²Stroke Center, Dong-A University Hospital, Busan, Republic of Korea

³Department of Intensive Care Medicine, Dong-A University Hospital, Busan, Republic of Korea

ORIGINAL ARTICLE

Received: October 29, 2019

Revised: December 5, 2019

Accepted: December 9, 2019

Corresponding Author:

Jae-Kwan Cha, MD, PhD

Department of Neurology, Dong-A
University Hospital, 26

Daesingongwon-ro, Seo-gu, Busan
49201, Republic of Korea

Tel: +82-51-240-5266

Fax: +82-51-244-8338

E-mail: nrcjk65@gmail.com

Background: It is unclear whether women diagnosed with acute ischemic stroke (AIS) have worse outcome after adjusting for several confounding factors such as age, initial stroke severity, and risk factors. In this study, we investigated sex disparities in long-term functional outcome after AIS.

Methods: We recruited patients with AIS prospectively registered in the Clinical Research Collaboration for Stroke in Korea database of Dong-A University Stroke Center between 2015 and 2018. We reviewed the patients' clinical demographics, living type (alone or cohabitating), laboratory and radiological findings, stroke severity, stroke subtype, and cardiovascular risk profile. We compared the long-term functional outcomes between men and women using the modified Rankin Scale score at 90 days and 1 year after AIS.

Results: A total of 2,711 patients with AIS were enrolled in this study. Women comprised 38.9% (1,055) of all participants. Compared with men, women were significantly older (72.7 ± 11.6 vs. 65.6 ± 12.2 , $P < 0.01$), showed more severe neurologic deficits (median National Institutes of Health Stroke Scale, 5 vs. 4, $P < 0.01$), and had a higher rate of living alone (57.1% vs. 42.9%, $P < 0.01$) and a higher prevalence of poor functional outcome at 90 days and 1 year after AIS. However, differences in history of statin use, hospital arrival time, and thrombolysis between the two sexes were not observed. After adjusting for several confounding factors, differences in initial neurologic deficits or long-term functional outcomes between sexes were not observed.

Conclusion: This study demonstrated the absence of sex disparities in the status of medical attention for thrombolysis.

Keywords: Stroke; Sex; Marital status; Treatment outcome

INTRODUCTION

Stroke is one of the leading causes of death and accounts for a significant burden not only in Western countries [1,2] but also in Asian countries including Korea [3]. Several studies have shown that women have a worse prognosis than men after acute ischemic stroke (AIS) [4-7]. The worse outcome in women might be relat-

ed to their advanced age [6,8,9], significant prevalence of atrial fibrillation (AF) [4,8], significantly severe initial neurologic deficit [4,5], and limited medical attention [4,5,10-12] including thrombolysis. Inconsistent results [8,13-15] were observed regarding the role of sex disparity in the prognosis after AIS. The results may vary among different ethnicities. In Japan, women initially showed a severe neurologic deficit and poor long-term out-

come after AIS [2]. However, more significant differences in social structure and health care for stroke patients are observed in Korea compared with other countries. Therefore, a comprehensive study is required to determine the presence of sexual disparities in initial neurological severity and long-term functional outcome in Korea.

This investigation primarily aimed to evaluate whether sex disparity influenced the outcomes of AIS in Korea after adjusting for patients' clinical demographics, socioeconomic status, vascular risk factors, and the status of medical attention for thrombolysis based on the Clinical Research Collaboration for Stroke in Korea (CRCS-K) prospective registry [16] data involving a single stroke center.

METHODS

We investigated patients with AIS prospectively enrolled in the CRCS-K Registry of Dong-A University Stroke Center from 2015 to 2018. We reviewed the patients' clinical demographics, living types (living alone or cohabitating), vascular risk factors, and laboratory and radiological findings. All participants' baseline National Institutes of Health Stroke Scale (NIHSS) scores were evaluated by stroke neurologists. Stroke subtypes were determined based on the Trial of Org 10172 in Acute Stroke Treatment classification [17]. To determine the differences in the status of medical attention for thrombolysis between men and women, we investigated the patients' hospital arrival time and performance of intervention (intravenous tissue plasminogen activator [IV t-PA] and/or mechanical thrombectomy). We compared the above various parameters between sexes.

The functional outcomes of survivors determined using the Modified Rankin Scale (mRS) score were followed up 90 days later and 1 year after stroke onset. The mRS scores were classified as follows: ≤ 2 (good functional outcome) and > 2 (poor functional outcome). These assessments were performed via telephone or face-to-face interview at the outpatient clinic. This study was approved by the local ethics committee (DAUHIRB-17-149). Written informed consent by the patients was waived due to a retrospective nature of our study.

Statistical analysis

The clinical characteristics of the patients were summarized, and the specific subgroups were described using descriptive statistics. The categorical variables of the groups were compared using Fisher's exact test or Pearson's chi-square test, while Student's *t* test and Mann-Whitney *U* test were used to compare the continuous variables of the groups. The odds ratios (ORs) for the comparison

of two groups were summarized with 95% confidence intervals (CIs) and *P* values using logistic regression analysis. To evaluate the association between the independent factors and the long-term functional outcomes after AIS, a multivariate model was created using a backward elimination method, and the probability threshold for removal was set at 0.10. The ORs were also adjusted for the factors that affected the response variable. *P* value less than 0.05 was considered statistically significant. Statistical analyses were performed using the SPSS ver. 21 (IBM Co., Armonk, NY, USA).

RESULTS

During the observation periods, 2,702 patients with AIS were enrolled in this study, with women comprising 38.9% (1,055 patients) of all participants. The mean age was 68.4 ± 12.4 years, and the median NIHSS score was 4. The baseline variables stratified according to sex are summarized in Table 1. Women were significantly older (72.7 ± 11.6 vs. 65.6 ± 12.22 , $P < 0.01$) and more often lived alone (57.1% vs. 42.9% , $P < 0.01$) than men with AIS. Women showed a significantly higher prevalence of AF and hypertension and a lower prevalence of smoking and previous history of coronary artery diseases than men. Women showed significantly higher NIHSS score (5.9 ± 5.9 vs. 7.1 ± 6.7 , $P < 0.01$) than men with AIS. However, after adjusting for several confounding factors (living type, age, acute management, risk factors, and stroke subtype), women (OR, 1.25; 95% CI, 0.97 to 1.62; $P = 0.09$) initially showed no significantly severe neurologic deficit after AIS (Supplementary Table 1). A significant difference between sexes in onset-to-door time, based on the use of IV t-PA and mechanical thrombectomy data, was not observed.

Functional outcomes of men and women are shown in Table 2. Women showed a higher prevalence of poor functional outcome at 90 days and 1 year than men after AIS. Age (OR, 1.06; 95% CI, 1.05 to 1.06; $P < 0.01$), living alone (OR, 1.36; 95% CI, 1.06 to 1.75; $P = 0.01$), previous history of AF (OR, 1.68; 95% CI, 1.10 to 2.56; $P = 0.02$), diabetes mellitus (OR, 1.18; 95% CI, 0.99 to 1.42; $P = 0.07$), previous history of cerebrovascular accident (OR, 1.44; 95% CI, 1.17 to 1.77; $P < 0.01$), and no previous history of statin use (OR, 1.51; 95% CI, 1.20 to 1.90; $P < 0.01$) were the independent prognostic factors for AIS. However, female sex (OR, 1.10; 95% CI, 0.89 to 1.36; $P = 0.37$) showed no independent significance for the poor functional outcomes after AIS. Similar results were reported 1 year after AIS (Table 3). The distribution of baseline characteristics and risk factors differed according to sex, but when comparing the functional outcomes between sexes in the same group, significant differences in variables except living alone

Table 1. Differences in baseline characteristics between men and women

Variable	Men (n=1,656)	Women (n=1,055)	P value
Age (yr)	65.6±12.2	72.7±11.6	<0.01
Living types			
Living alone	226 (13.6)	301 (28.5)	<0.01
Cohabiting	1,430 (86.4)	754 (71.5)	
Risk factors			
Hypertension	981 (59.2)	710 (67.3)	<0.01
Diabetes mellitus	508 (30.7)	312 (29.6)	0.54
Current or previous history of smoking	707 (42.7)	68 (6.4)	<0.01
Previous history of coronary artery disease	240 (14.5)	123 (11.7)	0.04
Previous history of cerebrovascular disease	325 (19.6)	208 (19.7)	0.95
Previous history of atrial fibrillation	331 (20.0)	316 (30.0)	<0.01
History of statin use	284 (17.1)	191 (18.1)	0.52
Time delay from hospital arrival time, median (IQR)	546 (160-1,486)	544 (179-1,390)	0.62
Time delay from hospital arrival time, range	7-11,408	12-11,230	
Arrival at the hospital 4.5 hr within onset	570 (34.4)	340 (32.2)	0.24
Use of intravenous tissue plasminogen activator	337 (24.9)	196 (22.3)	0.16
Door-to-needle time, median (IQR)	30 (23-39)	29 (23-38)	0.41
Door-to-needle time, range	10-124	11-290	
Mechanical thrombectomy	140 (8.5)	97 (9.2)	0.51
Door-to-puncture time, median (IQR)	103 (82-121)	104 (80-123)	0.99
Door-to-puncture time, range	16-445	35-1,049	
NIHSS score at admission	5.9±5.9	7.1±6.7	<0.01
Stroke subtype			
Large artery atherosclerosis	629 (38.4)	331 (31.6)	<0.01
Cardioembolism	322 (19.6)	321 (30.7)	
Small-vessel occlusion	306 (18.7)	182 (17.4)	
Stroke of other determined etiologies	48 (2.9)	15 (1.4)	
Stroke of undetermined etiology	335 (20.4)	198 (18.9)	

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

IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale.

Table 2. Sex differences in functional outcome after acute stroke

Variable	Men (n=1,656)	Women (n=1,055)	P value
mRS score at 90 days			
Good functional outcome (0-2)	1,060 (64.1)	552 (52.7)	<0.01
Poor functional outcome (3-6)	594 (35.9)	496 (47.3)	
mRS score at 1 year			
Good functional outcome (0-2)	821 (64.5)	432 (53.5)	<0.01
Poor functional outcome (3-6)	451 (35.5)	375 (46.5)	

Values are presented as number (%).

mRS, modified Rankin Scale.

(Supplementary Table 2) were not observed. As shown in Fig. 1, poor functional outcome was observed 90 days after AIS according to age and sex, with a similar prevalence across men and women of all ages except women aged greater than 80 years, who showed a significantly higher prevalence (Supplementary Table 3). However,

after adjusting for several confounding factors, women aged greater than 80 years showed no significant incidence of poor functional outcomes after AIS (OR, 1.39; 95% CI, 0.84 to 2.29; $P=0.20$) (Fig. 1).

DISCUSSION

In this study, we demonstrated that women had a substantially more severe neurologic deficit and a worse outcome at 90 days and 1 year after AIS than men. However, after adjusting for several confounding factors, female sex was not a significant contributing factor to severe initial neurologic deficit and worse long-term outcome after AIS in Korea.

Generally, female sex is an independent factor associated with worse outcome after AIS [4-7]. However, according to other studies, the worse outcome in women was associated with their age,

Table 3. Multiple logistic regression analysis regarding the predictors of poor functional outcome at 90 days and 1 year after stroke onset

Variable	90 days mRS score			1 year mRS score		
	OR	95% CI	P value	OR	95% CI	P value
Women	1.10	0.89–1.36	0.37	1.08	0.85–1.38	0.54
Living alone	1.50	1.21–1.85	<0.01	1.36	1.06–1.75	0.01
Age (yr)	1.06	1.05–1.06	<0.01	1.07	1.06–1.08	<0.01
Risk factors						
Diabetes mellitus	1.18	0.99–1.42	0.07	1.26	1.02–1.56	0.04
Smoking (ref=no smoking)			0.57			0.10
Current smoking status	1.12	0.89–1.42	0.34	1.33	1.01–1.75	0.04
Previous history of smoking status	1.11	0.86–1.44	0.43	1.24	0.92–1.68	0.16
Previous history of coronary artery disease	1.18	0.92–1.50	0.20	1.39	1.05–1.85	0.02
Previous history of cerebrovascular disease	1.44	1.17–1.77	<0.01	1.19	0.93–1.52	0.17
Previous history of atrial fibrillation	1.55	1.06–2.25	0.02	1.68	1.10–2.56	0.02
Previous history of statin use (ref=yes)	1.51	1.20–1.90	<0.01	1.61	1.22–2.12	<0.01
Stroke subtype (ref=small-vessel occlusion)			<0.01			<0.01
Large artery atherosclerosis	1.99	1.55–2.56	<0.01	2.15	1.58–2.92	<0.01
Cardioembolism	1.80	1.17–2.77	<0.01	2.12	1.30–3.47	<0.01
Stroke of other determined etiologies	1.60	0.79–3.24	0.20	3.07	1.35–6.94	<0.01
Stroke of undetermined etiology	1.45	1.09–1.93	0.01	1.76	1.25–2.48	<0.01

mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval.

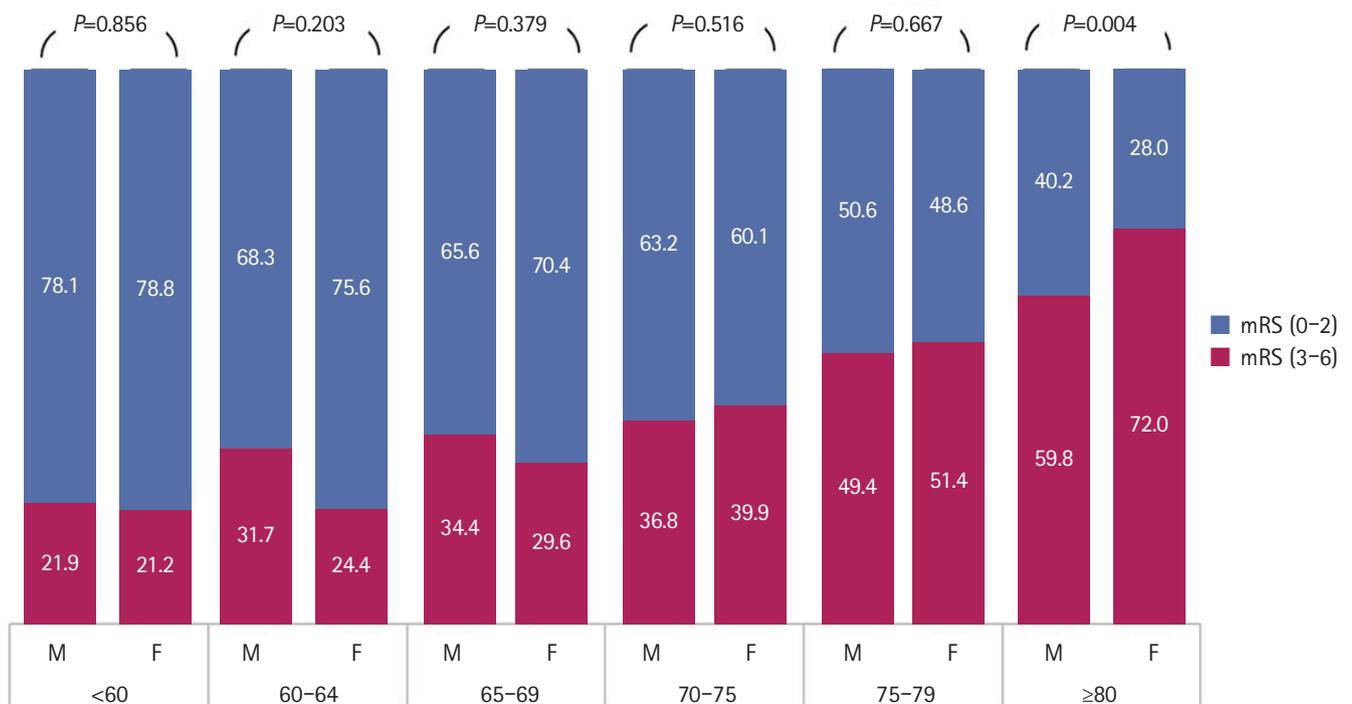


Fig. 1. Distribution of poor functional outcome at 90 days after the diagnosis of acute ischemic stroke by age and sex in the total population. Poor functional outcome (modified Rankin Scale [mRS] score >2). Any significant difference in poor functional outcome after acute ischemic stroke between both sexes in 80 years or older population (odds ratio, 1.39; 95% confidence interval, 0.84 to 2.29; $P=0.20$) (Supplementary Table 3) after adjusting for age, National Institutes of Health Stroke Scale score, living type, hospital arrival time, mechanical thrombectomy, previous history of statin use, previous history of atrial fibrillation, previous history of coronary artery disease, and stroke subtypes.

significant prevalence of AF, living alone, poor medical attention before admission, and higher initial NIHSS score [8,13-15].

In this study, women were approximately 7 years older with a higher prevalence of living alone than men, which is a common trend worldwide [4-7]. Thus, women had poor control of risk factors before being diagnosed with AIS [18,19] and received limited medical attention before arriving at the emergency room [4,5] for thrombolysis [10-12]. However, we demonstrated that statin use was not different between sexes. Moreover, disparity between sexes was not observed in hospital arrival time, the use of IV t-PA, and mechanical thrombectomy after AIS. Almost all previous studies reported in western countries and Japan demonstrated that poor medical attention in women before and after AIS contributed significantly to poor long-term outcome. In Korea, as reported previously, well-developed medical insurance and public transportation for emergent patients were associated with the prevention of poor functional outcome in women after AIS [7]. Notably, in this study, a significant difference in age-specific prognosis was not observed between sexes, different from a previous study that showed significantly worse outcomes after AIS in patients aged 85 years and above [8].

Living alone has been considered a critical factor for worse outcome [20,21]. In this study, although living alone was one of the key factors associated with worse outcome in the whole population after AIS, it was not restricted to women (Supplementary Table 4). In this study, the rate of living alone in women was twice that of men. Notably, the mean age of women living alone was significantly higher than that of men. We presumed that bereavement might have contributed to single living because of the substantially longer lifespan in women. In contrast, living alone in men might be related to other causes such as divorce, home loss, and domestic discord caused by financial crisis rather than natural death of their spouse. A previous study demonstrated that living alone by men aged less than 70 years had a significantly higher impact on the outcomes after AIS compared with women. The study presumed that men were more dependent on spousal encouragement in seeking medical attention for cardiovascular diseases compared with women, and men living alone have higher chances of consuming an unhealthy diet and exhibiting poor health behaviors such as smoking and heavy drinking than women living alone or cohabitating with others [21-23]. Therefore, single men may manifest a negative impact after AIS, similar to women. Hence, further studies are required to validate this hypothesis.

The previous studies showed worse outcomes in women after AIS after adjusting for age and confounding risk factors. They suggested that a rapid decrease of endogenous estrogen diminished its anti-inflammatory and neuroprotective effects [24] and increased

the susceptibility of cells to programmed cell death [25]. Furthermore, in Korea, a unique lifestyle based on a patriarchal-feudalistic chauvinism and Confucianism might contribute to the occurrence of worse outcomes in women after AIS [7,26]. However, the social status of women in Korea has changed dramatically in several aspects due to increased employment rate, improvement of subjective personal health status, and the role of women in institutionalization [27]. Due to the changes mentioned above, it is likely that women have better improved their vulnerability to AIS in Korea compared with the previous reports.

Despite the several significant results, the study has some limitations. First, this was a single-center study, and the findings do not represent nationwide data. Second, we used mRS as a parameter of long-term functional outcome after AIS, which does not represent all the sequelae. Therefore, a variety of tools are required to measure mood, function, and quality of life among women diagnosed with AIS.

This study showed no significant differences between sexes in Korea in initial severity and long-term functional outcome after AIS, in contrast to a previous report.

ARTICLE INFORMATION

Conflict of interest

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

ORCID

Byung Cheol Gwak, <https://orcid.org/0000-0001-8130-4484>

Ga Yeon Kim, <https://orcid.org/0000-0003-4314-7646>

Hyo Ji Park, <https://orcid.org/0000-0002-8250-1428>

Su Min Kwon, <https://orcid.org/0000-0002-3830-4443>

Seung Il O, <https://orcid.org/0000-0002-3742-7070>

Dae-Hyun Kim, <https://orcid.org/0000-0001-9761-7792>

Jin-Heon Jeong, <https://orcid.org/0000-0002-5878-9206>

Jae-Kwan Cha, <https://orcid.org/0000-0002-1049-5196>

Author contributions

Conceptualization: DHK. Data curation & Formal analysis: SMK and SIO. Investigation: HJP. Supervision: JKC. Visualization & Writing—original draft: BCG and GYK. Writing—review editing: JHJ.

Additional information

The supplement is available at <https://doi.org/10.18700/jnc.190108>.

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Supplementary Table 1. Univariate and multivariate analyses regarding the predictors of the initial National Institutes of Health Stroke Scale score

Variable	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Women	1.44 (1.23–1.70)	0.000	1.25 (0.97–1.62)	0.089
Living alone	1.57 (1.29–1.90)	0.000	1.73 (1.35–2.21)	0.000
Age (yr)	1.03 (1.02–1.03)	0.000	1.02 (1.02–1.03)	0.000
Arrival at the hospital 4.5 hr after onset	0.59 (0.50–0.69)	0.000	2.29 (1.07–4.94)	0.034
Use of intravenous tissue plasminogen activator (ref=yes)	4.44 (3.61–5.45)	0.000	6.29 (2.94–13.47)	0.000
Intraarterial thrombectomy (ref=no)	0.05 (0.04–0.08)	0.000	0.14 (0.09–0.23)	0.000
Risk factors				
Diabetes mellitus	0.70 (0.59–0.84)	0.000	0.69 (0.55–0.87)	0.001
Smoking				
Previous history of smoking	0.81 (0.65–1.02)	0.068	0.97 (0.70–1.34)	0.843
Current smoking	0.77 (0.64–0.93)	0.006	1.33 (1.00–1.76)	0.053
Previous history of statin use (ref=no)	1.33 (1.07–1.65)	0.009	1.54 (1.17–2.04)	0.002
Previous history of coronary artery disease	1.32 (1.05–1.65)	0.017	0.99 (0.73–1.33)	0.927
Previous history of cerebrovascular disease	0.86 (0.70–1.05)	0.137		
Previous history of atrial fibrillation	1.32 (1.05–1.65)	0.017	0.99 (0.73–1.33)	0.927
Stroke subtype (ref=small-vessel occlusion)				
Large artery atherosclerosis	2.89 (2.15–3.90)	0.000	2.65 (1.91–3.68)	0.000
Cardioembolism	10.13 (7.45–13.79)	0.000	7.99 (4.72–13.54)	0.000
Stroke of other determined etiologies	1.93 (1.01–3.69)	0.048	1.87 (0.80–4.37)	0.149
Stroke of undetermined etiology	3.73 (2.71–5.13)	0.000	2.82 (1.96–4.05)	0.000

OR, odds ratio; CI, confidence interval.

Supplementary Table 2. Logistic regression analysis regarding sex differences for the predictors of poor functional outcome at 90 days and 1 year after stroke onset

Variable	mRS score at 90 days			mRS score at 1 year		
	OR	95% CI	P value	OR	95% CI	P value
Living type						
Cohabiting	1.035	0.792–1.354	0.799	0.875	0.618–1.240	0.452
Living alone	1.225	0.681–2.205	0.497	2.686	1.174–6.145	0.019
Age (yr)						
<60	1.278	0.593–2.756	0.531	0.740	0.250–2.186	0.586
60–64	0.578	0.271–1.232	0.156	0.602	0.208–1.744	0.35
65–69	1.120	0.525–2.393	0.769	1.116	0.418–2.977	0.826
70–74	0.854	0.440–1.660	0.642	1.095	0.496–2.421	0.822
75–79	1.054	0.611–1.821	0.849	1.413	0.644–3.097	0.389
≥80	1.388	0.840–2.294	0.200	1.062	0.545–2.071	0.859
Arrival at the hospital 4.5 hr after onset						
No	1.064	0.719–1.575	0.756	1.147	0.643–2.045	0.643
Yes	1.006	0.737–1.374	0.969	0.935	0.638–1.372	0.732
Use of intravenous tissue plasminogen activator						
No	0.993	0.719–1.371	0.966	0.895	0.608–1.316	0.572
Yes	1.512	0.930–2.458	0.095	1.306	0.740–2.305	0.357
Intraarterial thrombectomy						
No	1.080	0.833–1.401	0.560	1.004	0.717–1.407	0.980
Yes	0.805	0.394–1.645	0.552	0.774	0.272–2.198	0.630
Risk factors						
Diabetes mellitus						
No	1.151	0.861–1.538	0.342	1.211	0.823–1.784	0.332
Yes	0.858	0.547–1.344	0.503	0.753	0.426–1.331	0.329
Smoking						
No smoking	0.962	0.732–1.263	0.779	0.898	0.629–1.283	0.555
Current smoking	1.886	0.997–3.569	0.051	1.506	0.707–3.210	0.289
Previous history of smoking	1.175	0.412–3.356	0.763	3.500	0.665–18.416	0.139
Previous history of coronary artery disease						
No	1.092	0.841–1.419	0.510	1.066	0.758–1.498	0.714
Yes	0.852	0.441–1.647	0.634	0.727	0.303–1.741	0.474
Previous history of cerebrovascular accident disease						
No	1.031	0.781–1.362	0.828	1.042	0.730–1.488	0.821
Yes	1.178	0.712–1.951	0.523	0.896	0.442–1.818	0.761
Previous history of atrial fibrillation						
No	1.079	0.812–1.434	0.602	1.027	0.712–1.480	0.888
Yes	1.018	0.638–1.623	0.941	0.985	0.528–1.838	0.962
Previous history of statin use						
No	0.952	0.731–1.241	0.718	0.949	0.677–1.331	0.763
Yes	1.857	0.975–3.536	0.060	1.558	0.626–3.877	0.341
NIHSS score at admission						
0–5	0.928	0.671–1.283	0.650	0.782	0.500–1.224	0.283
6–13	1.269	0.816–1.972	0.291	1.468	0.850–2.535	0.168
≥14	1.106	0.544–2.250	0.780	0.953	0.397–2.291	0.915
Stroke subtype						
Small-vessel occlusion	1.164	0.650–2.085	0.610	1.770	0.781–4.012	0.172
Large artery atherosclerosis	1.106	0.730–1.675	0.635	1.108	0.649–1.891	0.708
Cardioembolism	0.968	0.607–1.545	0.893	0.861	0.468–1.584	0.630
Stroke of other determined etiologies	1.829	0.146–22.961	0.640	0.000	0.000	1.000
Stroke of undetermined etiology	1.025	0.579–1.813	0.933	0.769	0.368–1.607	0.485

mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale.

Supplementary Table 3. Baseline characteristics of cases stratified by living type

Variable	Total		Men		Women		P value
	Living alone	Cohabiting	Living alone	Cohabiting	Living alone	Cohabiting	
Number	527 (19.4)	2,184 (80.6)	226 (13.6)	1,430 (86.4)	301 (28.5)	754 (71.5)	
Age (yr)	71.1±12.5	67.7±12.4	64.0±13.3	65.9±12.0	76.6±8.4	71.2±12.3	<0.1
Risk factors							
Hypertension	352 (66.8)	1,339 (61.3)	140 (61.9)	841 (58.8)	212 (70.4)	498 (66.0)	0.17
Diabetes mellitus	153 (29.0)	667 (30.5)	56 (24.8)	452 (31.6)	97 (32.2)	215 (28.5)	0.23
Smoking status	151 (28.7)	624 (28.6)	130 (57.5)	577 (40.3)	21 (7.0)	47 (6.2)	0.27
Previous history of coronary artery disease	75 (14.2)	288 (13.2)	31 (13.7)	209 (14.6)	44 (14.6)	79 (10.5)	0.06
Previous history of cerebrovascular disease	96 (18.2)	437 (20.0)	40 (17.7)	285 (19.9)	56 (18.6)	152 (20.2)	0.57
Previous history of atrial fibrillation	141 (26.8)	506 (23.2)	38 (16.8)	293 (20.5)	103 (34.2)	213 (28.2)	0.06
History of statin use	81 (15.4)	394 (18.0)	29 (12.8)	255 (17.8)	52 (17.3)	139 (18.4)	0.66
Time delay from onset to hospital arrival, median (IQR)	617-1,604	530.5-1,212.25	653-1,883.5	531-1,269.75	600-1,433	527-1,107.5	0.22
Time delay from onset to hospital arrival, range	12-11,213	7-11,408	19-11,213	7-11,408	12-11,127	13-11,230	
Arrival at the hospital 4.5 hr within onset	159 (30.2)	751 (34.4)	70 (31.0)	500 (35.0)	89 (29.6)	251 (33.3)	0.24
Use of intravenous tissue plasminogen activator	79 (18.2)	454 (25.3)	34 (18.4)	303 (26.0)	45 (18.1)	151 (24.0)	0.06
Door-to-needle time, median (IQR)	32-17	29-16	32-17	30-16	32-15	29-15.5	0.16
Door-to-needle time, range	10-290	10-171	10-55	10-124	11-290	11-171	
Intraarterial thrombectomy	39 (7.4)	198 (9.1)	14 (6.2)	126 (8.8)	25 (8.3)	72 (9.5)	0.53
Door-to-puncture time, median (IQR)	109-39	102.5-39.5	106.5-28.5	101.5-42.25	124-46	103.5-40.5	
Door-to-puncture time, range	52-181	16-1,049	72-150	16-445	52-181	35-1,049	
NIHSS score at admission	7.4±6.4	6.1±6.2	6.7±6.1	5.7±5.9	7.9±6.6	6.8±6.7	0.02
Stroke subtype							
Large artery atherosclerosis	192 (36.7)	768 (35.5)	91 (40.8)	538 (38.0)	101 (33.7)	230 (30.8)	0.05
Cardioembolism	132 (25.2)	511 (23.6)	33 (14.8)	289 (20.4)	99 (33.0)	222 (29.7)	
Small-vessel occlusion	83 (15.9)	405 (18.7)	40 (17.9)	266 (18.8)	43 (14.3)	139 (18.6)	
Stroke of other determined etiologies	6 (1.1)	57 (2.6)	6 (2.7)	42 (3.0)	0	15 (2.0)	
Stroke of undetermined etiology	110 (21.0)	423 (19.5)	53 (23.8)	282 (19.9)	57 (19.0)	141 (18.9)	
mRS score poor functional outcome (3-6) at 90 days	271 (51.5)	819 (37.6)	96 (42.5)	498 (34.9)	175 (58.3)	321 (42.9)	<0.01
mRS score poor functional outcome (3-6) at 1 year	205 (50.1)	621 (37.2)	66 (38.8)	385 (34.9)	139 (58.2)	236 (41.5)	<0.01

Values are presented as mean±SD or number (%). IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

Supplementary Table 4. Univariate and multivariate analyses regarding the predictors of outcome (mRS score) at 90 days after acute ischemic stroke

Variable	Univariate			Multivariate				
	Total		Greater than 80 years	Total		Greater than 80 years		
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value		
Women	1.60 (1.37–1.88)	0.000	1.73 (1.19–2.51)	0.004	1.06 (0.83–1.35)	0.648	1.39 (0.84–2.29)	0.200
Living alone	1.76 (1.45–2.13)	0.000	1.26 (0.83–1.91)	0.281	1.32 (1.03–1.69)	0.026	0.90 (0.54–1.51)	0.691
Age	1.06 (1.05–1.07)	0.000	1.12 (1.05–1.19)	0.000	1.06 (1.05–1.07)	0.000	1.14 (1.06–1.22)	0.001
Onset to hospital (min)	1.00 (1.00–1.00)	0.634	1.00 (1.00–1.00)	0.299				
Arrival at the hospital 4.5 hr after onset	1.16 (0.99–1.37)	0.072	1.13 (0.76–1.67)	0.555	1.45 (1.16–1.81)	0.001	1.72 (1.05–2.82)	0.032
Use of intravenous tissue plasminogen activator	1.11 (0.91–1.35)	0.301	0.99 (0.60–1.63)	0.967				
Door-to-needle time (min)	1.00 (1.00–1.01)	0.311	1.01 (0.97–1.05)	0.490				
Intraarterial thrombectomy	1.96 (1.50–2.57)	0.000	2.40 (1.09–5.28)	0.029	0.41 (0.28–0.61)	0.000	0.93 (0.36–2.43)	0.888
Door-to-puncture time (min)	1.00 (0.99–1.00)	0.287	1.01 (0.99–1.04)	0.341				
Risk factor								
Diabetic mellitus	1.15 (0.98–1.36)	0.094	0.84 (0.56–1.25)	0.385	1.41 (1.15–1.74)	0.001	1.01 (0.61–1.67)	0.975
Smoking								
Current smoking	0.57 (0.48–0.69)	0.000	0.66 (0.35–1.24)	0.193	1.06 (0.81–1.39)	0.671	1.06 (0.49–2.31)	0.875
Previous history of smoking	0.89 (0.71–1.10)	0.278	0.79 (0.46–1.33)	0.367	1.20 (0.89–1.61)	0.243	1.02 (0.51–2.03)	0.964
Previous history of statin use	0.79 (0.64–0.97)	0.022	0.79 (0.48–1.28)	0.332	0.70 (0.54–0.91)	0.008	0.68 (0.37–1.26)	0.221
Previous history of coronary artery disease	1.51 (1.21–1.88)	0.000	1.47 (0.89–2.44)	0.135	1.21 (0.91–1.61)	0.180	2.05 (1.08–3.87)	0.028
Previous history of cerebrovascular disease	1.50 (1.24–1.82)	0.000	1.18 (0.74–1.87)	0.481	1.61 (1.27–2.04)	0.000	1.54 (0.88–2.68)	0.127
Previous history of atrial fibrillation	2.30 (1.92–2.75)	0.000	1.72 (1.16–2.55)	0.006	1.74 (1.12–2.69)	0.014	1.09 (0.47–2.53)	0.833
NIHSS score at admission	1.22 (1.20–1.24)	0.000	1.25 (1.19–1.31)	0.000	1.27 (1.24–1.30)	0.000	1.27 (1.20–1.35)	0.000
Stroke subtype (ref=small-vessel occlusion)								
Large artery atherosclerosis	1.99 (1.57–2.53)	0.000	2.58 (1.44–4.63)	0.001	1.41 (1.08–1.86)	0.013	2.27 (1.18–4.36)	0.014
Cardioembolism	3.43 (2.66–4.42)	0.000	3.36 (1.91–5.92)	0.000	0.57 (0.34–0.94)	0.029	0.94 (0.35–2.51)	0.894
Stroke of other determined etiologies	0.66 (0.34–1.28)	0.220			1.23 (0.56–2.69)	0.611		
Stroke of undetermined etiology	1.71 (1.31–2.23)	0.000	2.37 (1.27–4.41)	0.006	0.81 (0.59–1.12)	0.207	1.34 (0.65–2.77)	0.434

mRS, modified Rankin Scale; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale.

Oxygen supplementation via high-flow nasal cannula is an effective treatment for pneumocephalus

Deok-Soo Lee, MD¹; Jae-Kwan Cha, MD¹; Dong Hyun Lee, MD²;
Ki Sup Byun, MD²; Jin-Heon Jeong, MD^{1,2}

¹Department of Neurology, Stroke Center, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Republic of Korea

²Department of Intensive Care Medicine, Dong-A University Hospital, Dong-A University College of Medicine, Busan, Republic of Korea

CASE REPORT

Received: August 20, 2019

Revised: September 27, 2019

Accepted: October 11, 2019

Corresponding Author:

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

Background: Oxygen supplementation through a high-flow nasal cannula (HFNC) is a powerful technique that promotes the absorption of air by delivering high concentrations of oxygen to patients who are not intubated, and may be a viable treatment option for pneumocephalus.

Case Report: A 75-year-old female presented in a stuporous state. She had received an epidural injection due to back pain 2 hours ago. Non-contrast brain computed tomography revealed a pneumocephalus at the interhemispheric fissure and the prepontine cistern. HFNC oxygen therapy at 60 L/min with a fraction of inspired oxygen of 1 was started. By the next morning, her mental status had recovered and a repeat brain computed tomography 15 hours later revealed complete absorption of the pneumocephalus.

Conclusion: Supplemental high oxygen via HFNC can be successfully used in patients with pneumocephalus who are not intubated and mechanically ventilated.

Keywords: Pneumocephalus; High-flow nasal cannula; Oxygen therapy

INTRODUCTION

Pneumocephalus is defined as the presence of air or gas in the intracranial cavity [1]. Although, pneumocephalus commonly occurs after trauma, it can also be associated with other conditions including neurosurgical procedures, infection, neoplasm, barotrauma, and spinal and epidural anesthesia [1]. Treatment of pneumocephalus is controversial; however, supplementation with high concentrations of oxygen can promote the absorption

of pneumocephalus [2-4]. High-flow nasal cannula (HFNC) oxygen supplementation technique is commonly used in intensive care units to supply high concentrations of oxygen to patients without intubation [5-7]. Oxygen therapy via HFNC can be a viable treatment option for pneumocephalus [8].

We report a case of pneumocephalus that occurred following an epidural injection and was successfully treated with supplemental oxygen delivery via HFNC.

CASE REPORT

A 75-year-old female presented in a stuporous state. Her medical history included basal ganglia infarction and hypertension. Two hours ago, she received an epidural injection due to back pain. A mixture of lidocaine and triamcinolone was injected into the epidural space of the thoracic spinal cord. Twenty minutes after the injection, she experienced nausea, followed by decreased consciousness to the level of stupor. Epinephrine was administered for suspicion of anaphylaxis. Although her mental status improved

to drowsy, she remained confused and was transferred to the emergency room of our hospital.

Vital signs on admission were normal. She was somnolent and confused but other neurological examinations were unremarkable. Routine laboratory tests, including arterial blood gas analysis (pH, 7.449; PCO₂, 45.2 mm Hg; PO₂, 73.2 mm Hg; and SaO₂, 94.1%), were normal. Non-contrast brain computed tomography revealed a pneumocephalus at the interhemispheric fissure and the prepontine cistern (Fig. 1). Brain magnetic resonance imaging confirmed the pneumocephalus (Fig. 1). Although the patient

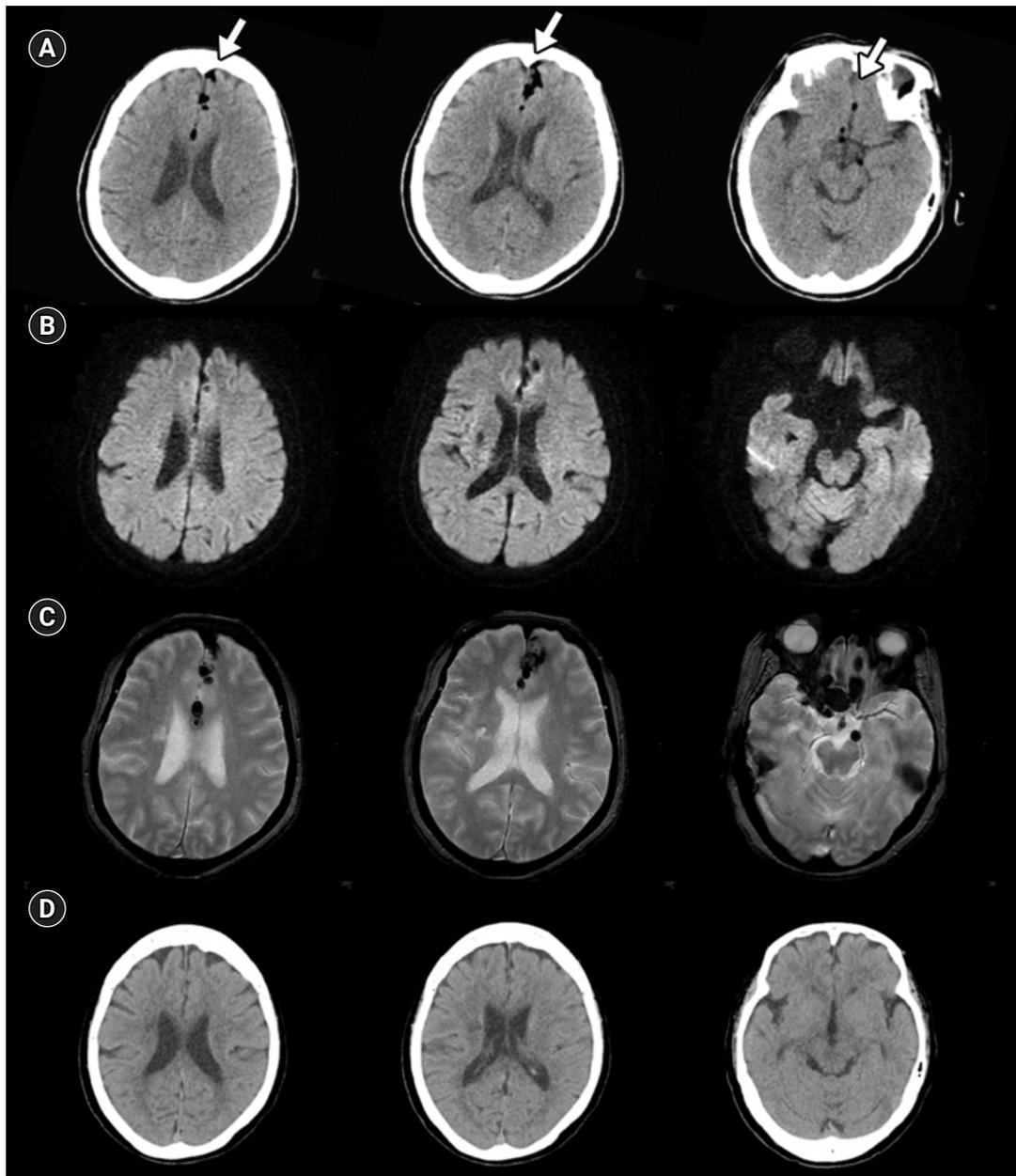


Fig. 1. (A) Non-contrast brain computed tomography revealing pneumocephalus at the interhemispheric fissure and the prepontine cistern (white arrows). (B) Diffusion-weighted image and (C) gradient-echo also reveal pneumocephalus. (D) Follow-up brain computed tomography 15 hours later demonstrates the complete absorption of the pneumocephalus.

was in a stuporous state, vital signs, including respiration, were stable. We decided to employ a noninvasive oxygen device, and oxygen therapy via HFNC at 60 L/min with a fraction of inspired oxygen (FiO_2) of 1 was started (Fig. 2). After 6 hours, arterial oxygen partial pressure increased from 73.2 to 472 mm Hg. Seventeen hours after symptom onset, her mental status returned to alert and repeat brain computed tomography 15 hours later revealed the complete absorption of the pneumocephalus (Fig. 1).

DISCUSSION

This case demonstrated that a symptomatic pneumocephalus can be successfully treated using oxygen supplementation via HFNC. After application of HFNC, the patient's symptoms improved and brain computed tomography performed 1 day later revealed absorption of the pneumocephalus. High-concentration oxygen therapy has been suggested to be effective for symptomatic pneumocephalus [2-4]. To provide a consistent FiO_2 , patients require mechanical ventilation after endotracheal intubation [9]. Although conventional oxygen devices, such as nasal cannulas or oxygen masks, can also be used, high concentrations of oxygen are not consistently delivered [6,7]. HFNC may be an effective treat-

ment option for pneumocephalus to administer high concentrations of oxygen without the need for endotracheal intubation.

In this patient, pneumocephalus developed after an epidural injection. Previous case reports have described pneumocephalus after epidural injection, and it was presumed that the dura mater was damaged during the procedure [10]. The loss-of-resistance to air technique is commonly used to confirm entry into the epidural space, which is considered the source of air entry. When the spinal needle reaches the epidural space, resistance quickly disappears, and air in the syringe may be inadvertently injected.

Mild cases of pneumocephalus without clinical manifestations usually resolve without treatment and are absorbed spontaneously. More severe pneumocephalus, however, can cause headache, nausea, vomiting, seizure, lethargy, and neurological deficits [11]. Supplemental oxygen is a commonly accepted treatment for pneumocephalus with clinical symptoms [1-4]. Oxygen augmentation reduces pulmonary nitrogen levels, creating a nitrogen gradient, and nitrogen in the pneumocephalus diffuses into the lungs via the blood [2]. Some prospective studies have shown that oxygen therapy can reduce pneumocephalus after neurosurgery [3,4]. One case series reported that HFNC improved pneumocephalus symptoms in postneurosurgical patients within a few hours [8].

HFNC is an effective and powerful technique increasingly used in intensive care units. Several studies have demonstrated that HFNC improves the management of hypoxic respiratory failure and reduces the number of patients who require reintubations [5]. HFNC provides high flow rates (up to 60 L/min) through nasal cannulas by delivering heated and humidified oxygen. Patients undergoing oxygen therapy with HFNC exhibit better tolerance and experience greater comfort than with conventional oxygen-delivery devices [6,7]. Due to these advantages, HFNC can be used for various indications, including pneumocephalus, in the neurological intensive care unit.

This case demonstrated the therapeutic effect of HFNC in a patient with pneumocephalus. Owing to the limited extent of pneumocephalus on the first brain computed tomography, it is difficult to rule out spontaneous improvement. However, the application of HFNC may have contributed to the rapid recovery.

In conclusion, supplemental oxygen via HFNC can be successfully used in patients with pneumocephalus who are not intubated and mechanically ventilated.

ARTICLE INFORMATION

Conflict of interest

Dr. JH Jeong is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision

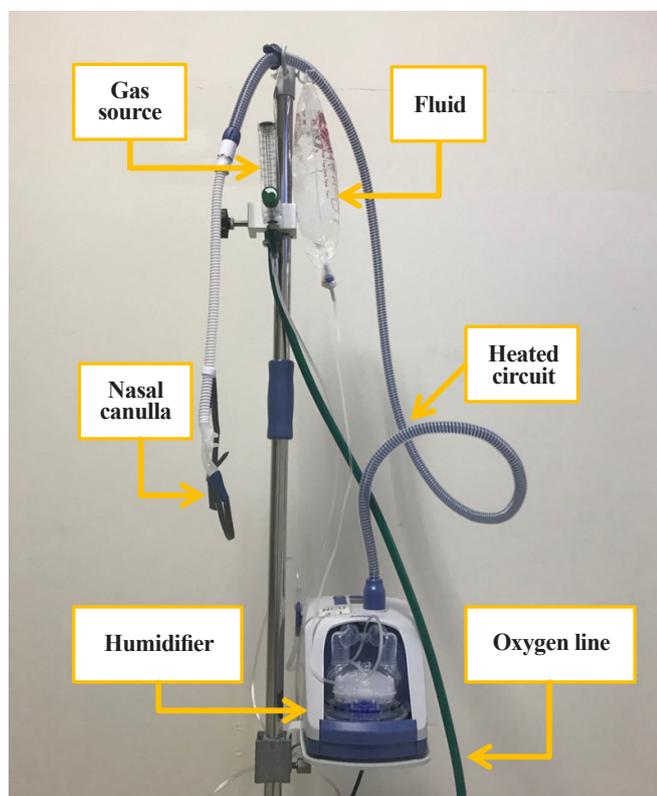


Fig. 2. High-flow nasal cannula oxygen therapy at 60 L/min, with fraction of inspired oxygen (FiO_2) of 1, was started.

process of this article. There are no other potential conflicts of interest relevant to this article to declare.

Funding

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (grant number: 2018R1C1B5086622).

ORCID

Deok-Soo Lee, <https://orcid.org/0000-0003-0373-8054>

Jae-Kwan Cha, <https://orcid.org/0000-0002-1049-5196>

Dong Hyun Lee, <https://orcid.org/0000-0001-6253-3396>

Ki Sup Byun, <https://orcid.org/0000-0002-6670-5471>

Jin-Heon Jeong, <https://orcid.org/0000-0002-5878-9206>

Author contributions

Conceptualization: DSL, JKC, JHJ. Data curation & Formal analysis: DSL, DHL, KSB, JHJ. Visualization & Writing—original draft: DSL, JKC, JHJ. Writing—review editing: DSL, DHL, KSB, JHJ.

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Transvenous Onyx embolization of cavernous sinus dural arteriovenous fistula using a balloon catheter in the arterial side for flow control

Chul-Hoo Kang, MD¹; Jieun Roh, MD¹; Jeong A Yeom, MD¹;
Sang Won Lee, MD, PhD²; Seung Kug Baik, MD, PhD¹

¹Department of Radiology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Republic of Korea

²Department of Neurosurgery, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Republic of Korea

CASE REPORT

Received: July 4, 2019

Revised: August 21, 2019

Accepted: August 22, 2019

Corresponding Author:

Seung Kug Baik, MD, PhD

Department of Radiology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Republic of Korea
Tel: +82-55-360-1834

Fax: +82-55-360-1848

E-mail: skbaik9@gmail.com

Background: Cavernous sinus (CS) dural arteriovenous fistulas (DAVFs) are abnormal arteriovenous shunts involving the dura mater, located within or near the walls of the CS. Transvenous embolization is considered to be an effective treatment for CS DAVF. We describe a novel technique for the use of transvenous Onyx embolization in the treatment of CS DAVF, which uses a temporary balloon to occlude the arterial side for flow control.

Case Report: A 63-year-old woman presented with ocular pain and ptosis of the left eye. Cerebral angiography showed a left CS DAVF fed by multiple branches of the left external carotid artery. We successfully treated the CS DAVF using transvenous Onyx embolization with temporary balloon occlusion of the proximal feeding artery to decrease the shunted flow.

Conclusion: Transvenous Onyx embolization with flow control via temporary balloon occlusion may be a useful technique for the embolization of CS DAVFs with multiple arterial feeders.

Keywords: Cavernous sinus; Arteriovenous fistula; Endovascular technique; Balloon occlusion

INTRODUCTION

Cavernous sinus (CS) dural arteriovenous fistulas (DAVFs) are abnormal arteriovenous shunts involving the dura mater, located within or near the walls of the CS [1]. Although the natural course of CS DAVFs is relatively benign, high-risk lesions with venous reflux require treatment due to ocular symptoms, cranial nerve palsy, and venous hypertension.

Currently, endovascular management is the primary treatment for DAVFs. Various methods have been described for the treat-

ment of CS DAVFs, including transarterial and transvenous embolization. Transarterial feeder vessel embolization may be performed, but is frequently inadequate for curative treatment. Some lesions derive their meningeal supply from branches of the intracranial circulation which cannot be accessed or embolized safely [2]. Thus, transvenous embolization is generally considered to be a more effective treatment for CS DAVF [1,2]. Onyx (eV3, Irvine, CA, USA) is a new liquid embolic agent that has been found to be useful in treating DAVF [3,4], and transvenous Onyx embolization has been found to be safe and effective as a

treatment for CS DAVFs [3,4]. However, the use of Onyx in a transvenous approach has limitations. Injecting Onyx against the flow of the fistula is technically challenging; the tendency for the compound to follow the direction of flow increases the risk of embolization of a normal draining vein and migration to an unwanted site.

Here, we report the case of a 63-year-old woman with a CS DAVF fed by multiple head and neck arteries, who was successfully treated using transvenous Onyx embolization with temporary balloon occlusion of the proximal feeding artery to decrease the shunted flow.

CASE REPORT

A 63-year-old woman presented with a 2-month history of ocular pain, incomplete ptosis, and decreased visual acuity of the left eye. Clinically, ocular movement abnormalities suggestive of cranial neuropathy was not observed. Cerebral angiography showed a left-side dominant CS DAVF fed by the bilateral meningohypophyseal trunks of the internal carotid artery, the left distal internal maxillary artery, the left middle meningeal artery, and the left ascending pharyngeal artery. The venous outflow drained into both superior ophthalmic veins (SOVs, left-side dominant) and both inferior petrosal sinuses (IPs, right-side dominant) (Fig. 1).

The CS DAVF was treated immediately because the patient's symptoms were severe, and we chose the transvenous approach because the lesion involved multiple fine feeding arteries. The procedure was performed using a biplane angiography unit (Axion Artis zee biplane, Siemens, Forchheim, Germany). After placement of the guiding catheter, heparin was administered as an intravenous bolus (50 IU/kg of body weight, 3,000 to 5,000 IU) followed by an infusion of 1,000 IU per hour.

A 6F Envoy guiding catheter (Cordis Corporation, Hialeah, FL, USA) was placed into the proximal left external carotid artery (ECA) for selective angiography. The late venous phase of the left external carotid angiogram revealed the right IPS and internal jugular vein (IJV). Therefore, the right IPS was chosen for the endovascular approach. Another 6F Envoy guiding catheter was placed into the right IJV, and two microcatheters (Excelsior 1018, Stryker, Kalamazoo, MI, USA) were advanced over the guidewire (Synchro 010, Stryker) into the left CS via the right IPS and the intercavernous sinus. One microcatheter was placed at the orifice of the left SOV, and the other on the venous side of the main fistula.

First, a coil was packed through one microcatheter to prevent migration of the Onyx into the SOV. The coil was retrieved after

the Onyx embolization. Next, 0.25 mL of dimethyl sulfoxide (DMSO) was slowly infused through the other microcatheter over a 90-second period. To control the shunted blood flow at the left ECA, a balloon catheter (Scepter C, 4 × 10 mm, Micro-Vention Inc., Tustin, CA, USA) was placed into the proximal left ECA. The balloon was inflated, and then the Onyx-18 injection was started. The left ECA angiogram was monitored during the intermittent Onyx-18 injection using a 6F Envoy catheter placed in the left proximal ECA. The procedure was completed as soon as the left ECA angiogram revealed complete obliteration of the DAVF (Fig. 2). In total, 4.4 mL of Onyx-18 was injected over 66 minutes. The microcatheter used for the Onyx injection was readily retrieved.

No postprocedural complications or additional cranial nerve palsies were observed. The patient was discharged on postprocedure day 10. Her symptoms improved within several weeks, and a transfemoral cerebral angiography at the 6-month post-embolization showed complete obliteration of the CS DAVF (Fig. 3).

DISCUSSION

CS DAVFs account for 20% to 40% of all intracranial DAVFs [5]. Ocular symptoms caused by anterior venous drainage are the most common symptoms of CS DAVF. Aggressive neurological symptoms are rare due to the benign venous drainage pattern, but can occur in association with dangerous venous drainage patterns, including cortical venous reflux (hemorrhagic infarction), deep venous drainage (hemorrhage, edema), and thrombosis of the central retinal vein (blindness) [6]. The spontaneous regression rate of CS DAVFs is high, occurring in 10% to 50% of cases [5]. Given the low prevalence of aggressive symptoms and relatively high spontaneous regression rates, most cases can be treated conservatively. However, patients with progressive and intolerable symptoms require more active treatment. CS DAVFs can be treated using a transarterial or a transvenous approach. The transvenous approach is most commonly used for CS DAVFs because the transarterial approach is a more complex and less effective technique.

A wide variety of embolic agents are available for DAVF embolization, including polyvinyl alcohol particles, coils, N-butyl cyanoacrylate (NBCA), and DMSO solvent materials such as Onyx, Squid, and precipitating hydrophobic injectable liquid. Of those, coils and DMSO solvent materials such as Onyx are the most commonly used agents, with each having advantages and disadvantages.

Coils are placed in a controlled manner and are more easily deployed in the desired position than is Onyx. However, coils are

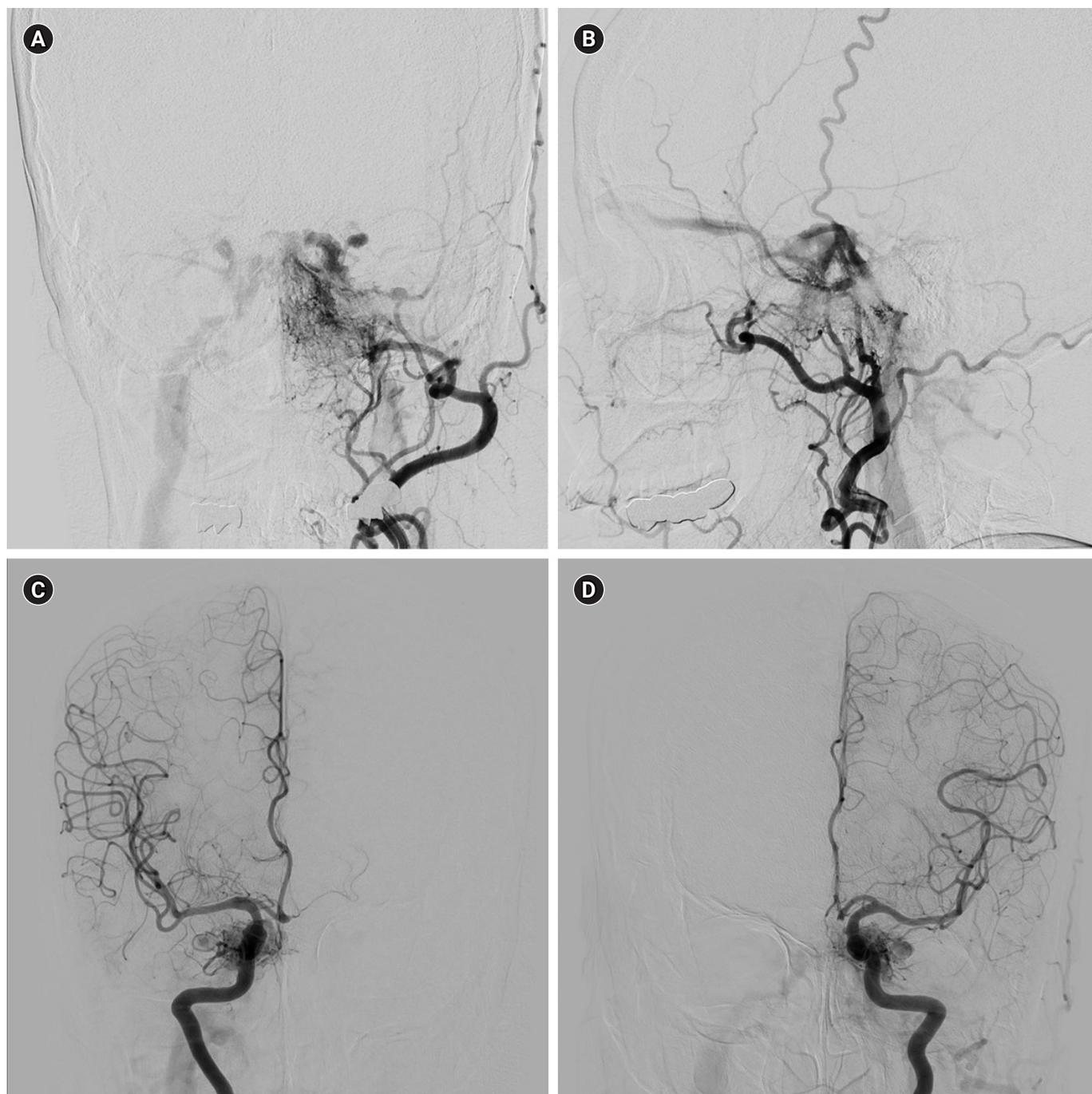


Fig. 1. Left external carotid artery (ECA) angiography, (A) frontal projection and (B) lateral projection, showing a left cavernous sinus (CS) dural arteriovenous fistula fed by the left distal internal maxillary artery, the left middle meningeal artery, and the left ascending pharyngeal artery, drained to the both superior ophthalmic vein (left side dominant) and the both inferior petrosal sinus (right side dominant). (C) Right internal carotid artery (ICA) angiography and (D) left ICA angiography, showing shunted flow from the bilateral meningohypophyseal trunk to the CS.

associated with a lower rate of complete obliteration. Moreover, coils are more thrombogenic than Onyx and can lead to progressive thrombosis causing mass effects. To achieve complete occlusion of CS DAVFs, the CS needs to be densely packed with coils. Nishino et al. [7] found that paradoxical worsening (the devel-

opment of new or worsening symptoms or signs after embolization) occurred in 39.4% of patients after transvenous coil embolization, which was correlated with the volume of coils in the CS [8]. Paradoxical worsening may be attributed to progressive thrombosis of the CS, mass effects from the embolic materials, or

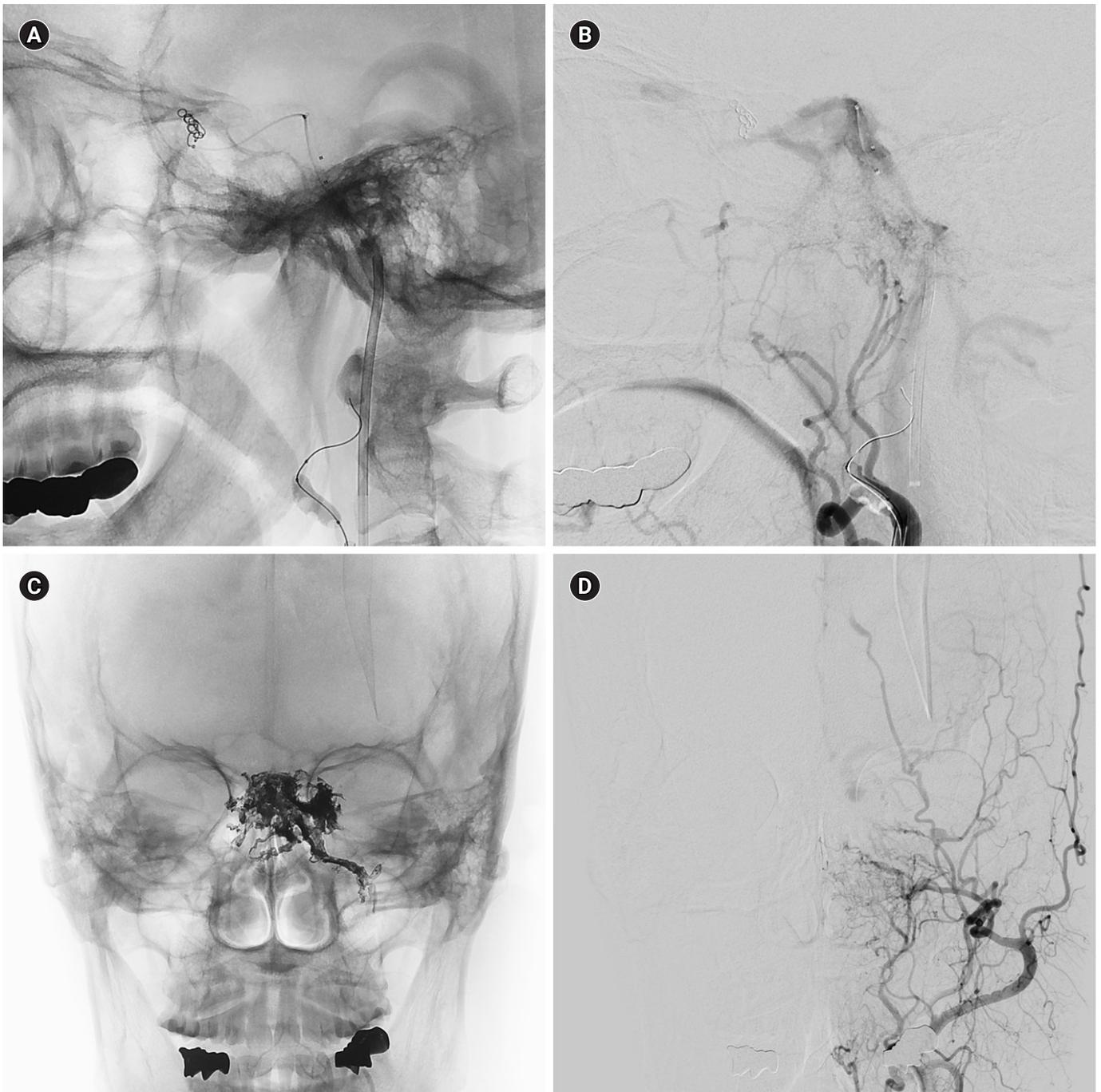


Fig. 2. (A) Native image, lateral projection showing deployed coil at the orifice of superior ophthalmic vein and inflated balloon into the proximal left external carotid artery (ECA). (B) Left ECA angiography during balloon inflation, lateral projection showing diminished blood flow from the left ECA. (C) Final Onyx cast. (D) Final angiography of the left ECA, frontal projection showing complete obliteration of the cavernous sinus dural arteriovenous fistula.

direct injury to the nerve by the coils or the microwire/microcatheter [1,8].

Onyx embolization is less controlled than coil placement, however, this material is associated with a higher rate of complete obliteration [9]. Furthermore, because Onyx is less thrombogen-

ic than coils, paradoxical worsening occurs less frequently after Onyx embolization. Nevertheless, paradoxical worsening can occur after Onyx embolization [10], possibly caused by CS thrombosis and swelling, or due to the angiotoxic effect of DMSO [4]. The incidence of Onyx embolization-induced paradoxical wors-

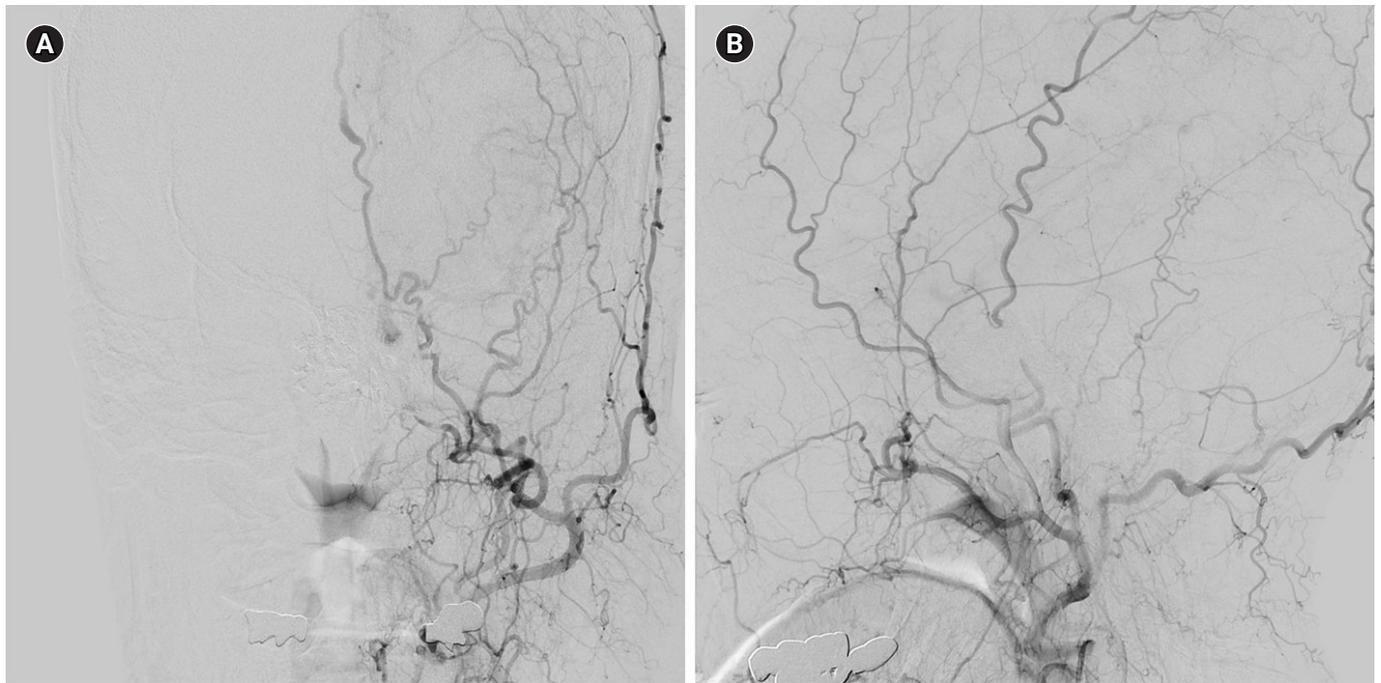


Fig. 3. Left external carotid artery angiography at 6-month post-embolization, (A) frontal projection and (B) lateral projection showing complete obliteration of the cavernous sinus dural arteriovenous fistula.

ening is not known because no large case series or well-controlled studies have addressed the issue. Importantly, most cases of paradoxical worsening after coil embolization or Onyx embolization fully recovered [10,11].

Onyx, which is an ethylene vinyl alcohol copolymer preparation, has several advantages for endovascular treatment. Onyx laminates along the vessel wall and is less adhesive and more cohesive than NBCA. Furthermore, the slower polymerization rate and cohesive nature of Onyx allows it to be injected over a period of several minutes to over an hour, enabling more controlled embolization.

Although several cases of transarterial balloon catheter-assisted Onyx embolization of traumatic carotid cavernous fistulas and of intracranial DAVFs other than CS DAVFs have been reported previously [12-14], ours is the first to describe the transvenous Onyx embolization of a CS DAVF using a balloon catheter on the arterial side to control flow.

When using Onyx, it is essential to allow time for the material to create a plug around the tip of the microcatheter, which enables the forward flow of Onyx. The formation of an Onyx plug in the CS is challenging, given the shunted flow and high pressure. Thus, in previous reports, coils were inserted before injecting Onyx to act as a template for the material [5,9,15].

However, by controlling blood flow, Onyx embolization can be performed without coils. Thus, flow control is an important as-

pect of Onyx controllability. Flow can be modulated using selective or nonselective methods. Selective control reduces blood flow from the main feeder of multiple feeding arteries and includes the plug and push, pressure cooker, balloon-assisted embolization, and wedge techniques. Nonselective control reduces the blood flow from multiple feeding arteries by placing a balloon proximal to the common trunk of multiple feeders.

We chose Onyx embolization to treat our patient with CS DAVF because Onyx is less thrombogenic and has a higher rate of complete obliteration. However, the possibility that the shunted flow at the fistula could prevent formation of the Onyx plug or cause the Onyx to migrate to an unintended site necessitated the use of flow control. Selective control was not an option in our case due to the presence of multiple fine feeding arteries. Instead, we used a balloon catheter to control blood flow and injected Onyx into the venous side of the fistula. No unintended Onyx migration occurred, no procedure-related complications, including paradoxical worsening, were observed, and the CS DAVF was completely occluded.

The treatment of DAVFs using transvenous Onyx embolization with arterial flow control has several advantages. Firstly, because Onyx is less thrombogenic than coils, it is associated with a lower rate of paradoxical worsening. Secondly, flow control decreases flow velocity on the venous side of the DAVF, which in turn decreases distal migration of the Onyx. Therefore, the trans-

venous approach can achieve higher obliteration rates and lower complication rates than coil embolization.

We report the successful endovascular treatment of a CS DAVF. Transvenous Onyx embolization with flow control via temporary balloon occlusion may be a useful technique for the embolization of CS DAVFs with multiple arterial feeders.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

ORCID

Chul-Hoo Kang, <https://orcid.org/0000-0002-4176-0941>

Jieun Roh, <https://orcid.org/0000-0002-6876-3990>

Jeong A Yeom, <https://orcid.org/0000-0002-0328-7989>

Sang Won Lee, <https://orcid.org/0000-0002-3199-7072>

Seung Kug Baik, <https://orcid.org/0000-0001-5408-747X>

Author contributions

Conceptualization: CHK, SWL and SKB. Data curation & Formal analysis: CHK and JAY. Visualization & Writing—original draft: CHK and JR. Writing—review editing: CHK and SKB.

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Intraarterial therapy for middle cerebral artery dissection with intramural hematoma detection on susceptibility-weighted imaging

Changhyo Yoon, MD¹; Seunguk Jung, MD^{1,2}; Heejeong Jeong, MD, PhD¹; Eunbin Cho, MD, PhD^{1,2}; Tae-Won Yang, MD¹; Seung Joo Kim, MD¹; Ki-Jong Park, MD, PhD^{1,2}; Seung Soo Kim, MD³; Hyun Park, MD, PhD³

¹Department of Neurology, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea

²Department of Neurology and Institute of Health Science, Gyeongsang National University School of Medicine, Jinju, Republic of Korea

³Department of Neurosurgery, Gyeongsang National University Changwon Hospital, Changwon, Republic of Korea

CASE REPORT

Received: October 14, 2019

Revised: November 25, 2019

Accepted: November 29, 2019

Corresponding Author:

Seunguk Jung, MD

Department of Neurology, Gyeongsang National University Changwon Hospital, 11 Samjeongja-ro, Seongsan-gu, Changwon 51472, Republic of Korea

Tel: +82-55-214-3814

Fax: +82-55-214-2638

E-mail: seunguk1358@gmail.com

Background: Intracranial artery dissection (IAD) may be an underdiagnosed cause of large vessel occlusion. The safety and efficacy of intra-arterial therapy (IAT) in patients with IAD are largely unknown. We report the case of a patient with IAD who was successfully treated with IAT.

Case Report: A 27-year-old man with a sudden-onset sensory dominant aphasia was admitted to our hospital around 16 hours after disease onset. Brain magnetic resonance angiography revealed an occlusion in the left distal middle cerebral artery (MCA). On the susceptibility-weighted imaging, bead-shaped dark signals were observed in the left MCA bifurcation, and intramural hematoma was suspected. We performed thrombectomy and permanent stenting for the dissecting MCA occlusion and achieved complete recanalization.

Conclusion: The IMH on susceptibility-weighted imaging led us to suspect that the large vessel occlusion was due to the IAD. Further research is needed to address the efficacy and safety of IAT in patients with IAD.

Keywords: Middle cerebral artery; Blood vessel dissection; Thrombectomy

INTRODUCTION

Spontaneous intracranial artery dissection (IAD) may be an underdiagnosed cause of acute ischemic stroke. IAD is more frequently reported in the Asian population [1]. The pathophysiology of IAD and the cause of its prevalence in the Asian population are largely unknown. The radiological diagnosis of IAD in patients with acute ischemic stroke is often challenging because of the small size of intracranial arteries, and the subtle and nonspecific radiological findings. The pathognomonic radiological findings of

IAD are intramural hematoma (IMH), intimal flap, and double lumen. In stenooclusive lesions without the aforementioned radiological evidence, IAD is difficult to predict. Recent advances in intraarterial techniques and thrombectomy devices have led to a high rate of recanalization in patients with large vessel occlusion (LVO). Intraarterial therapy (IAT) has become an essential treatment for patients with acute LVO. However, IAT in patients with IAD could have a high risk of arterial rupture and subsequent subarachnoid hemorrhage. Therefore, identifying the etiology of the LVO before the procedure can be useful in the development of an

effective and safe treatment strategy.

We report a case of acute middle cerebral artery (MCA) occlusion suspected to have an arterial dissection etiology based on susceptibility-weighted imaging (SWI) findings. The condition was successfully treated with IAT.

CASE REPORT

A 27-year-old man with a sudden-onset sensory dominant aphasia was admitted to the emergency department (ED) at 3:07 PM on March 19, 2018. When he got up at 11:00 AM, he noticed his condition. His last known well time was 11:00 PM the previous night. Previously, he was healthy and did not have any head trauma. His family history was also unremarkable. He was a current smoker with a 7-pack-year smoking history and denied alcohol consumption. His weight, height, and body mass index were 72.1 kg, 178 cm, and 22.76 kg/m², respectively. On neurological examination, he was alert but could not obey simple commands. He could say more than three sentences but with incoherent content.

We concluded that these symptoms were compatible with Wernicke's aphasia. His motor strength was normal, and he showed no Babinski's sign or ankle clonus. The baseline National Institutes of Health Stroke Scale (NIHSS) score was 6. The brain magnetic resonance imaging (MRI) performed at another hospital before his ED visit at our hospital revealed an acute cerebral infarction on diffusion-weighted imaging (Fig. 1A, 1B). Signs of hyperintense vessels were found on fluid-attenuated inversion recovery imaging, and an occlusion was found in the left distal MCA on magnetic resonance (MR) angiography (Fig. 1C, 1D). SWI revealed bead-shaped dark signals in the area of the bifurcation site of the left MCA (Fig. 2A-2D), and bright signal intensities were observed on the phase map (Fig. 2E-2H). We performed emergency multimodal computed tomography (CT, Philips Healthcare, Eindhoven, The Netherlands) that included perfusion maps. We decided to perform IAT because of a large mismatch between the core, defined as a cerebral blood volume of <2 mL/100 g, and the penumbra, defined as a relative mean transit time of >145% when compared with the contralateral side (Fig. 1E, 1F).

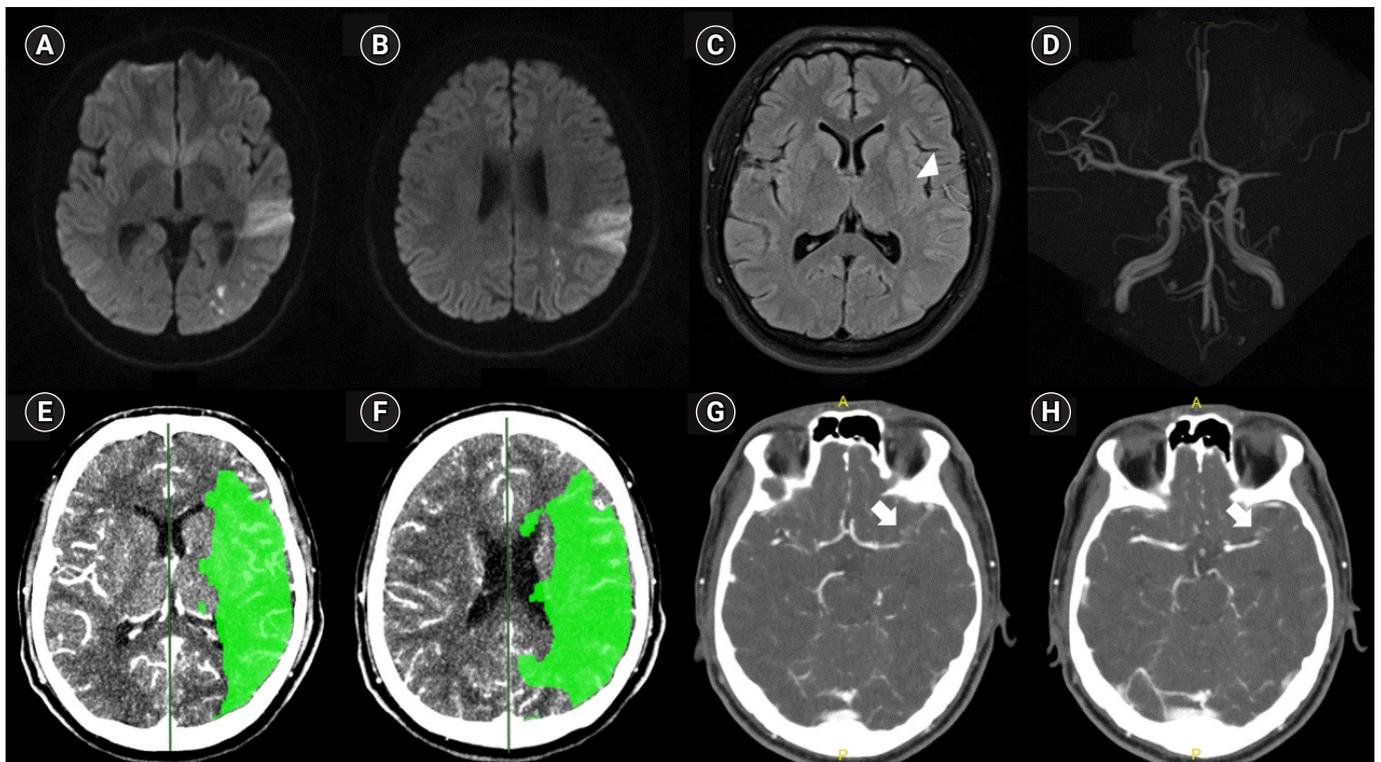


Fig. 1. Magnetic resonance (MR) imaging scans of the brain performed in another hospital before admission. (A, B) The diffusion-weighted image shows multiple infarctions in the left temporoparietal lobes. (C) Hyperintense vessel signs (white arrowhead) on fluid-attenuated inversion recovery imaging. (D) MR angiogram showing an occlusion in the left distal middle cerebral artery. (E, F) Perfusion computed tomography (CT) image showing perfusion delay, defined as a relative mean transit time of >145% when compared with that on the contralateral side (green color), in the left middle cerebral arterial territory. No core infarct lesions, defined as a cerebral blood volume of <2 mL/100 g in the region on interest, were found. (G, H) Focal enlarged vessels with contrast enhancement (white arrows) on the CT angiography source images.

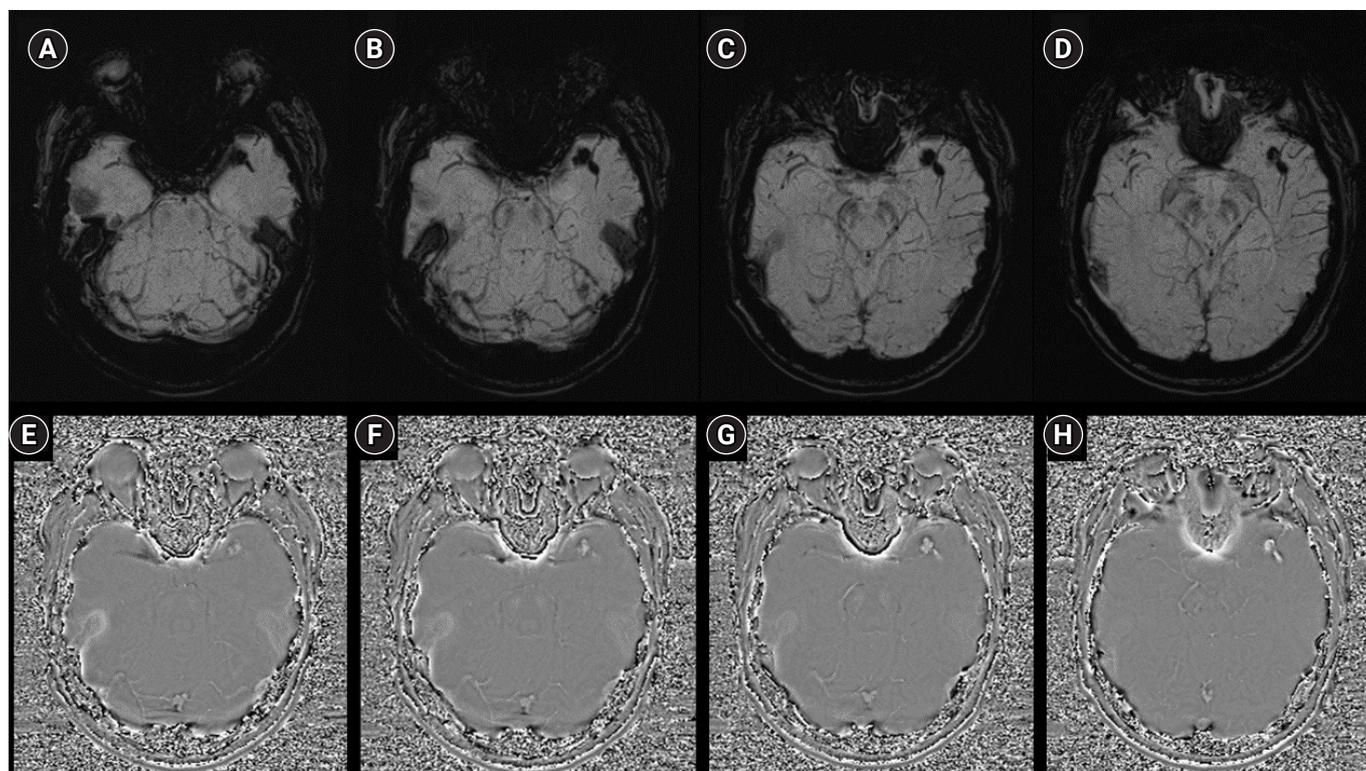


Fig. 2. (A–D) Susceptibility-weighted image demonstrating bead-shaped dark signals in the area of the bifurcation site of the left middle cerebral artery. (E–H) Corresponding bright signal intensities on the phase map.

Focal enlarged vessels with contrast enhancement were observed on the CT angiography source images (Fig. 1G, 1H). The initial blood pressure was 137/70 mm Hg, and the heart rate was 80 beats per minute. The results of the complete blood count, erythrocyte sedimentation rate, C-reactive protein level, urinalysis result, plasma electrolytes, and kidney, liver, and thyroid function tests were normal. The results of the serology tests for anti-Ro/SSA, anti-La/SSB, antinuclear, antidouble-stranded DNA, anti-neutrophil cytoplasmic, and antiphospholipid antibodies were negative. The results of the human immunodeficiency virus, hepatitis B and C, and Venereal Disease Research Laboratory serology tests were also normal. The findings from the transthoracic echocardiography and 24-hour Holter examination were unremarkable.

A 9-Fr balloon guide catheter (Optimo, Tokai Medical Products, Kasugai, Japan) was introduced through a femoral sheath into the left carotid artery. A heparinized saline solution was continuously perfused through the catheter during the procedure. The initial internal carotid artery angiography revealed an occlusion in the left distal MCA (Fig. 3A, 3D). Thrombectomy was performed with the Trevo device (Stryker Neurovascular, Fremont, CA, USA), a retrievable self-expanding stent, and the left distal M1 and M2 inferior divisions were recanalized. After the thrombectomy, a filling

defect in the left distal M1 and an occlusion in the left M2 superior division were found (Fig. 3B, 3E). Although we performed thrombectomy two more times for the recanalization of the left M2 superior division, recanalization was not achieved. The antegrade flow was restored when the stent was deployed, and we performed permanent stenting between the left distal M1 and M2 superior divisions by using a self-expandable stent (3.0 × 15-mm Wingspan, Boston Scientific, Natick, MA, USA). Finally, we achieved complete recanalization of modified thrombolysis in cerebral infarction 3 (Fig. 3C, 3F). His neurological deficits recovered spontaneously. Both his NIHSS score at discharge and 90-day modified Rankin Scale score were 0.

DISCUSSION

To our knowledge, this is the first case of an MCA occlusion due to IAD, which was suspected, based on the IMH sign on SWI, and successfully treated with IAT. IMH is one of the pathognomonic radiological findings of IAD. IMH usually leads to an eccentric thickening of the arterial wall, with enlargement of the external diameter of the dissected artery. IMH can be observed as a hyperintense signal at 48 to 72 hours after onset on T1-weighted MRI. In several retrospective observational studies using conven-

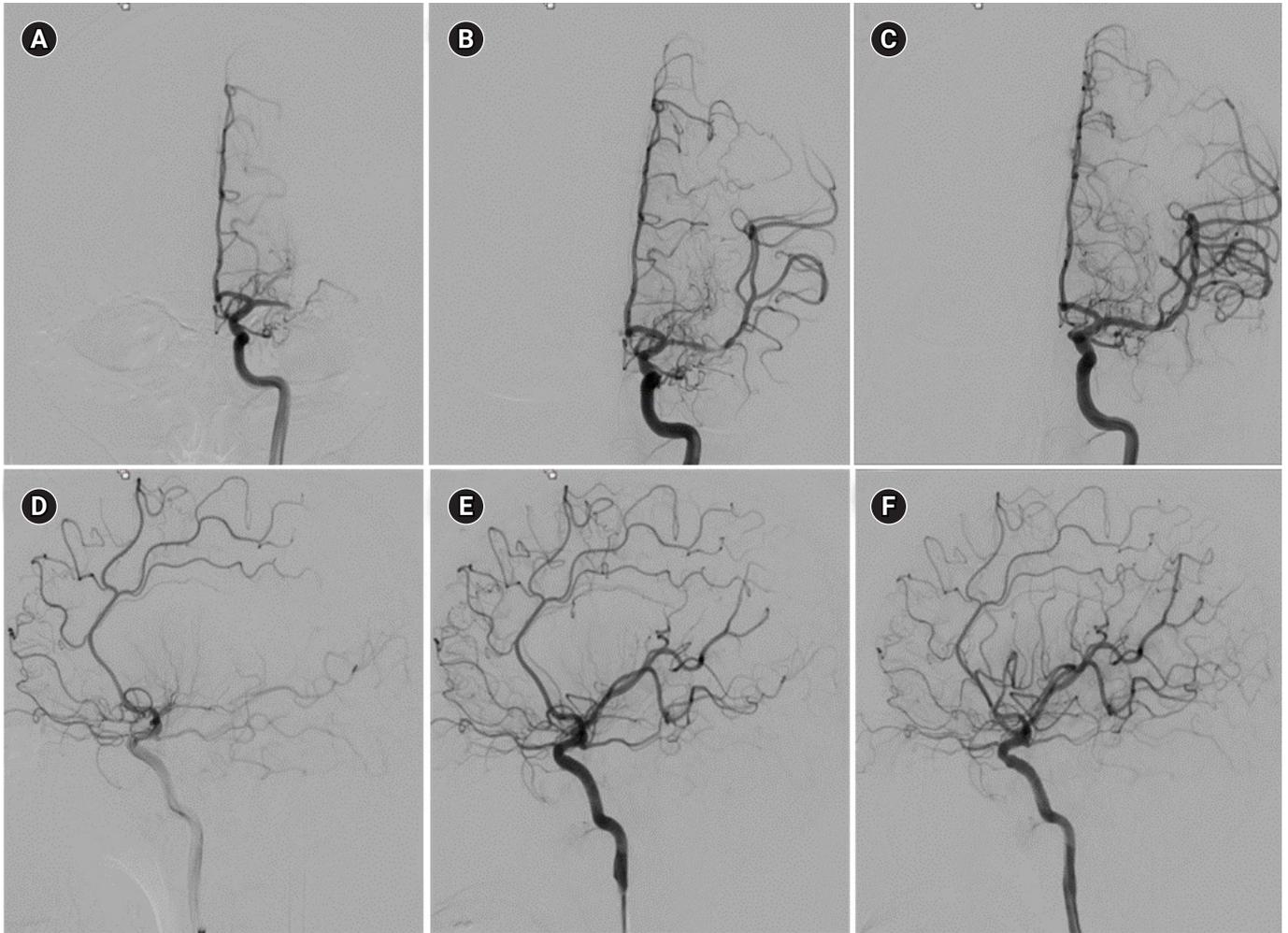


Fig. 3. Left internal carotid artery angiography (ICAG) images (A–C: frontal view; D–F: lateral view). (A, D) The initial ICAG image shows an occlusion in the left distal middle cerebral artery (MCA). (B, E) After the thrombectomy using a stent retriever, a partial filling defect in the left distal M1 and an occlusion in the left M2 superior division were found. (C, F) Final angiogram after permanent stenting between the left distal M1 and M2 superior divisions, showing complete recanalization of the left MCA.

tional MRI, IMH was detected in only 32% to 34% of intracranial vertebrobasilar dissection cases [2,3]. The poor detection rate could be explained by the fact that IMH in the acute stage is rarely detectable on T1-weighted imaging because isointense hematomas are often obscured by surrounding tissue. IMT may be detected only in the subacute and early chronic stages owing to its paramagnetic effects [3]. Although the detection of IMH can be improved with high-resolution (HR) 3-T contrast-enhanced MRI or three-dimensional spin-echo T1 black-blood imaging, it also depends on the acquisition time from IAD occurrence [4,5]. However, the detection rate for dissections was higher with SWI than with the conventional MRI and may be less dependent on the MR acquisition time than any other MR modalities in terms of detection of hematomas [3,6]. In a retrospective study, IMH detected on SWI was positive in nine of 10 vertebral artery dissec-

tions. The author showed that SWI had high sensitivity (90%) and specificity (96.6%) for detecting the IMH sign [7]. Among the patients, five underwent HR fat-suppression T1-weighted MRI. The eccentric high signal at the site of dissection, which was suggestive of IMH, was positive in only two of the five patients. The median time to the MRI studies was much longer in the patients with IMH (132 hours; range, 120 to 144) than in those without IMH on HR-MRI (10 hours; range, 5 to 16) [7]. SWI alone cannot differentiate IMH from calcification because it is sensitive to both paramagnetic and diamagnetic compounds. The phase map plays an important role in differentiating between hematoma and calcifications, as both have opposing signal intensities on the phase map [8]. In our case, the corresponding bright signals were observed in the phase map and were compatible with hematoma. Whether the IMH sign on SWI and T1-weighted MRI may

also be seen in vulnerable atherosclerotic plaques with hemorrhage is unclear. Focal enlargement of the external diameter on T1-weighted imaging is associated with IMH [1]. In our case, enlarged vessels with contrast enhancement were observed on the CT angiography source images. Intraluminal clots in occlusive vessels may be seen as hypointense signals within the vascular cisterns on SWI and termed as the “susceptibility vessel sign (SVS).” IMH and SVS, especially in the occluded vessel, are difficult to differentiate on SWI. However, SVS is usually shown as a mass on SWI. In our case, the dark signals on the SWI had a bead-like appearance; therefore, IMH could develop in the occlusive spiral dissection. Spontaneous recanalization after stenting without clot retrieval also suggests arterial dissection rather than cardiac embolism.

Although IAT has become an essential treatment strategy in patients with acute LVO, its efficacy and safety in acute dissecting intracranial artery occlusion have not been evaluated, especially in the anterior circulation. Some observational studies have reported periprocedural hemorrhagic complications after endovascular treatment in 0% to 22% of patients with ischemic stroke from IAD [1]. If neurological symptoms are mild, it is better to avoid the procedure. If the procedure is inevitable because of disabling stroke, direct stenting after careful navigation through the true lumen might reduce the risk of periprocedural complications from repeated procedures. Therefore, identifying the etiology of the LVO before the procedure can be useful in the development of an effective and safe treatment strategy.

In conclusion, the IMH sign on SWI led us to suspect that the LVO was due to the IAD, and this finding is unaffected by the acquisition time from symptom onset. However, angiography may be necessary for the definite diagnosis of dissection because the reliability of the IMH sign on SWI has not been fully determined. This is needed to identify which features suggest IMH in arterial dissection rather than in intraplaque hemorrhage, and SVS in cardioembolic stroke. Further research is also needed to address the efficacy and safety in patients with disabling stroke from acute dissecting LVO.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

ORCID

Changhyo Yoon, <https://orcid.org/0000-0002-8875-6333>

Seunguk Jung, <http://orcid.org/0000-0003-2331-024X>

Heejeong Jeong, <https://orcid.org/0000-0001-6531-1860>

Eunbin Cho, <https://orcid.org/0000-0003-2021-8587>

Tae-Won Yang, <https://orcid.org/0000-0002-8113-2384>

Seung Joo Kim, <https://orcid.org/0000-0001-9391-1767>

Ki-Jong Park, <https://orcid.org/0000-0003-4391-6265>

Seung Soo Kim, <https://orcid.org/0000-0002-2114-4594>

Hyun Park, <https://orcid.org/0000-0002-2422-4389>

Author contributions

Conceptualization: CY, SJ, SSK, and HP. Visualization & Writing—original draft: CY and SJ. Writing—review editing: HJ, EC, TWY, SJK, and KJP.

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Huge uterine myoma as a cause of thromboembolic stroke

Hyun Joon Lee, MD; Dong Hoon Shin, MD

Department of Neurology, Gachon University Gil Medical Center, Incheon, Republic of Korea

CASE REPORT

Received: September 2, 2019

Revised: November 8, 2019

Accepted: November 12, 2019

Corresponding Author:

Dong Hoon Shin, MD
Department of Neurology, Gachon
University Gil Medical Center, 21
Namdong-daero 774beon-gil,
Namdong-gu, Incheon 21565, Republic
of Korea
Tel: +82-32-460-3346
Fax: +83-32-460-3344
E-mail: dr.donghoon.shin@gmail.com

Background: Embolic stroke undetermined source (ESUS), which is defined as nonlacunar infarction in the absence of cardioembolic sources, proximal artery stenosis excluded by echocardiogram, holter monitoring and vascular images, is reported to account for 9% to 25% of ischemic stroke. Because the source of embolism remains unclear, it is an important task to find the etiology for secondary prevention of stroke recurrent.

Case Report: We report a case of uterine myoma found in an embolic stroke patient with incidentally found a huge uterine myoma and related deep vein thrombosis.

Conclusion: Uterine myoma in a middle-aged woman can be thought to be the etiological cause that can contributor to deep vein thrombosis, and it is necessary to pay attention as the etiology of ESUS.

Keywords: Embolic stroke undetermined source; Embolic stroke; Myoma

INTRODUCTION

Embolic stroke undetermined source (ESUS) proposed by an International Working Group of Neurologists is a new definition to reassess the term cryptogenic stroke and change the vague defined entity of cryptogenic stroke to more clinically useful for future secondary prevention trials [1]. ESUS is defined as a nonlacunar infarct without large artery stenosis or cardioembolic sources, which is established by a stepwise diagnostic work-up. It is hypothesized that anticoagulation therapy is more efficacious than antiplatelet

therapy for secondary prevention in ESUS patients [2].

Understanding the etiology of cerebral infarction is necessary to determine the prognosis or treatment of the patients. There are very rare cases of deep vein thrombosis and pulmonary thromboembolism caused by uterine myoma. In addition, there are very few reports of systemic embolism such as stroke caused by the presence of patent foramen ovale (PFO) in patients in these cases [3]. We describe a case of top of basilar syndrome in a young female patient with deep venous thrombosis due to venous compression by large uterine myoma.

CASE REPORT

A 43-year-old woman came to our hospital with loss of consciousness that occurred in the house just before hospital visit. She arrived in the emergency room 45 minutes after symptom occurred. She had no past medical history and was neither smoking nor drinking alcohol. At the time of admission, the vital sign showed a blood pressure of 119/66 mm Hg, a heart rate of 76/min, a respiratory rate of 24/min, and a body temperature of 36.2°C. In neurological examinations, level of consciousness was stuporous, and higher cortical function could not be assessed. Both pupils were dilated 5 mm/7 mm, and no light reflex was seen. The patient had no motor weakness, deep tendon reflex was normoreflexia, no pathologic reflex shown. In the emergency room, brain computed tomography (CT), CT angiography, and CT perfusion were performed. Although there were no remarkable findings on brain CT (Fig. 1A) and no stenosis or occlusion on brain CT angiography (Fig. 1E), brain CT perfusion showed mildly decreased cerebral blood flow and cerebral blood volume in left midbrain (Fig. 1B-1D). We started to infuse tissue plasminogen activator (tPA) intravenously after 1 hour and 40 minutes from symptom onset. Because there was no occluded vessel on brain CT angiography, we did not consider further treatment like mechanical thrombectomy. In laboratory test, protein C activity was decreased to 31% (normal

range, 55% to 123%), cancer antigen-125 (CA-125) was mildly elevated to 39.5 U/mL (normal range, <35). However, there were no more abnormal results in complete blood count, lipid profiles, hemoglobin A1c, thyroid function, liver, and renal function. Other blood tests related to hypercoagulability and vasculopathies including protein S activity, antithrombin III, prothrombin, antiphospholipid antibody, anticardiolipin antibody, lupus anticoagulant, antinuclear antibody, anti-beta2-glycoprotein 1 (GP 1) antibody showed negative. In magnetic resonance imaging including diffusion weighted image (DWI) and angiography, which was performed after 24 hours from tPA infusion, DWI showed hyperintensity lesions at the right side of the cerebellum, at the bilaterally thalamus, midbrain, pons (Fig. 2A) and MR angiography showed no stenosis or atherosclerotic changes (Fig. 2B). The patient admitted to intensive care unit and took anti platelet (aspirin 100 mg/day, clopidogrel 75 mg/day), 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (atorvastatin 20 mg) agents for secondary prevention. Her 24 hours holter monitoring and transthoracic echocardiography were all normal. Because CA-125 was elevated in laboratory findings, abdominal pelvis CT was performed to find the presence of pelvic mass. A large sized uterine myoma of 7.5 cm was found (Fig. 3A). Femoral CT angiography was also performed, there were multiple thrombus was found in both common iliac vein and femoral vein (Fig. 3B). For deep vein

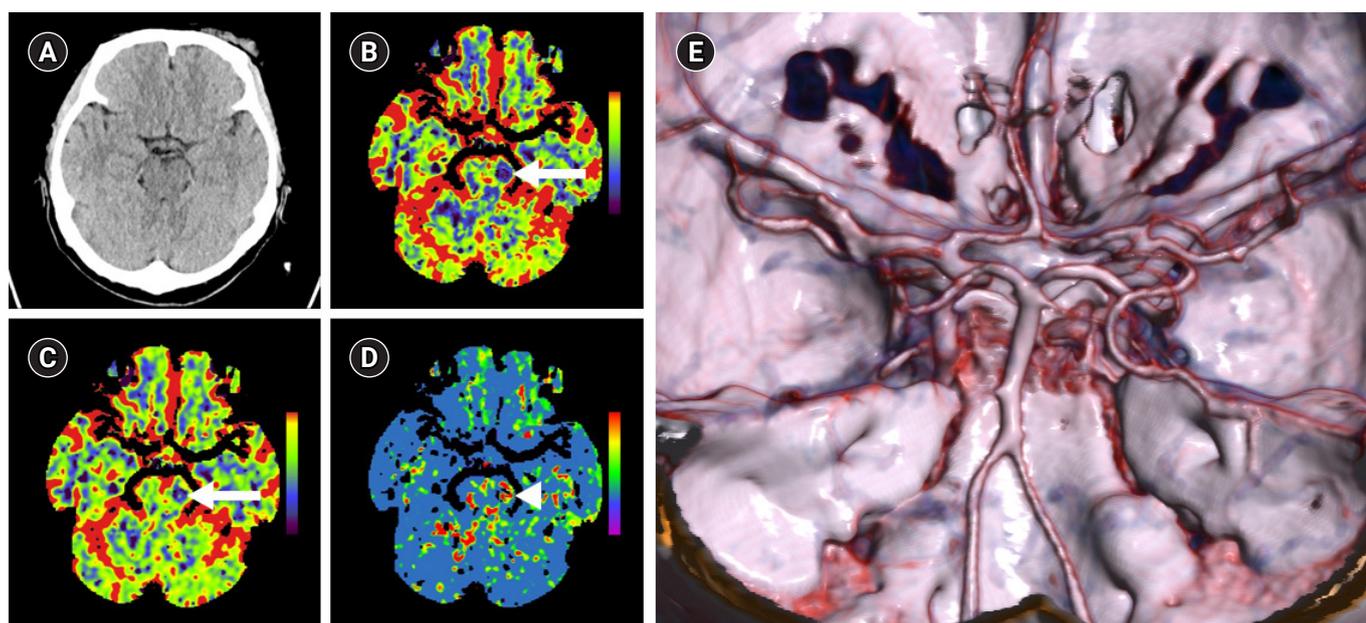


Fig. 1. Brain computed tomography (CT) and CT angiography were performed immediately after arrival at the emergency room. (A) There was no remarkable finding on brain CT. (B) Cerebral blood flow and (C) cerebral blood volume map shows decreased perfusion of the left midbrain (arrows). (D) Mean transit time map shows a prolongation within the same region (arrowhead), indicative of core infarct in the left midbrain. (E) There were no stenosis or occlusion on basilar artery and the other vessels.

thrombosis, the antiplatelet agent was changed to an anticoagulant agent (dabigatran 300 mg/day). Transcranial Doppler was performed but showed normal results. Neither the bubble test nor the transesophageal echocardiography (TEE) was performed because valsalva maneuver could not be performed due to stuporous mentality. Protein C activity was rechecked 3 months later and the result was restored to normal as 64%.

DISCUSSION

As improving understand for stroke pathophysiology and achieving advances in imaging, vague defined entity of cryptogenic stroke was reassessed as ESUS to improve the efficacy of secondary stroke prevention by International Working Group of Neurologists in 2014 [1]. ESUS is known to account for an average of

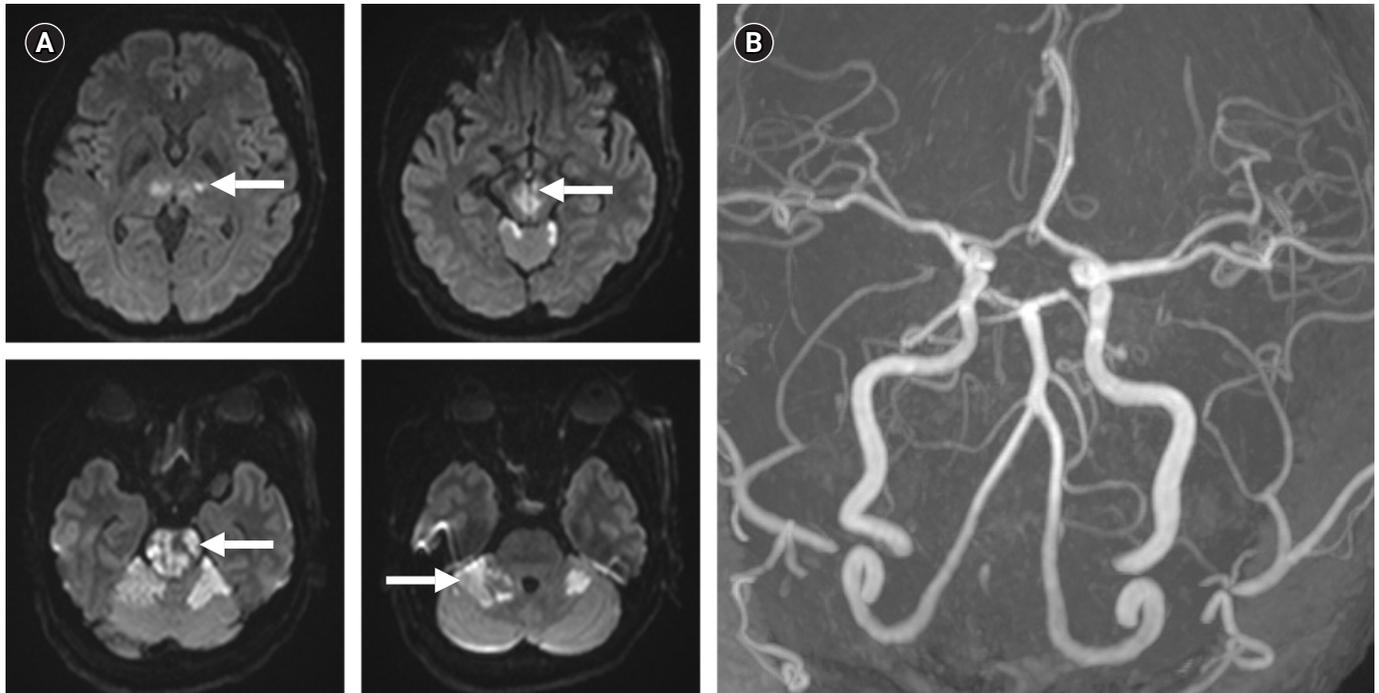


Fig. 2. (A) Diffusion-weighted imaging, performed after 1 day from symptom onset, showed acute ischemic lesion in the bilateral thalamus, midbrain, pons and right cerebellum (arrows). (B) Magnetic resonance angiography which was performed after 1 day from symptom onset, showed no stenosis or occlusion.

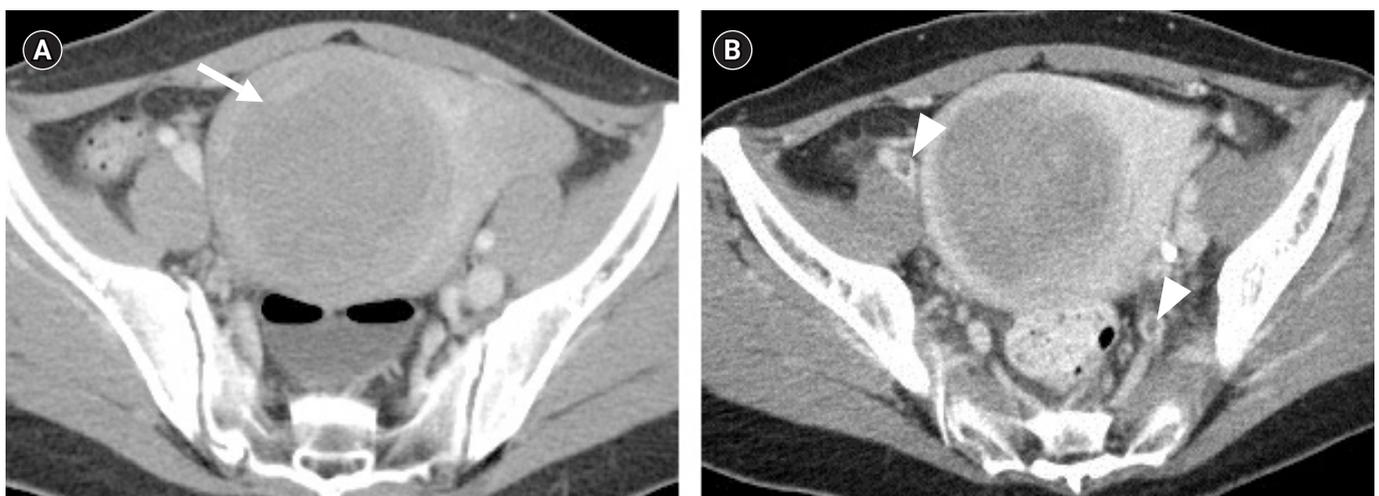


Fig. 3. (A) There was a 7.5 cm uterine myoma with several small myomas in pelvic cavity (arrow). (B) Femoral computed tomographic angiography reveals contrast filling defects in the right external iliac vein, left internal iliac vein (arrowheads).

17% according to a study of ischemic stroke patients [1]. The most common cause of ESUS patients is paroxysmal atrial fibrillation. Recently, various studies have revealed a strong relationship with PFO and ESUS [2]. However, there are various causes such as vascular atherosclerotic ulcer, PFO, and embolism associated with cancer [3].

Searching the cause of embolus in ESUS is very important for establishing secondary prevention plan. Although systemic thromboembolism to lung, kidneys, spleen, and brain is a very rare complication of uterine myoma, there are several reports that uterine myoma can cause systemic embolism. One suggested mechanism is that uterine myoma may cause severe anemia and reactive thrombocytosis, leading to arterial thrombosis and thus recurrent cerebral infarct in patient without no PFO and no thrombus in pelvic organ [4,5]. Other suggested mechanism is that deep venous thrombosis due to compression of the lower extremity vein caused by a huge uterine myoma may enter systemic circulation through PFO and cause relapsing paradoxical cerebral embolism [6-8].

Because there was the presence of multiple thrombosis in both lower extremity veins without anemia or coagulopathy in this case, we thought the paradoxical embolism of deep vein thrombosis by large uterine myoma through PFO is the etiology of this case rather than anemia and coagulopathy although she could not confirm the PFO by performing TEE or bubble test due to stuporous mentality. Failure to identify the right-to-left shunt is a limitation of this case. In here, we report this case because uterine myoma in a middle-aged woman can be thought to be the etiological cause that can contributor to deep vein thrombosis, and it is necessary to pay attention as the etiology of ESUS.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

ORCID

Hyun Joon Lee, <https://orcid.org/0000-0001-6295-182X>

Dong Hoon Shin, <https://orcid.org/0000-0002-1103-1983>

Author contributions

Conceptualization: LHJ and SDH. Data curation & Formal analysis: LHJ and SDH. Investigation: LHJ and SDH. Methodology: LHJ and SDH. Project administration: LHJ and SDH. Resources: LHJ and SDH. Supervision: LHJ and SDH. Validation: LHJ and SDH. Visualization & Writing—original draft: LHJ and SDH. Writing—review editing: LHJ and SDH.

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Acute subarachnoid hemorrhage due to giant vertebrobasilar dolichoectasia

Jun-Yop Kim, MD¹; Ji-Woong Kim, MD¹; Mi-Jin Yoon, MD²;
Seung-Han Suk, MD, PhD¹

¹Department of Neurology, Wonkwang University Sanbon Hospital, Wonkwang University School of Medicine, Gunpo, Republic of Korea

²Department of Radiology, Wonkwang University Sanbon Hospital, Wonkwang University School of Medicine, Gunpo, Republic of Korea

CASE REPORT

Received: May 6, 2019

Revised: July 30, 2019

Accepted: August 8, 2019

Corresponding Author:

Seung-Han Suk, MD, PhD
Department of Neurology, Wonkwang
University Sanbon Hospital, Wonkwang
University School of Medicine, 327
Sanbon-ro, Gunpo 15865, Republic of
Korea

Tel: +82-31-390-2300

Fax: +82-31-398-2223

E-mail: suksh@wonkwang.ac.kr

Background: Vertebrobasilar dolichoectasia (VBD) is a dilatative arteriopathy of the vertebrobasilar artery. Subarachnoid hemorrhage (SAH) is a rare but fatal complication of VBD.

Case Report: A 65-year-old man was brought to the emergency room with altered mental status. Computed tomography angiography revealed the presence of SAH, and the rupture site was suspected to be the dolichoectatic portion of the vertebrobasilar artery. Twelve years previously, the patient had developed a right pontine infarct, and VBD had been detected. The basilar artery had dilated to a diameter of 22 mm and contained a mural thrombus. The patient's noncompliance to antihypertensive treatment led to VBD progression and a hemifacial spasm. He was admitted to the intensive care unit for conservative treatment. Consciousness was restored, but he developed quadriplegia.

Conclusion: In patients with a giant VBD, strict blood-pressure control is important to prevent fatal complications. Targeted surgical or endovascular procedures may improve patient outcomes but require further studies.

Keywords: Vertebrobasilar dolichoectasia; Hypertension; Subarachnoid hemorrhage

INTRODUCTION

Vertebrobasilar dolichoectasia (VBD) is an arteriopathy resulting in pathological elongation, twisting, and dilatation of the vertebrobasilar artery. Dolichoectasia mostly occurs in the posterior cerebral circulation, but it can also occur in the anterior cerebral circulation; the basilar artery is involved in >80% of cases. As the basilar artery gives off several branches at large angles, and the shearing forces are greater at the branching points, VBD can occur [1,2].

Although parameters for the diagnosis of VBD have not been established, Smoke et al. [3] proposed certain diagnostic criteria based on information obtained from imaging studies, including radiography, angiography, and computed tomography (CT), of the vertebral arteries. VBD is diagnosed if the arterial diameter is ≥ 4.5 mm or if the separation or branching point of the dorsum sellae is above the suprasellar cistern (Table 1).

Here, we report a case of left arm paralysis caused by pontine hemorrhage in a patient who developed quadriplegia following

Table 1. Diagnostic criteria for basilar artery dolichoectasia based on computed tomography

Basilar artery diameter
Normal range: 1.9–4.5 mm
Ectasia: diameters greater than 4.5 mm
Basilar artery height (plane of the basilar bifurcation) ^{a)}
0 At or below the dorsum sellae
1 Within the suprasellar cistern (one cut above the dorsum)
2 At the level of the third ventricle floor (one cut above the suprasellar cistern)
3 Indenting and elevating the floor of the third ventricle (two or more cuts above the suprasellar cistern)
Basilar artery position (most lateral position of the basilar artery) ^{a)}
0 Midline throughout
1 Medial to lateral margin of the clivus or dorsum sellae
2 Lateral to lateral margin of the clivus or dorsum sellae
3 In the cerebellopontine angle cistern

Modified from Smoker et al. *AJNR Am J Neuroradiol* 1986;7:55–60, with permission of American Society of Neuroradiology [3].

^{a)}Value of 2 or more suggests presence of abnormalities.

subarachnoid hemorrhage (SAH) due to rupture of VBD.

CASE REPORT

In 2017, a 65-year-old man was brought to the emergency room with altered mental status. At the time of admission, his blood pressure was slightly elevated to 150/90 mm Hg, but the other vital signs were normal. Neurological examination showed that he was stuporous and unable to open his eyes on command. Limb weakness was not apparent, and he demonstrated an avoidance response to the painful stimulus. Both the pupils were 2 mm in diameter and showed normal light reactivity. Emergency CT angiography showed enlarged right vertebral and basilar arteries with a diameter of 23 mm. The right vertebral artery twisted from the V3 portion to the V4 portion where it crossed to the left, and its diameter began to increase. The basilar artery enlarged until the point of origin of the superior cerebellar artery and compressed the left brainstem. Angiography revealed the presence of SAH, which was associated with intraventricular hemorrhage and hydrocephalus. SAH mainly involved the posterior fossa adjacent to the dilated basilar artery, near the basilar and sylvian cisterns, indicating that VBD was the rupture site (Fig. 1).

The patient had visited a hospital in 2002 with left upper limb motor weakness and dizziness and was diagnosed with a right pontine infarct. Magnetic resonance imaging of the brain revealed VBD with mural thrombus (Fig. 2). Therefore, the patient was treated with antiplatelet and antihypertensive agents to prevent both secondary stroke and complications of VBD. In the follow-up, a left hemifacial spasm was observed in 2003 because of a mass effect exerted by VBD. We considered intravascular surgery to control his symptoms, but because of the position and length of the dolichoectatic vertebrobasilar artery, the procedure

would have carried a high risk, and the patient refused to undergo it. We continued the existing treatment and regularly monitored the patient. The patient was prescribed with medications and recommended necessary lifestyle modifications to control the blood pressure. However, because of noncompliance to the conservative therapy, his blood pressure was not controlled. In the follow-up visits, the doses of antihypertensive medications were continuously increased, as his blood pressure was uncontrolled. In 2014, his blood pressure was maintained at approximately 140/90 mm Hg even with four treatment regimens. We continued to emphasize on the need for increase in physical activity and lifestyle changes; however, he could not perform the suggested physical activities because of left upper limb muscle weakness. Moreover, he did not change his dietary behavior, and his body weight continued to increase. He developed diabetes in 2013. Five months before the onset of SAH, he was admitted to the hospital with sudden weight gain and hyperglycemia, which was uncontrolled with insulin. His blood pressure during hospitalization increased to 160/110 mm Hg, and he showed no response to various conservative treatments. This may have contributed to the development of SAH 15 years after the diagnosis of VBD.

The patient was admitted to the intensive care unit (ICU). We first administered intravenous nimodipine to control the blood pressure and prevent vasospasm. After admission, the patient had severe expectoration and developed fever. We continued antibiotic treatment for aspiration pneumonia. However, as the symptoms persisted and worsened, impeding the patient's breathing, we performed tracheostomy to maintain the airway. The patient developed quadriplegia on hospitalization day 5. On hospitalization day 7, he began to recover, with improvement in the level of consciousness. He could open his eyes on hospitalization day 14. On

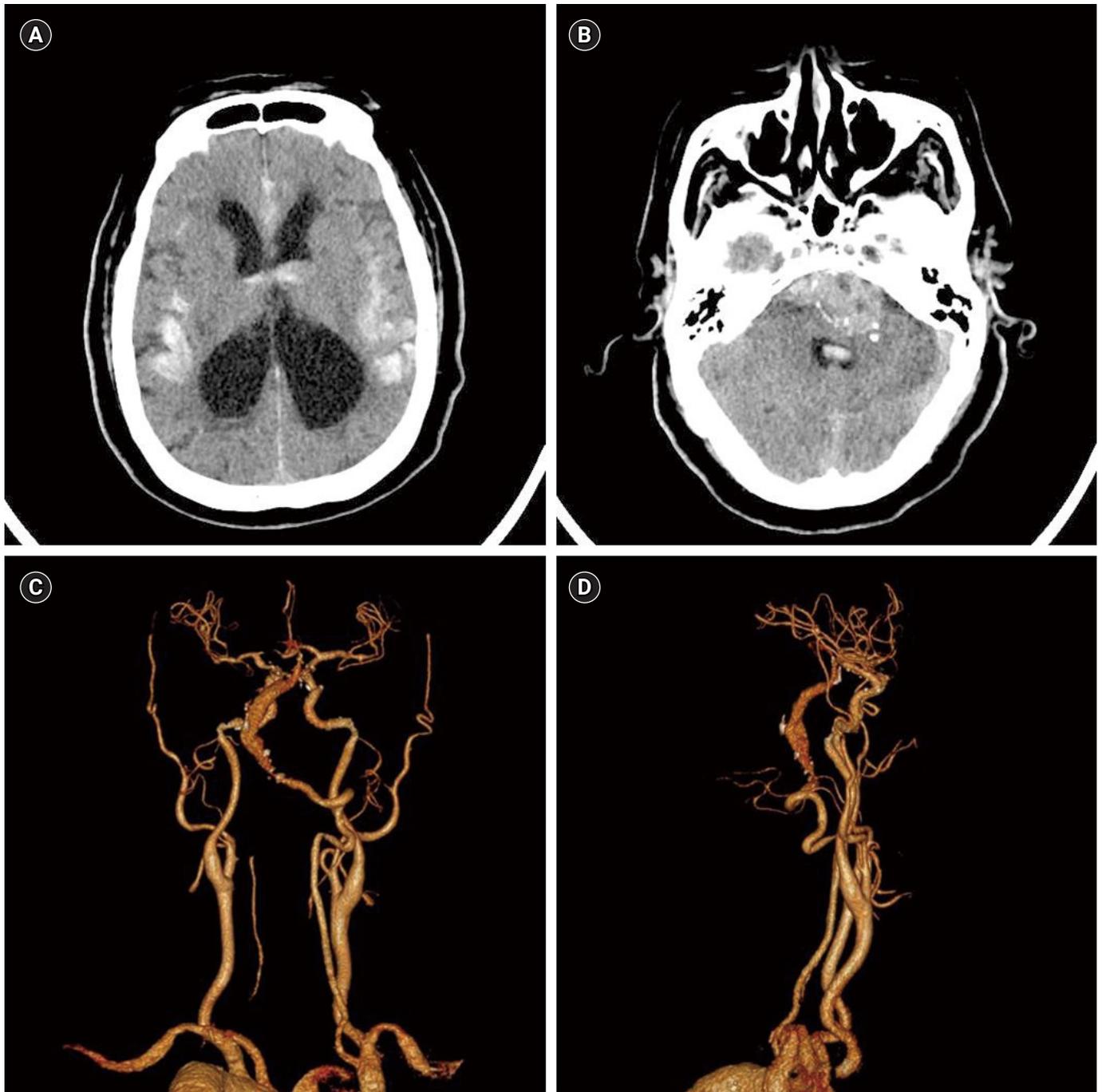


Fig. 1. (A) Computed tomography of the brain revealed subarachnoid hemorrhage with intraventricular hemorrhage and hydrocephalus. (B) Subarachnoid hemorrhage involved the posterior fossa near the fusiform aneurysm of the basilar artery, the basilar cistern, and both the sylvian cisterns. (C, D) Computed tomography angiography of the brain showing a giant vertebrobasilar dolichoectasia involving the right vestibular and basilar arteries.

hospitalization day 25, the patient was completely conscious. Repeat CT showed partial resolution of subarachnoid and intraventricular hemorrhages. He was transferred to the general ward after approximately 30 days in ICU. He was recently admitted to a long-term care facility to manage his quadriplegic bedridden condition.

DISCUSSION

On histology, VBD shows fragmentation of the internal elastic lamina and hyperplasia of the intima. Neovascularization progresses with thickened intima and is accompanied by intermural

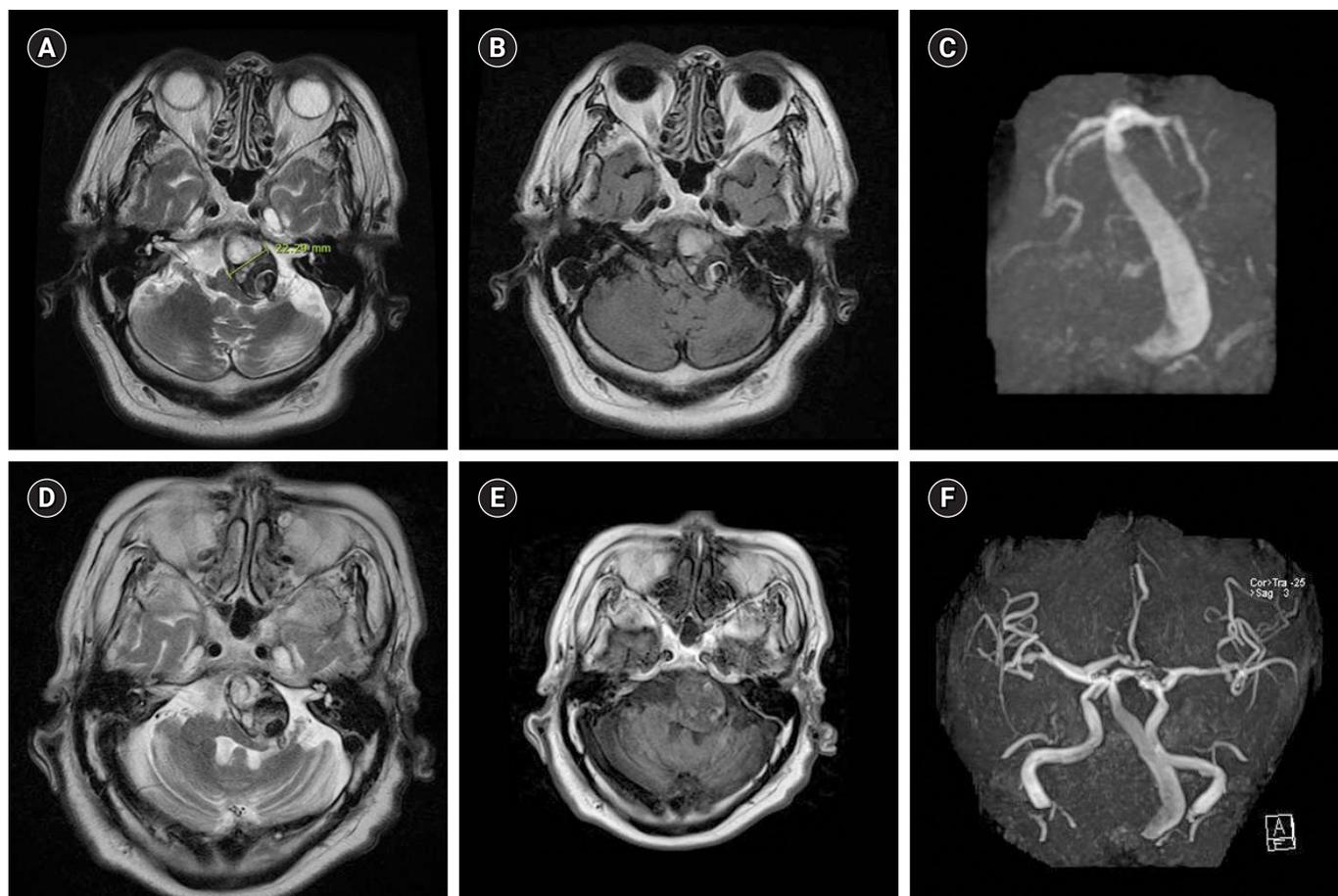


Fig. 2. (A, B) Magnetic resonance imaging (MRI) showing a giant vertebrobasilar dolichoectasia (22 mm in diameter) with a large mural thrombus within the tortuous basilar artery shifting the brainstem toward the right side. (C) Magnetic resonance angiography (MRA) demonstrating narrowing of the lumen of the basilar artery because of a thrombus. (D-F) MRI and MRA performed 5 months before the subarachnoid hemorrhage appeared showing no significant changes in the dimensions of the artery with vertebrobasilar dolichoectasia.

hemorrhage and thrombus [4].

Hemodynamic stress on the vessel wall causes degeneration of elastin and collagen, which comprise the internal elastic lamina, resulting in weakening of the arterial wall. Intimal thickening appears to adapt to these changes. Many risk factors are associated with these conditions. The age and sex of the patient, vascular causes, such as hypertension, metabolic disorders, such as Fabry and Pompe diseases, and hereditary diseases, such as Marfan syndrome, may affect the formation of vascular interstitial structures [2,5].

Patients with VBD may be asymptomatic or present with symptoms of an ischemic cerebral infarction or transient cerebral ischemia due to thrombus formation. They may also experience intracranial hemorrhage due to rupture of the dilated vessel and become symptomatic because of compression of the cerebral nerves, brain stem, and ventricles [2].

To date, there is no known method to prevent VBD. Therefore, currently, empirical treatment is performed for secondary prevention and symptomatic control of the fatal complications of

VBD [1,2].

Intravascular thrombus formation is common in vessels with VBD, secondary to vasodilatation and decreased blood flow velocity. Therefore, occlusion of a perforated artery by a thrombus or embolus can occur with VBD [6]. If the ectatic vessels compress the cranial nerves, symptomatic manifestations, such as a hemifacial spasm and trigeminal neuralgia, may occur [7,8]. In addition, patients may present with dementia secondary to hydrocephalus, caused by compression of the third ventricle [9].

SAH is observed in approximately 1% of the patients with VBD following rupture of the elongated and tortuous vessels. Although rare, SAH has a high mortality rate. Arterial rupture could be caused by local inflammation and ischemic changes in the blood vessel wall following a decrease in vascular resistance associated with the progress of vasodilatation and thrombosis due to VBD [10].

The most common risk factors for VBD-related bleeding are the extent of venous dilatation and degeneration, arterial hypertension, the use of antiplatelet agents or anticoagulants, and the

female sex [11]. To prevent rupture of VBD, strict blood pressure control is mandated. It is also necessary to exercise due caution while administering antiplatelet agents and anticoagulants for prevention of ischemic diseases in patients with a giant VBD [2].

Intravascular surgery can be considered to preempt the vessel rupture and reduce pressure on the nearby structures. However, as in our case, VBD in the basilar trunk may present with some clinical difficulties. Arteries with VBD do not have a defined neck. The basilar trunk has many perforating arteries supplying blood to the pons; surgery at this location is difficult [12].

Proximal ligation or parent vessel occlusion may be considered, but the overall prognosis is poor compared to dolichoectasia in the vertebral or posterior cerebral artery [13]. Recently, flow-diverting stents have been used in patients with VBD, but the overall prognosis is poor in patients with mass effects or SAH [14]. A study on the treatment options for these patients is needed.

In the present case, the patient was initially admitted and diagnosed with pontine infarction and started on medications. However, the patient did not adhere to the prescribed treatment or follow the recommended lifestyle changes to control hypertension. A hemifacial spasm occurred, but he rejected endovascular therapy.

In summary, comprehensive management of vascular risk factors, including strict control of blood pressure, is important for the prognostic outcome of a giant VBD. Endovascular therapy should be considered after weighing the risk and benefit to patients. Further studies and technical advances are needed.

ARTICLE INFORMATION

Conflict of interest

No potential conflict of interest relevant to this article.

Funding

This work was supported by the Wonkwang Research Grant in 2019.

ORCID

Jun-Yop Kim, <https://orcid.org/0000-0002-4560-0291>

Ji-Woong Kim, <https://orcid.org/0000-0002-7432-2585>

Mi-Jin Yoon, <https://orcid.org/0000-0002-7799-3966>

Seung-Han Suk, <https://orcid.org/0000-0002-8732-5021>

Author contributions

Conceptualization: JYK and SHS. Data curation & Formal analysis: JYK and JW. Visualization & Writing—original draft: JYK, MJY, and SHS. Writing—review editing: JYK and SHS.

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Enacted April 1, 2008
Last revised March 25, 2019

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CONTACT US

Editor-in-Chief: Sang-Beom Jeon, MD, PhD

Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea

Tel: +82-2-3010-3440, Fax: +82-2-474-4691

E-mail: editor@e-jnc.org

Editorial Office: The Korean Neurocritical Care Society

Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea

Tel: +82-2-3010-3440, Fax: +82-2-474-4691

E-mail: office@e-jnc.org

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- Articles in academic journals

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